Compounding Practices in Europe

Extemporaneously Compounded Oral Medicines in European Hospital Pharmacies

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Extemporaneously Compounded Oral Medicines in European Hospital Pharmacies

This thesis describes research conducted in the UCL School of Pharmacy between October 2006 and September 2010, under the supervision of Professor Kevin Taylor and Dr Catherine Tuleu. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

To my grandparents

Aos meus avós

Maria Benedita e Humberto

Abstract

Pharmaceutical compounding corresponds to the preparation of customised medicines in order to meet the specific needs of patients, which cannot be met by the proprietary medicines provided by the pharmaceutical industry. Historically, pharmaceutical compounding dates back to the very origins of pharmacy and, ever since, it has been an integral part of pharmacy practice. Nevertheless, little is known regarding current compounding practices in Europe and, therefore, the aim of this project was to identify and characterise the oral compounded medicines most frequently dispensed in European hospital pharmacies.

The research method adopted was a large-scale, international (European) survey and the research instrument was a self-completion (country-specific) questionnaire. A total of 11 European countries were included in the research: Portugal, UK, Switzerland, Poland, Netherlands, Denmark, Slovenia, Finland, Spain, France and Germany. For most countries, a purposive sample of hospitals was contacted and invited to contribute data regarding the oral compounded medicines most frequently dispensed in their pharmacies. The pilot-study was launched in Portugal but fieldwork was undertaken in most countries. Information regarding legislation, professional organisations and information sources relevant to pharmaceutical compounding was also collected.

The oral compounded medicines most frequently dispensed in hospital pharmacy varied considerably throughout Europe, from traditional cachets in Poland to complex tablets in the Netherlands and Denmark. A wide range of active substances, including NTI drugs, and dosage strengths were dispensed. Compounded medicines were prepared individually and also in batches of variable sizes. There is little consistency of compounding practices in Europe and there is a need for common legislation, professional organisations and information sources. This project corresponds to the largest and most complex research in pharmaceutical compounding across Europe and aims to contribute to the harmonisation of quality and safety of compounded medicines in Europe.

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List of Abbreviations

ABDA	*Bundesvereinigung Deutscher Apothekerverbände*
ACSM	Association of Commercial Specials Manufacturers
ADME	Absorption, distribution, metabolism and elimination
AEFF	*Asociación Española de Farmacéuticos Formulistas*
AEMPS	*Agencia Española de Medicamentos y Productos Sanitarios*
AFA	*Asociación de Formulistas de Andalucía*
AFSSAPS	*Agence Française de Sécurité Sanitaire des Produits de Santé*
ANVISA	*Agência Nacional de Vigilância Sanitária*
APFH	*Associação Portuguesa de Farmacêuticos Hospitalares*
Aprofarm	*Asociación Profesional Independiente de Farmacéuticos Formuladores*
ATC	Anatomical Therapeutic Chemical
BOE	*Boletín Oficial del Estado*
BP	British Pharmacopoeia
BPC	British Pharmaceutical Codex
BNF/BNFC	British National Formulary / British National Formulary for Children
CETMED	*Centro Tecnológico do Medicamento*
CIOM	Chemo-Induced Oral Mucositis
CNS	Central Nervous System
COFM	*Colegio Oficial de Farmacéuticos de Madrid*
CGCOF	*Consejo General de Colegios Oficiales de Farmacéuticos*
CPPR	Centre for Paediatric Pharmacy Research
CSHP	California Society of Health-System Pharmacists
DHSS	Department of Health and Social Security
EAHP	European Association of Hospital Pharmacies
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEAS	European External Action Service
EMA/EMEA	European Medicines Agency
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
ed.	Editor(s)
edn.	Edition
e.g.	*Exempli gratia* / For example
eMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EU	European Union

EuPFI	European Paediatric Formulation Initiative
FIP	International Pharmaceutical Federation
FDA	Food and Drug Administration
FGP	*Formulário Galénico Português*
FNA	*Formularium der Nederlandse Apothekers*
FP	*Farmacopeia Portuguesa*
FS	*Formularium Slovenicum*
GI	Gastrointestinal
GCP	Good Compounding Practices
GMP	Good Manufacturing Practices
GMP-Z/H	Good Manufacturing Practices in Hospital Pharmacy
HCl	Hydrochloride
HFA-DB	European Health for All Database
HIV	Human Immunodeficiency Virus
HOPE	European Hospital and Healthcare Federation
IACP	International Academy of Compounding Pharmacists
ICH	International Conference on Harmonisation
i.e.	*Id est* / That is
IJPC	International Journal of Pharmaceutical Compounding
IPB	Institute of Pharmaceutics and Biopharmaceutics
ITMI	*Instituto Tecnológico del Medicamento Individualizado*
IV	Intravenous
INFARMED	*Autoridade Nacional do Medicamento e Produtos de Saúde*
ISPhC	International Society of Pharmaceutical Compounding
IU	International Units
JPAG	Joint Pharmaceutical Analysis Group
KNMP	*Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie*
LEF	*Laboratório de Estudos Farmacêuticos*
MC	Maria Carvalho
MHRA	Medicines and Healthcare products Regulatory Agency
n/a	Not applicable
NAM	National Agency for Medicines
NBTC	Netherlands Board of Tourism & Conventions
NHS	National Health Service
NPPG	Neonatal and Paediatric Pharmacists Group
NRF	*Neues Rezeptur-Formularium*

NTI	Narrow Therapeutic Index
NVZA	*Nederlandse Vereniging van Ziekenhuisapothekers*
OED	Oxford English Dictionary
ORS	Oral Rehydration Salts
pp.	Pages
PDF	Portable Document Format
PhEur	European Pharmacopoeia
PhHelv	*Pharmacopoea Helvetica*
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Co-operation Scheme
POD	*Produit Officinal Divisé*
PTFarm	*Polskie Towarzystwo Farmaceutyczne*
PUI-DLC	*Pharmacies à Usage Intérieur - Département des Laboratoires de Contrôles*
QA/QC	Quality Assurance / Quality Control
qs	*Quantum sufficiat* / sufficient
RPSGB/RPS	Royal Pharmaceutical Society of Great Britain
SDD	Selective Decontamination of the Digestive tract
SIG	Paediatrics Special Interest Group
SF	Sugar Free
SG	Spela Godec
SOP	Standard Operating Procedure(s)
SOTP	*Societe des Officinaux sous-Traitants en Preparations*
Swissmedic	Swiss Agency for Therapeutic Products
TPN	Total Parenteral Nutrition
UCL/UCLH	University College London / University College London Hospitals
UFP	*Universidade Fernando Pessoa*
UK	United Kingdom of Great Britain and Northern Ireland
ULLA	European University Consortium for Pharmaceutical Research
	Uppsala, Leiden, London, Amsterdam, Paris and Copenhagen
UNICEF	United Nations Children's Fund
US/USA	United States of America
USP-NF	United States Pharmacopeia - National Formulary
vs	Versus
WHO	World Health Organization
WINAp	*Wetenschappelijk Instituut Nederlandse Apothekers*
JAZMP	*Javna agencija Republike Slovenije za zdravila in medicinske pripomočke*

1. Introduction

1.1 Pharmaceutical compounding

Pharmaceutical compounding corresponds to the preparation of customised medicines in order to meet the specific needs of patients. The pharmaceutical industry provides patients with proprietary medicines based on a "one-size-fits-all" approach, but there are individual needs that require personalised therapy. In these situations, compounded medicines are an invaluable alternative that allows patients the benefit of a bespoke treatment.

1.1.1 Historical context of compounding

The origins of pharmacy date back to antiquity where primitive men mixed animal, vegetable and mineral substances for medicinal purposes. Archaeological research shows evidence of the preparation of medicines *secundum artem*[1] by many early civilizations and throughout history. This practice is well documented in the Bible, and the apothecary[2] is considered one of the earliest professions (Allen, 2003a; Marriott *et al.*, 2010). The historic role of the apothecary as the individual involved in the preparation of medicines represents the heritage of pharmacy, and is symbolized by the traditional mortar and pestle (D'Angelo, 1997; Anderson, 2005; RPS, no date).

The art (and later the science) of preparing medicines are at the very origins of pharmacy and, ever since, compounding has been an integral part of pharmacy practice (Allen, 2005a; Higby, 2005). Consequently, present and past definitions of pharmacy and pharmacists include the concept of compounding, or preparation of medicines (Allen, 2005a), as the following:

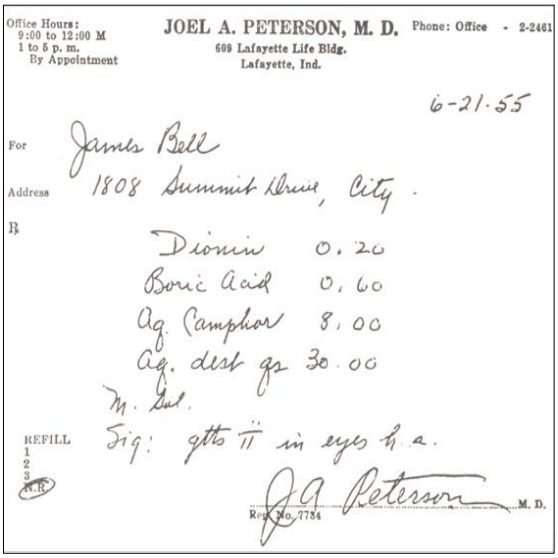
- Pharmacy is the science or practice of preparing and dispensing medicinal drugs (*OED*, 2004); the making or compounding of medicines (Weiner and Simpson, 1989).

[1] *Secundum artem* – according to art – in accordance with the rules of the art (*OED,* 1989).
[2] Apothecary, the earlier name for one who prepared and sold drugs for medicinal purposes (*OED*, 1989).

- A pharmacist is a person who is professionally qualified to prepare and dispense medicinal drugs (*OED*, 2008); a person prepared to formulate, dispense and provide clinical information on drugs or medications to health professionals and patients (Myers, 2002).

Although compounding involves other health care professionals, pharmacists possess unique skills and knowledge that are not duplicated by any other profession. Pharmacists, experts in pharmaceutical science, put together chemistry, physics, biology and mathematics into the practice of pharmaceutical compounding (Jenkins *et al.*, 1957; Taylor and Harding, 1999; Allen, 2005a).

The prescription for a compounded medicine, an order written by a doctor (or other authorised health care professionals) directing the pharmacist to prepare a specific medicine for an individual patient, has also ancient roots and is traditionally hand-written, as shown in Figure 1.1 (Jenkins *et al.*, 1957), though electronic prescriptions for compounded medicines are now more frequently encountered (Figure 1.2) (Joint Formulary Committee, 2008).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Aq. dest qs 30.00
M. Sol.
Sig: gtts ii in eyes t.i.d.

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Reg. No. 7754 J. A. Peterson M. D.

Figure 1.1 (left) Example of a past prescription for dermatology compounding (adapted from Jenkins *et al.*, 1957) and Figure 1.2 (right) Example of a contemporary prescription for paediatric compounding (courtesy of *Farmácia Lordelo*[3]).

[3] *Farmácia Lordelo* is a community pharmacy in *Vila Real*, Portugal, specialised in pharmaceutical compounding (Farmácia Lordelo, 2009).

In the past, all prescriptions were for compounded medicines and it was not until the early 1900s, with the advent of industrialisation and drug manufacturing, that these prescriptions were gradually substituted by prescriptions for proprietary medicines[4]. In the USA (United States of America), by the 1930s about 75% of the prescriptions were for compounded medicines, whereas by the 1950s only 26%, by 1962 just 3-4% and by 1973 about 1% of prescriptions were for compounded medicines. Over the years, the pharmaceutical industry took over the production of most medicines and the need for compounded medicines declined, with considerable impact on the practice of pharmacy (Allen, 2003a; 2005a; 2005b). The pharmacist's traditional role of preparing compounded medicines gradually changed to that of dispensing proprietary medicines (Anderson, 2005). Despite the undeniable value of proprietary medicines, these are manufactured in only limited presentations (specific dosage forms and specific strengths) and in accordance with established windows of activity, which are adequate for the majority of patients but there are always individuals and health conditions that demand a personalised approach to treatment and, in these situations, the pharmaceutical industry is not able to meet their needs in a cost-effective manner (Allen, 2005a). Therefore, pharmaceutical compounding continues to be performed as an integral and fundamental part of contemporary pharmacy practice, providing alternative therapeutic options and meeting individualised patient needs. The flexibility of compounded medicines have become increasingly recognised as more attention has been given to patients as unique individuals (Allen, 2005c). In parallel, the practice of compounding has advanced beyond the traditional art, although at different rates in different countries (Anderson, 2005), and contemporary compounding is a highly technical and complex practice. These factors have contributed to the continued existence of pharmaceutical compounding and, along with the impetus to enhance quality standards, are responsible for the high quality compounded medicines that are prepared today (Allen, 2006a).

[4]A proprietary medicinal product corresponds to any ready-prepared medicinal product placed on the market under a special name and in a special pack (European Parliament and the Council, 2001). Equivalent terms for proprietary medicinal products include the following: licensed, industrialised and commercial medicines.

1.1.2 **Definition and practice of compounding**

In accordance with the US Pharmacopeial Convention (2005), pharmaceutical compounding "involves the preparation, mixing, assembling, packaging and labelling of a medicine (…) under an initiative based on the doctor-patient-pharmacist (triad) relationship in the course of professional practice". The term "compounded medicines" stand for compounded drugs, compounded preparations and compounded formulations (US Pharmacopeial Convention, 2005).

The US Food and Drug Administration (FDA) states that pharmaceutical compounding "is an age-old practice in which pharmacists combine, mix or alter ingredients to create unique medications that meet specific needs of individual patients". This practice must not involve the preparation of medicines that are "essential copies" of available licensed medicines. In addition, compounding must not include substances that were removed from the market because of safety or efficacy issues, or substances that have not been approved for use in medicines (FDA, 2007).

Compounding corresponds, then, to the preparation of unlicensed medicines (sterile and non-sterile) in order to meet specific patient needs, which are not met by the licensed medicines available. Compounded medicines are traditionally prepared extemporaneously in community and hospital pharmacies for individualised patients. Notwithstanding this, compounded medicines may also be prepared in advance (of a patient's request), in other settings apart from a pharmacy and in batches (of variable sizes).

1.1.2.1 **Triad relationship: doctor-patient-pharmacist**

Pharmaceutical compounding is characterised by the traditional triad relationship doctor-patient-pharmacist, which is represented when a doctor prescribes a compounded medicine that is prepared by a pharmacist for a specific patient (Figure 1.3). This triad relationship is the foundation for pharmaceutical compounding (Allen, 2005a; McElhiney, 2006a).

Pharmaceutical compounding is also characterised by the Rx symbol, which stands for *recipe*, take (RPS, 2005; Marriott *et al.*, 2010) (Figure 1.3).

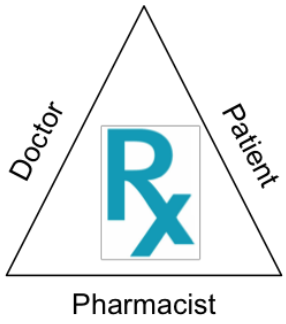

Figure 1.3 Triad relationship: doctor-patient-pharmacist.

Pharmacists are an essential member of the health care team and play a crucial role in the triad relationship, as the intermediary between patients and their doctors (Williams, 2010). Other health care professionals and caregivers may also be included in this relationship as, for instance, the nurses who administer the medicines to hospitalised patients (McElhiney, 2009; Trissel, 2009). A good interaction between all members of the triad relationship is crucial for taking medicines to best effect (Joint Formulary Committee, 2008).

1.1.2.2 **Therapeutic alternative to proprietary medicines**

Compounded medicines should be regarded as a therapeutic alternative only, and exclusively, when there are no suitable proprietary medicines on the market. Compounded medicines should not substitute for corresponding licensed medicines when these are commercially available, not even for economical reasons (Sundberg, 1997; Allen, 2005a) because of the risks associated with compounding (Section 1.1.3).

In addition, if the medicines needed are actually available as licensed medicines in other countries, the importation of the respective licensed medicines should always be considered first. Notwithstanding this, there is usually a limited knowledge of the availability of licensed medicines in other countries, and importation is often very difficult (Nunn, 2003). Therefore, it is accepted that the time and bureaucracy required for the importation of medicines may compromise the patients' health and, in these situations, pharmaceutical compounding represents the therapeutic alternative of choice.

1.1.2.3 **Compounding vs manufacturing**

A medicinal product may be obtained either by manufacturing (majority) or by compounding / extemporaneous preparation (exception), two distinct methods that yield proprietary medicines and compounded medicines, respectively (Table 1.1).

Proprietary medicines have a marketing authorisation, which is obtained either by a centralised authorisation procedure or by national authorisation procedures. The European Medicines Agency (EMA/EMEA), which protects and promotes public health through the evaluation and supervision of medicines for human use, is responsible for the centralised procedure. This procedure results in a single marketing authorisation, valid in all European Union countries (also in Iceland, Liechtenstein and Norway), and is compulsory for certain medicines (e.g. treatment of cancer). National medicines authorities, on the other hand, are responsible for the national authorisations and each EU Member State has its own procedures. For the simultaneous authorisation of medicines in several countries, there are also the decentralised and mutual-recognition procedures (EMA, 2012a).

As opposed to proprietary medicines, compounded medicines are exempt of a marketing authorisation (Section 14.1). The criterion that best differentiates compounding from manufacturing is the existence of the triad relationship (Section 1.1.2.1) (McElhiney, 2006a) and the smaller scale of preparation[5] in compounding (US Pharmacopeial Convention, 2005). Manufacturing is the more recent, common practice (Section 1.1.1) and the larger scale of production[6] requires compliance with GMP (Good Manufacturing Practice). The safety and efficacy of compounded medicines is not assured and, therefore, compounding is a more risky practice (Section 1.1.3).

Both proprietary medicines and raw materials in bulk are used in the preparation of compounded medicines, which are assigned a beyond-use-

[5]The term “preparation” should be used when referring to a compounded medicine (Allen, 2007c).
[6]The term “production” should be used when referring to a proprietary medicine (Allen, 2007c).

date[7] (US Pharmacopeial Convention, 2005), whereas only raw materials in bulk are used in the production of proprietary medicines, which are assigned an expiry date (Table 1.1). Raw materials in bulk should preferably be used in the preparation of medicines, particularly when these are prepared on a large scale (i.e. production of proprietary medicines and preparation of compounded medicines in batches). The use of proprietary medicines in compounding is convenient as it is not always easy to acess the respective raw materials in bulk (and in reasonable small quantities). However, proprietary medicines not only include the required active substance(s) but also a number of excipients that may compromise the resulting compounded medicines.

Table 1.1 Comparison of pharmaceutical compounding and manufacturing (adapted from McElhiney, 2006a).

Main differences	Compounding	Manufacturing
Output	Compounded medicine	Proprietary medicine
Timescale	50 centuries	2 centuries
Need	Exception	Majority
Terminology	Preparation	Production
Scale	Smaller/Individual	Larger
GMP requirements	No	Yes
Safety and efficacy	Not assured	Assured
Risk	Higher	Lower
Raw materials	Proprietary medicines or bulk	Bulk
Date assigned	Beyond-use date (shorter)	Expiry date (longer)

[7]The beyond-use-date is the date after which a compounded preparation is not to be used and is determined from the date the preparation is compounded. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiry dates to manufactured drug product (US Pharmacopeial Convention, 2005).

For instance, in the preparation of a liquid dosage form from crushed tablets, insoluble excipients may compromise the medicine's appeareance (e.g. coatings) whereas soluble excipients may compromise the medicine's stability (e.g. pH); the filtration of insoluble excipients, although common practice, may remove signifcant ammounts of active substance(s), if extraction from tablets is not complete (Ahmed *et al.*, 1987; Boulton *et al.*, 1994; Fawcett *et al.*, 1995; Woods, no date). In addition, depending on the brand of the proprietary medicines used, the resulting compounded medicines may be considerably different. For instance, according to Ashworth (2011), a mercaptopurine oral suspension prepared with Mylan tablets results in a "creamy and smooth" suspension whereas with Roxanne tablets results in a "globby and gritty" suspension.

1.1.2.4 **Activities not included in compounding**

Not included in the definition and practice of compounding are: off-label use (of proprietary medicines), reconstitution and repackaging of medicines. None of these activities affect the integrity of medicines and therefore, the output is still the proprietary or compounded medicine and not an alternative (compounded) medicine. Also not included in the definition and practice of compounding is the handling of medicines that does not involve the preparation of an alternative (compounded) medicine.

a. **Off-label use**

The term off-label use refers to the use of a proprietary medicine outside the labelled (licensed) indications, as follows: therapeutic indications, age group, dosage and/or route of administration, for which the medicine is not licensed. The terms off-label use, off-label prescribing and off-label medicines are commonly used interchangeably and represent an unlicensed use of a licensed medicine. Off-label use must not be confused with unlicensed medicines since the later are exempt from the requirement of a marketing authorisation and, as a result, do not have any labelled (licensed) indications. In conclusion, the use of a medicine outside the labelled indications (off-label use) should only apply to proprietary medicines. The confusion of these

concepts is very common in the literature (Brion *et al.*, 2003; Pandolfini and Bonati, 2005).

The use of both unlicensed medicines and licensed medicines for unlicensed indications (off-label use) is often necessary, particularly in paediatric patients, since the licensed indications frequently do not cover the therapeutic needs of this age group (Joint Formulary Committee, 2008). It has been estimated that 50-70% of the prescriptions include an off-label use of a proprietary medicine (Allen, 2007a). Information sources such as the Micromedex and the BNFC (British National Formulary for Children, Section 4.2.2) provide practical guidance on the off-label use of medicines (Standing and Tuleu, 2005; McElhiney, 2009).

b. **Reconstitution of medicines**

Pharmaceutical compounding does not include reconstitution of medicines (CSHP, 2010) but the definition of both is often confused (Lam, no date). Reconstitution of medicines involves the reconstitution of liquids or solids into a final liquid dosage form. According to the European Directorate for the Quality of Medicines & HealthCare (EDQM, 2007), a directorate of the Council of Europe, some preparations for oral use are prepared by dilution of concentrated liquid preparations (reconstitution of liquids); or from powders or granules for the preparation of oral solutions or suspensions, oral drops or syrups, using a suitable vehicle (reconstitution of solids). The final preparations must comply with the requirements for the respective dosage forms (EDQM, 2007). Reconstitution of medicines is an activity performed in accordance with the directions of the manufacturer as, for instance, the reconstitution of the oral antibiotic Augmentin 125/31 SF (Sugar Free) Suspension (eMC, 2010a) and the reconstitution of the antibiotic Augmentin 500/100 Intravenous (IV) (eMC, 2010b). Oral antibiotics for reconstitution are presented as a powder in a multidose container with sufficient space for the addition of purified water (Edafiogho and Winfield, 2004), whereas IV antibiotics for reconstitution are usually presented as a sterile powder in a vial with sufficient space for the addition of water for injections or other sterile vehicle. The antibiotics presented as powders are commonly stable for up to 2 years whereas, when reconstituted, the stability is considerably reduced

(normally 10-14 days for oral antibiotics and just a few hours for IV antibiotics) (Edafiogho and Winfield, 2004). No official guidelines for reconstitution exist as yet (Torniainen, 2007) apart from the risk assessment considered in the Resolution CM/ResAP(2011)1 (Council of Europe, 2011). Whenever directed, reconstitution is required for the intended use of medicines and, therefore, should be clearly distinguished from the practice of pharmaceutical compounding.

c. **Repackaging of medicines**

Repackaging is defined as the "act of removing a preparation from its original primary container and placing it into another primary container, usually of smaller size" (US Pharmacopeial Convention, 2005).

This practice is often associated with parcelling oral solid dosage forms, such as tablets and capsules, into single-dose (often single-unit) containers but it also applies to liquid and semi-solid dosage forms as, for instance, repackaging a multidose oral liquid into unidose oral syringes and repackaging a multidose cream into unidose blister packs. In addition, repackaging is often associated with parcelling proprietary medicines but it also applies to parcelling compounded medicines.

Repackaging is a common practice in the hospital setting, in which large packs are converted into "patient packs". Although time consuming and labour intensive, it represents a very important aspect of pharmacy practice because it may not only significantly reduce waste of medicines but it may also reduce medication errors and, consequently, improve patient safety (US Pharmacopeial Convention, 2005; McElhiney, 2010).

d. **Handling of medicines**

Handling of medicines includes all manipulations of medicines by health care professionals and patients that aim to facilitate the intake of medicines, mainly: segmenting tablets and opening capsules. Segmenting tablets may also be performed to adjust dosage strengths and for economic reasons since, in general, different strengths of the same drug cost about the same (Sam, 2002; Allen, 2005d).

This practice is performed in a variety of settings, from the patients' home to hospitals' wards. In a study performed in a UK (United Kingdom of Great Britain and Northern Ireland) paediatric hospital, Tuleu *et al.* (2003) confirmed that cutting or grinding tablets on the wards was a very common practice for nurses. Notwithstanding, Tuleu *et al.* (2005) concluded that cutting nifedipine tablets did not provide accurate and reproducible dosing (even when using proprietary tablet cutters). Furthermore, there are tablets that cannot be segmented without affecting the appropriate release of the active substance(s), as in the case of some modified-release tablets (Marriott and Kirby, 2009). Segmenting tablets is occasionally considered in the literature as pharmaceutical compounding (Brion *et al.*, 2003) but this practice should be clearly distinguished as a separate activity. Handling of medicines by health care professionals and patients should be avoided as much as possible and, when unavoidable, it should be performed with caution to prevent dosing deviations.

Ideally, the handling of medicines (i.e. segmenting tablets and opening capsules) should be substituted by the preparation of compounded medicines (adapted to the individual patient needs) (Sam, 2002). Pharmaceutical compounding is a regulated practice performed in registered facilities, by registered professionals, as opposed to the unreliable manipulation of medicines, which can be performed in an uncontrolled manner.

1.1.3 **Risks associated with compounding**

The quality, safety and efficacy of compounded medicines is not guaranteed and these medicines are exempt from a marketing authorisation or product licence, unlike proprietary medicines. For these reasons, compounded medicines are considered by the authorities as unapproved (FDA, 2009) or unlicensed medicines (MHRA, 2008).

Compounded medicines should only be dispensed when no suitable licensed alternative is available (Joint Formulary Committee, 2008) and it is suggested that patients should be aware that these medicines are not approved (FDA, 2007; *CompoundingToday*, 2011a).

According to the FDA (2011a), “some compounded drugs may present risks to patients because compounded drugs have not been evaluated for safety and effectiveness”. The practice of pharmaceutical compounding carries significant risk but there are clinical needs that can only be met by unapproved or unlicensed medicines. Therefore, the risk-benefit balance of compounded medicines must be considered at all times and, as for proprietary medicines, the benefits of administering the medicine should be greater than the associated risks (Joint Formulary Committee, 2008).

Compounded medicines have endangered public health in a few unfortunate events worldwide, some with devastating repercussions. A single error in compounding can easily result in a patient’s death. Examples of such unfortunate events will be described throughout the thesis. The FDA is aware of more than 200 adverse events involving 71 compounded medicines since 1990 (Allen, 2003b; FDA, 2007). When pharmaceutical compounding is not performed properly, patients are exposed to potentially very serious health risks (FDA, 2011b). Compounding errors can be made at all stages of the preparation, from the selection of raw materials to the labelling of the final medicine. Standard operating procedures (SOP) should be put in place and no pharmacy should be involved in pharmaceutical compounding without an ongoing QC program (Allen, 2003b).

All health care professionals play an important role in reducing compounding errors. Doctors and pharmacists have the responsibility to guarantee that patients take effective, safe and quality compounded medicines and the authorities have the responsibility to develop appropriate guidelines (EAHP, 2008).

1.1.4 **Importance of compounding**

Compounding provides invaluable alternative medicines to the pharmaceutical industry as there are specific situations in which the proprietary medicines available do not meet particular patient needs, as follows:

1. Need for alternative dosage forms

The acceptance ability of a dosage form to a particular patient depends on the patients and their health conditions. The majority of proprietary medicines are available in solid dosage forms (tablets and capsules), which usually represent a problem for the paediatric population; for patients with swallowing difficulties (dysphagia), commonly the geriatric population and also for patients for whom the oral route is compromised (e.g. in oral cancer) (Allen, 2005b; McNulty, 2007; Barbosa, 2009).

2. Need for particular dosages/strengths

Proprietary medicines are available in standardised dosage strengths but there are specific situations in which patients need personalised strengths as, for instance, the paediatric population (depending on the age and body weight / surface area) and the geriatric population (considering concomitant diseases and organ failures) (Allen, 2005b; Barbosa, 2009).

3. Need for alternative raw materials

There are specific raw materials that are not well tolerated by particular patients, such as: colorants (hypersensitive patients), lactose (intolerant), parabens (allergic), phenylalanine (phenylketonuria) and sucrose (diabetic patients) (Allen, 2005e; Barbosa, 2009).

4. Need for alternative organoleptic characteristics

The flavour, colour and texture of medicines are determinant factors in patients' compliance to therapy, particularly in the paediatric and geriatric populations. Personalisation of the organoleptic characteristics of medicines in order to meet the individual preferences is possible by means of pharmaceutical compounding (Allen, 1997a). For instance, unpleasant bitter substances, such as promethazine HCl and quinine sulfate, may be successfully masked with orange or raspberry syrup (Kloesel, 2001; *CompoundingToday*, 2005).

Additionally, there are specific situations in which the necessary proprietary medicines are not available from the pharmaceutical industry, as follows:

1. Medicines' shortages

Occasionally, the pharmaceutical industry is not able to meet the demand for particular medicines, and proprietary medicines become temporarily unavailable. Limited production capability, manufacturing problems and lack of raw materials are some of the common causes for shortage of medicines. In these situations, pharmaceutical compounding is a valuable resource to "bridge the gap" until the proprietary medicines are once again commercially available (Allen, 2005b; Donyai, 2006).

2. Discontinued medicines

There is a long and growing list of important proprietary medicines that have been discontinued by the pharmaceutical industry, mainly for commercial reasons and which consequently are no longer available to patients. Pharmaceutical compounding offers these patients the possibility to continue their treatments by means of compounded medicines (Ashworth, 2002a; Allen, 2005b).

Finally, there are situations in which necessary proprietary medicines have never been made available by the pharmaceutical industry:

1. Special combinations

There are patients who need several proprietary medicines, and these could be brought together in one single dosage form to ease the process of administration (i.e. polypharmacy) as, for instance, special combinations in oncology patients (Section 1.1.5) and dermatology patients (e.g. hydroquinone, retinoic acid and glycolic acid in hyperpigmentation disorders) (Allen, 2004; 2005e; Barbosa, 2009).

2. Orphan medicines

Orphan medicines are medicines for diagnosing, preventing or treating rare diseases[8] which, under normal market conditions, have little interest for pharmaceutical industry because these are intended for a small number of patients only (EMA, no date). Compounded medicines for rare diseases are an invaluable resource for these patients and, in many cases, represent the

[8]Rare diseases are life-threatening, or chronically debilitating conditions, that affect no more than 5 in 10,000 people in the EU (European Union) (EMA, no date).

only therapeutic option available. Examples of orphan medicines include 3,4-diaminopyridine for Lambert-Eaton myasthenic syndrome and pyridoxal phosphate for neonatal epilepsy (Dooms, 2010).

1.1.5 **Specialties of compounding**

Pharmaceutical compounding is a valuable therapeutic option in all areas of medicine, with particular importance in the following specialties:

1. Paediatric compounding (considered separately in Section 1.1.5.1)
2. Geriatric compounding

The aging population is growing and the elderly are faced with age-related conditions that often demand a personalised approach to treatment as, for example, polymedication, swallowing difficulties (dysphagia) and compliance issues. Compounded medicines add value to geriatric and hospice[9] care by helping patients live in a more dignified manner (Allen, 2002a; 2009a).

3. Dermatology compounding

Dermatology conditions often require personalised therapy to adjust the treatment to the patients' skin type and disorders (Barbosa, 2009). Furthermore, although there have been significant advances in the treatment of dermatology conditions, there are traditional compounded medicines that remain useful in current practice (Parish and Witkowski, 2000). Some of the dermatology conditions that benefit from pharmaceutical compounding are hyperpigmentation (Allen, 2004), psoriasis (Williams and Humphreys, 2011) and wounds (Allen, 2002b; Helmke, 2004a; 2004b).

4. Gastroenterology compounding

There are many gastrointestinal (GI) disorders and there is need for particular medicines, which are not commercially available, that can be made available through compounding (Allen, 2005f). Examples include: ranitidine HCl 15 mg/mL oral liquid and omeprazole 2 mg/mL oral liquid, both for the treatment of ulcers (e.g. gastric and duodenal) and other GI disorders (e.g. pathological hypersecretory conditions) (Allen, 2006b; 2007b).

[9]Hospice is a concept of care designed for end-of-life patients and focus on the physical and emotional needs of patients in the final stages of life in order to ensure that these achieve the best quality of life in their remaining time (Kuntz, 2006a).

5. Dentistry compounding

Dentists and dental patients benefit from pharmaceutical compounding as this practice allows a wide range of therapeutic alternatives. Mouthwashes, for instance, are one of the most frequently compounded dosage forms in dentistry, and may include specific combinations which are not commercially available because of the need for extended stability in proprietary medicines (Allen, 2002c; Fonseca, 2006).

6. Oncology compounding

The treatment of cancer often involves special combinations of active substances to ease the administration of medicines. Without pharmaceutical compounding, these active substances would have to be given individually and, therefore, compounded “cocktails” are a valuable alternative for cancer patients (Allen, 2005b). These treatments compromise the immune system of patients, who become more vulnerable to opportunistic infections, for instance, oral mucositis. Compounded mouthwashes for chemo-induced oral mucositis (CIOM) play a major role in the quality of life of cancer patients (Section 3.4.4) (McElhiney, 2008a).

7. Ophthalmology compounding

The preparation of sterile compounded medicines is an integral part of pharmaceutical compounding practice. Pharmacists are often requested to prepare ophthalmic compounded medicines to meet particular individual needs, for instance, medicines without preservatives; and to replace the increasing number of discontinued proprietary medicines, for example: epinephrine bitartrate ophthalmic solution and tetracycline HCl ophthalmic ointment (Ashworth, 2002b; Batistuzzo, 2010; Sautou, 2011).

8. Veterinary compounding

The preparation of compounded medicines for animals has always been part of veterinary medicine. A few decades ago, only a few proprietary medicines were approved for veterinary use and, although more veterinary medicines are nowadays available on the market, there are always situations in which animals require a personalised medicine adapted to their specific needs (Papich, 2005). Veterinary compounding is a complex practice since

different species of animals have different pathophysiology and, consequently, different response to medicines (Allen, 1997b; 2009b). In a regional survey conducted by the International Journal of Pharmaceutical Compounding (IJPC), it was concluded that the top 5 veterinary compounded medicines were the following: potassium bromide capsules; metronidazole suspension; methimazole oral liquid; diethylstilbestrol capsules; and potassium bromide solution (Davis, 1999).

1.1.5.1 **Paediatric compounding**

"Paediatrics does not deal with miniature men and women": this renowned statement by Abraham Jacobi (1830-1919), father of American paediatrics, is still today the fundamental principal of paediatrics. The paediatric population is very different from adults and corresponds to a heterogeneous group, from preterm newborn infants to adolescents[10], with a spectrum of different pathophysiologies associated with growth and development. There are substantial changes in body proportions and composition during growth and development, and this dynamic process of maturation is what makes the paediatric population so special and so different from adults (Kearns *et al.*, 2003; WHO, 2007). These age-related changes profoundly affect the absorption, distribution, metabolism and excretion (ADME) of medicines and, consequently, the response of the paediatric population to therapy. Issues to consider are, for instance, immaturity of the GI tract and consequent reduced gastric acid secretion and prolonged gastric emptying (impacting on absorption); immaturity of the blood-brain barrier and consequent facilitated penetration of medicines into the CNS (Central Nervous System) (distribution); immaturity of the hepatic and renal functions and consequent altered metabolizing and clearance capacities (metabolism and excretion).

The paediatric population has, therefore, an increased sensibility or toxicity to medicines and these issues have to be considered when developing medicines for such a vulnerable group. In addition to different physiologies, there are also paediatric-specific pathologies that differentiate this population

[10]The paediatric population may be categorised as follows: preterm newborn infants (<37 weeks); term newborn infants (0–27 days); infants and toddlers (28 days – 23 months); children (2–11 years); and adolescents (12–16 or 18 years, depending on the country) (EMEA, 2001).

from adults, for instance respiratory distress syndrome and patent ductus arteriosus (EMEA, 2001; WHO, 2007; Paediatric Formulary Committee, 2008; EMEA, 2009).

As a result, the paediatric population requires age-appropriate formulations, but the development of such particular medicines represents, almost always, a major challenge to the pharmaceutical industry (EMEA, 2006). Not only is the paediatric population a heterogeneous and vulnerable group, but the corresponding clinical trials are also more difficult to conduct than for adults, take much longer, cost considerably more and raise several ethical questions (EMA, 2007), which together potentially delay the marketing of medicines.

The paediatric population represents a relatively small market size[11] and, consequently, paediatric indications are usually not profitable (or have a limited return on investment). For these reasons, the majority of proprietary medicines do not have paediatric indications and, as a result, 50% to 90% of the medicines used in paediatrics have not been studied in this population (EMA, 2007; Nahata and Allen, 2008). Paediatric patients have therefore been described as “therapeutic or pharmaceutical orphans” (Shirkey, 1963) since the medicines available are mainly proprietary medicines used “off-label” (Section 1.1.2) or, alternatively, compounded medicines prepared extemporaneously.

Pharmaceutical compounding assumes particularly high importance in the paediatric population, especially for tackling the need for particular strengths - based on body weight (mg/kg) or surface area (mg/m^2) - and the need for alternative dosage forms (Section 1.1.4) (Nahata and Allen, 2008). Compounded medicines are, and will continue to be, a major means by which medicines are made available to paediatric patients (Standing and Tuleu, 2005).

[11]Only 20% of the EU population (≈100 million) is aged less than 16 years (EMA, 2007).

1.2 **Hospital pharmacy**

The supply of medicines in hospitals is provided by the hospital pharmacy, a specific department within the hospital in which medicines are made available to patients by a dedicated team of health care professionals, usually comprising pharmacists and pharmacy technicians. The art, practice and profession of choosing, preparing, storing, compounding and dispensing medicines and medical devices in the hospital setting are the responsibility of the hospital pharmacy (EAHP, 2009). In addition, hospital pharmacists play an active role in the pharmacotherapeutic care and treatment of patients by cooperating with doctors in the clinical decision-making and ensuring a safe, effective and rational use of quality medicines (Gala, 2004; Štefančič, 2007). Nowadays, the concept of clinical pharmacy has gained widespread acceptance and importance and hospital services are evolving from being product-oriented to becoming more patient-oriented (Scott *et al.*, 2005). Pharmacists are an integral part of the hospital staff and their responsibilities have evolved in tandem with the advances in medicine and technology, and also with the expectations of today's informed society (Scott *et al.*, 2005). According to the European Association of Hospital Pharmacy (EAHP) (Section 14.2.1), hospital pharmacists are expected to ensure the "7 rights", as follows: right patient, right dose, right route, right time, right drug with the right information and right documentation (EAHP, 2009).

1.2.1 **Compounding in hospital pharmacy**

The provision of sterile and non-sterile compounded medicines in hospitals is of great importance considering the particular, and often critical, health conditions of hospitalised patients. Proprietary medicines are not always the most appropriate therapeutic option to meet those particular needs and, in these situations, pharmaceutical compounding is an invaluable therapeutic alternative. The extent of this practice varies from hospital to hospital, in accordance with the hospital specialties and number of beds; the doctor's prescribing habits; and the characteristics of the hospital pharmacy. Furthermore, hospitals which are engaged in clinical trials are likely to require additional compounded medicines for these particular studies (Allen, 2005b; Yska *et al.,* 2009). As a result, hospital pharmacies may prepare from just a

few individualised compounded medicines to batches of those medicines which are routinely demanded, in anticipation of doctors' prescriptions and standard hospital protocols (McElhiney, 2008b). Alternatively, hospital pharmacies may even outsource part (or all) of their compounding activities and dispense compounded medicines prepared by others (Allen, 2011). Hospitals operate under very tight budgetary constraints and, although the mortar and pestle are still fundamental in a compounding laboratory, there is also need for more sophisticated and technologically advanced equipment, particularly in batch compounding (Kuntz, 2006b; McElhiney, 2006b; 2006c), and not all hospitals are willing to make such an investment. Furthermore, hospital pharmacy staff should undergo specialist compounding education and training, and must also access up-to-date compounding information sources, which requires an additional investment for hospital pharmacy (McElhiney, 2006b; 2007). For these reasons, increasing numbers of hospitals are nowadays outsourcing their compounding activities and dispensing compounded medicines prepared by others (Allen, 2011).

Hospitals operate 24 hours per day and 7 days per week to provide around-the-clock patient care. Hospitalised patients may require medicines at anytime of the day or night and these have to be made available by the hospital pharmacy. Therefore, it is important that hospital pharmacies prepare (or outsource) compounded medicines in advance (McElhiney, 2008b) so that patients have all routinely required (proprietary and compounded) medicines readily available.

Hospitalised patients are not always conscious or able to actively participate in their treatment, which makes a significant difference when compared to the community pharmacy patients (McElhiney, 2006a) and increases the potential need for individualised therapy. In fact, hospital therapies including total parenteral nutrition (TPN) and IV admixtures are supplied predominantly as compounded medicines (Winckler, 2004; Allen, 2005b). Pharmaceutical compounding is a common and challenging practice in the hospital setting, but very little attention has been given to the preparation of non-sterile compounded medicines, as opposed to those which are sterile (McElhiney, 2006a).

1.2.1.1 **European context**

Only a few studies have been published addressing pharmaceutical compounding in Europe and, therefore, little is known regarding current compounding practices in European hospital pharmacies.

Every 5 years, the EAHP undertakes a survey on the state-of-the-art of hospital pharmacy in Europe. In 2005 (latest available survey), 22 European countries participated in the survey and data from 825 hospitals were collected (24% response rate), but this included only limited information on hospital compounding practices (EAHP, 2005; 2010a). This information will be addressed for each European country in the corresponding chapters, following the methodology.

In 1998, Conroy *et al.* (2000) determined the extent of use of both compounded medicines and proprietary medicines "off-label" in children, in a sample of 5 European hospitals (UK, Sweden, Germany, Italy and Netherlands) for a period of 4 weeks, and concluded that 46% of the 2,262 prescriptions included either compounded medicines or proprietary medicines "off-label". Out of these, only 164 (7.3%) prescriptions were for compounded medicines (the majority from the Netherlands) but no additional information was published regarding pharmaceutical compounding alone. This situation is common in the literature as the majority of studies consider the use of both unlicensed medicines and proprietary medicines "off-label" together (without differentiation) and no detailed information is usually published regarding the practice of pharmaceutical compounding (Cuzzolin *et al.*, 2003; Pandolfini and Bonati, 2005; Cuzzolin *et al.*, 2006; Giam and McLachlan, 2008).

In 2000, Brion *et al.* (2003) conducted wide-ranging research on the extemporaneous preparation of oral compounded medicines for children in European hospitals. A questionnaire was developed and distributed to 41 pharmacists, working or providing services to children's hospitals, in 18 European countries. The aims were to determine the most frequently prepared oral liquids, powders, capsules and segments (i.e. fragments of tablets), in a 6-month period, and to evaluate the respective "formulations" and stability. Only 21 (51%) questionnaires were returned, from a total of 16

European countries, but it was concluded that compounded medicines were prepared according to varying methods in Europe, and also that dosage forms were country-specific. Although the authors recognised that the sample of hospitals was too small to draw representative findings, this study was the first to address pharmaceutical compounding in a Europe-wide comparative analysis and the need for further research was highlighted (Conroy, 2003). Detailed results from Brion *et al*. (2003) will be addressed throughout this thesis, alongside the findings of the present research.

The Europe-wide studies described have focused particularly on paediatric patients and no research has been published so far including other specialties of compounding. In fact, there is currently no knowledge regarding the diversity and extent of compounded medicines dispensed to all hospitalised patients in a variety of hospital settings (rather than just paediatric hospitals) in Europe.

Furthermore, in Europe, there is lack of consensus with regards to compounding terminology and the words used to define and describe this practice are usually only correctly understood in context (Fenton-May, 2008). There is also a lack of consensus with regards to compounding standards of practice, and each European country has very different circumstances whether of facilities, equipment, staff training or expectations (Fenton-May, 2007). In one survey, stakeholders from 5 European hospitals in Spain, Denmark, Ireland and Finland were invited to describe their practices and it was evident that there are conflicting understandings of compounding. It was also clear that compounding regulations and information sources vary considerably between countries and that there is a strong need for a better understanding of compounding practices in Europe (Fenton-May, 2008).

1.3 **Aim and objectives**

The aim of this research was to identify and characterise the extemporaneously compounded oral medicines most frequently dispensed in European hospital pharmacies.

The objectives, for each European country included in the project, were derived in a systematic manner utilising the views of external stakeholders, experts and country-specific representatives, and corresponded to the following:

- To identify the official concept of compounded medicines, including types and definitions.
- To determine the national regulations and legal requirements for the practice of compounding.
- To recognise the most relevant professional organisations and information sources on compounding.
- To demonstrate the most frequently dispensed oral dosage forms.
- To identify the range of strengths and pack sizes associated with the different active substances.
- To categorise the most frequently dispensed oral compounded medicines according to their therapeutic classification.

2. **Methodology**

To identify and characterise the oral compounded medicines most frequently dispensed in European hospital pharmacies, the research adopted was a large-scale international survey and the method was a descriptive, cross-sectional study.

According to the literature, descriptive studies document or describe phenomena (i.e. the activities undertaken by pharmacists or other health care professionals). Descriptive studies provide important information with regards to pharmacy services and the use of medicines, and are essential for the improvement of services (Smith, 2005). Cross-sectional studies are often referred to as a type of a descriptive study, in which data are collected at one point in time. In these studies, the respondents are generally asked to report on events retrospectively (Bowling, 2002). For instance, a study of the compounded medicines dispensed in a UK paediatric hospital pharmacy retrieved data over a 12-month period (Tuleu *et al.*, 2003); this was a descriptive and cross-sectional study in which retrospective data were reported. In the present research project, European hospital pharmacies were requested to provide data already in existence and relating to the most recent available year. Hence, in this study retrospective data were collected across Europe, ranging from the year 2006 to 2009, depending on the date study was initiated in a particular country and on the availability of data in each hospital pharmacy. According to Giam and McLachlan (2008), the most common study periods in this field range from 2 to 4 months, but it was suggested that 12 months would best characterise compounding practices Europe-wide.

Survey research is viewed as a quantitative methodological approach in which data are collected from a sample in order to identify frequencies of events (Smith, 2002). Quantitative research is appropriate in situations where there is pre-existing knowledge of the phenomena of interest, which allows the use of standardised methods of data collection (Bowling, 2005). For example, in a retrospective survey conducted in New Zealand, the extent of extemporaneously compounded oral liquids prepared was determined and

quantitative data were obtained based on compounding logbooks and batch sheets (Kairuz *et al.*, 2007). In another study, the information regarding oral compounded medicines dispensed to paediatric patients in Portuguese hospitals was gathered by reference to records held by the hospital pharmaceutical services (Barros and Almeida, 2008). Almost all hospital pharmacies keep a record of the compounded medicines dispensed (although to different extents) and quantitative data may be obtained to document the prevalence of this practice. Compounding records identify the compounded medicines dispensed more accurately than the respective prescriptions (Giam and McLachlan, 2008). In the present research project, quantitative data were gathered at the hospital by a member of the pharmacy staff (in most cases), familiar with the record keeping of their compounding practices. A self-completion questionnaire was designed as the research instrument so that the required data were systematically and accurately collected. This instrument was further developed in order to generate country-specific questionnaires adapted to the specificities of each European country.

In summary, the international survey designed was therefore a descriptive and cross-sectional study that involved the collection of quantitative data across Europe by means of a country-specific questionnaire.

2.1 **International survey**

An international survey on pharmaceutical compounding in Europe is challenging. The continent of Europe is constituted by 49 countries (Figure 2.1), including 27 member states of the EU (European Union) and 22 non-member states (*Europa*, 2009). Considering only the member states of the EU, there are a total of 23 official languages (*Europa*, 2008), which represents a big challenge since different languages are often a strong limitation to clear and effective communication. It cannot be assumed that English is universally understood and language barriers have to be considered when planning a research project in Europe. A good interaction between researchers and all participants from different countries is absolutely crucial for success. Furthermore, access to relevant national literature may be limited as local information and publications are usually restricted to the

official language. Because of the potential impact of restricting literature reviews to only English language papers (Smith *et al.*, 2008), literature sources in the national official language should also be considered.

Figure 2.1 Map of Europe adapted from National Geographic Society (2009).

Besides different languages, international research challenges may include cultural contexts and traditions, different perspectives and local views that influence the acceptability, feasibility and validity of the research (Smith *et al.*, 2008). Because questions may not be interpreted as intended and some terms may be used differently, or not at all, in some countries (Smith, 1997a), it is very important to have a deep understanding of the cultural differences and national contexts of any research so that it does not impact the applicability and outcomes of a study.

Apart from these predictable challenges, common to all international settings, the study of pharmaceutical compounding brings even more complexity to the research. Pharmaceutical compounding is part of pharmacy practice worldwide, but the approach to preparing and dispensing compounded medicines varies considerably. In each country, several factors contribute to a unique approach to the practice of compounding, as follows:

- The tradition of pharmaceutical compounding as an integral part of pharmacy practice and its progress from the pre-industrialisation era until nowadays.
- The triad relationship doctor-patient-pharmacist (Section 1.1.2.1) and local prescribing and dispensing habits.
- The existence of a legal framework for pharmaceutical compounding.
- The existence of professional organisations dedicated to this practice.
- The availability of official and/or non-official specialist information sources.

Altogether, these factors are responsible for different approaches to pharmaceutical compounding and, as a result, instead of a single approach worldwide, country-specific approaches have to be considered. It may be necessary to adopt different research strategies in each country so that these variable factors are considered, which dramatically increases the complexity of the research, but is also key to its success.

2.1.1 **Country-specific questionnaire**

The research instrument developed for this survey was a self-completion country-specific questionnaire. A questionnaire is the most commonly adopted instrument in survey research and is the instrument of choice for collecting factual information, in a relatively inexpensive way and in a short period of time, from large and widespread samples (Smith, 2005). The study of pharmaceutical compounding in Europe requires a research instrument that is both flexible and adaptable to the specific practices in each country, and a universal/standardised questionnaire would not be possible. Actually, experience suggests that many instruments that have been developed and validated in one country are not culturally sensitive and are thus inappropriate for use in another country; flexible research instruments are crucial in international collaborative studies (Rosser *et al.*, 1997). Therefore, a country-specific questionnaire was developed for Portugal and it was subsequently customised to the majority of the European countries included in the research. The purpose of the customised differences within questionnaires was to ensure that comparable data were obtained for each country so that Europe-wide comparisons could be made. As a result, the

contents of the country-specific questionnaires varied slightly but the structure and layout were kept the same.

All questionnaires were self-completion in design in order for the respondents to insert the required data in their own time. In addition, questionnaires were designed to be sent preferably by email as this is the most accessible and efficient means of contacting a large and widespread sample of European hospitals. All questionnaires were developed in Microsoft Excel since this is the most commonly used computer-based programme to keep records and organize data into lists (Frye, 2004). Another advantage of sending Excel spreadsheets by email is that respondents are more likely to enter data electronically, which can then be easily fed directly into the database that will be used for analysis (Smith *et al.*, 2008). Further, for those who are not familiar with Microsoft Excel, questionnaires could be easily printed out and filled in by hand. In the development of the country-specific questionnaires, the goal was to enable the collection of the information as accurately and precisely as possible so that, if it the research were to be repeated, the results would be comparable country by country (Bowling, 2005).

The country-specific questionnaires will be addressed in the respective chapters in detail, considering the specific approaches to the practice of compounding in each European country.

2.1.2 **European hospital pharmacies**

Compounded medicines are prepared in hospital and community pharmacies worldwide, and only are rarely prepared in other settings (i.e. pharmaceutical industry). In some countries, there is a clear predominance of pharmaceutical compounding in one particular setting. For instance, in the USA and Brazil, the practice of compounding occurs to such a great extent in the community setting that there are specialty (compounding) pharmacies almost only preparing and dispensing compounded medicines (Carvalho, 2005). On the other hand, in the UK, pharmaceutical compounding rarely occurs in the community setting. Actually, according to Rennison and Portlock (2003), the practice of compounding in UK community pharmacies is too low to ensure that pharmacists maintain their expertise and competence and, as a result,

the authors suggested that the preparation of compounded medicines in the community setting was no longer appropriate. Throughout Europe, there is evidence of compounded medicines being prepared and dispensed in community pharmacies to different extents, as in the following pharmacies: *Farmácia Lordelo*, in Portugal (Carvalho, 2005); *Farmacia Marro*, in Spain (Marro, 2008); and *Faust Apoteke*, in Germany (Zueck, 2008). As opposed to this wide variability of compounding in community pharmacies worldwide, pharmaceutical compounding in hospital pharmacies is universal. Unlike the community pharmacy patient, the hospital pharmacy patient usually requires around-the-clock care and individualised therapy is often demanded to meet the immediate needs of the critically ill (McElhiney, 2006a). For this reason, pharmaceutical compounding is an essential component of pharmacy practice in hospitals, and compounded medicines are dispensed in hospital pharmacies worldwide. Consequently, the focus of this international research was not the community setting but rather European hospital pharmacies.

It is important to highlight that the international survey was specifically designed to collect data regarding the compounded medicines dispensed, and not just the compounded medicines prepared in hospital pharmacies. This distinction is crucial, particularly in a Europe-wide project, as not all compounded medicines dispensed in hospitals are necessarily prepared in the respective hospital pharmacies (i.e. these may be prepared in local community pharmacies). Therefore, so that the need for compounded medicines in the European hospital pharmacies can be accurately estimated, the questionnaires addressed the compounded medicines dispensed (to both inpatients and outpatients, when applicable) instead of the compounded medicines prepared in the hospital setting.

2.1.3 **Oral compounded medicines**

The practice of compounding can be broadly distinguished as sterile pharmaceutical compounding and non-sterile pharmaceutical compounding. Sterile compounded medicines require aseptic preparation and are subject to a test for sterility (US Pharmacopeial Convention, 2005). Because of the high-risks inherent to the preparation of sterile compounded medicines, this practice is quite well documented and regulated. On the other hand, the

preparation of non-sterile compounded medicines is less acknowledged and usually less regulated. According to McElhiney (2006a), although hospital pharmacies in the USA are seriously addressing their sterile compounding operations, very little attention is being given to non-sterile compounding practices; this is likely to be the same in Europe.

Non-sterile compounding includes the preparation of both oral and non-oral dosage forms but, due to the limited time and resources allocated to this international survey, it was decided not to include all non-sterile dosage forms in the research. Because of the increased risks inherent to the preparation of oral compounded medicines, all non-oral dosage forms were excluded from the focus of this research (e.g. liquid preparations for cutaneous application; rectal preparations) and only (non-sterile) oral dosage forms were considered for data collection and analysis.

Oral compounded medicines may be distinguished as solid dosage forms and liquid dosage forms, as follows:

a. **Solid dosage forms**

Capsules are solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active substance(s). Several categories of capsules may be distinguished, namely: hard capsules, soft capsules, gastro-resistant capsules, modified-release capsules and cachets (EDQM, 2007). The most common are hard gelatin capsules, which consist of 2 sections (one slipping over the other) and are supplied in a variety of sizes (000-5). Hard gelatin capsules are easily administered and filled either extemporaneously or commercially in large quantities (Rudnic and Schwartz, 2005). Manual (or semi-automatic) capsule machines are used in hospital pharmacies for the preparation of 50-100 (maximum 300) units of capsules at a time. The classic manually operated bench-top equipment consists of a series of stacked plates with holes, in which the size and number of the holes determines the size and number of capsules to be prepared (Podczeck, 2004). Nevertheless, non-standardised quantities of capsules (i.e. <50 units) may also be prepared in this bench-top equipment provided that the pharmacy has a device to temporarily seal the additional

holes. Unless otherwise indicated, an estimate of 50 units of capsules, per pack dispensed, was adopted for the purposes of overall data comparison, as explained in Section 5.4.2.1.

Powders (oral) are preparations consisting of solid, loose and dry particles of varying degrees of fineness, which contain 1 or more active substances (with or without excipients). Oral powders are usually administered in, or with, water or another suitable liquid, and may also by swallowed directly. Oral powders are presented as single-dose or multidose preparations; single-dose powders are enclosed in individual containers, such as sachets or vials (EDQM, 2007). Oral powders may also be dispensed in envelopes or pots; multidose powders require the provision of a measuring device capable of delivering the quantity prescribed (EDQM, 2007). Powders are one of the oldest dosage forms but have been largely replaced by capsules and tablets because, although stable and flexible, these are very time-consuming to prepare (O'Connor *et al.*, 2005) and are difficult to administer without waste. Unless otherwise indicated, an estimate of 13 units of oral powders, per pack dispensed, was adopted for the purposes of overall data comparison, as explained in Section 3.4.2.

Tablets are solid preparations, each containing a single dose of one or more active substances, and they are obtained by compressing uniform volumes of particles (or by another appropriate manufacturing technique). Some tablets are swallowed whole, others after chewed; some are dissolved or dispersed in water before being administered and others are retained in the mouth (where the active substance is liberated) (EDQM, 2007). Tablets are a popular dosage form because of the economy of preparation on a large scale, stability and ease of administration (Rudnic and Schwartz, 2005). The preparation of tablets requires specific tableting equipment and not all pharmacies can afford such an investment.

b. **Liquid dosage forms**

Liquid preparations for oral use are usually solutions, emulsions or suspensions containing 1 or more active substances in a suitable vehicle. Several categories of these preparations may be distinguished, including the following: oral solutions, emulsions and suspensions; powders and granules

for oral solutions and suspensions; oral drops; and syrups (EDQM, 2007). However, this distinction is not always straightforward (Section 4.4.3), particularly in relation to solutions, suspensions and syrups, as it depends on the characteristics of the respective oral liquids (e.g. solubility and consistency); and also in relation to oral drops, as it depends on the characteristics of the container / additional devices (e.g. dropper).

Oral liquids may be supplied in single-dose or multidose containers and, for the purposes of overall data comparison, quantities <10 mL were taken to correspond to unidose whereas quantities >10 mL corresponded to multidose containers (Section 5.4.2.2), unless otherwise indicated. For quantities =10 mL, data entries were considered individually and within the respective national databases. In addition, an estimate of 12 units of unidose oral liquids, per pack dispensed, was adopted for the purposes of overall data comparison, unless otherwise indicated, as explained in Section 5.4.2.2.

Although oral liquids may be rapidly prepared, allow dosing flexibility (by variable volumes) and are easy to administer (particularly to paediatric and geriatric patients, Section 1.1.5), their formulation and stability are usually complex. Issues with solubility; uniformity; taste masking and physical, chemical and microbiological stability must be considered when preparing oral liquid compounded medicines (Woods, no date). Several categories of excipients are usually required to ensure optimal formulations (e.g. suspending agents, buffers and preservatives) and to enhance compliance (e.g. sweetening and flavouring agents). However, the choice of excipients must also consider the patients' pathophysiology (e.g. ethanol is not recommended in paediatric patients and sucrose is not recommended in diabetic patients), which adds even more complexity to the extemporaneous preparation of oral liquid dosage forms.

The preparation of compounded medicines in variable strengths is facilitated when oral solids (capsules and powders) are prepared, as opposed to liquid dosage forms that usually require more complicated dosing calculations. On the other hand, oral liquids allow dosing flexibility, which is not easily achieved with solid dosage forms.

Although the aim was to identify and characterise the extemporaneously compounded oral medicines, for the purposes of this research, extemporaneously does not mean a medicine prepared just before being dispensed/administered but, instead, refers to compounded medicines in general, including those prepared in advance. This terminology was adopted because it is closely associated with the concept of compounded medicines in the UK.

2.2 **Sampling methods**

The population of interest in this project was hospital pharmacies in Europe, which represented a very large and numerous sampling frame. It would be impractical and unnecessary to recruit all hospital pharmacies spread across Europe. By selecting a sample from the complete population, it is possible to conduct more detailed research within limited time, staff and resources. Also, better quality data may be achieved since there is more time for checking and analysing the information collected (Bowling, 2002; Smith *et al.*, 2008). Due to the complexity of the Europe-wide research, sampling the hospital pharmacies was not straightforward and a multi-stage sampling procedure was adopted:

- 1st stage: sample of European countries (primary sampling units).
- 2nd stage: sample of hospital pharmacies (within each European country).

2.2.1 **Sample of European countries**

Identification of, and access to, the population of interest is one of the first considerations of any researcher (Smith, 1997b). When sampling the European countries, the first consideration to be made was the following: are all European countries equally relevant to the purpose of the research? Europe is a large and heterogeneous continent constituted by 49 countries (Figure 2.1), including 27 members of the EU and 22 non-members; the members of the EU cover most of the continent and more countries are expected to join the Union. The EU brings together the European countries committed to closer cooperation and, thanks to the Union, citizens of the member countries can travel, live and work anywhere in Europe. This fundamental right of the EU citizens to move cross-borders raises many

challenges; with regards to health care, patients and professionals have an easier access to health systems abroad within the EU and are more interconnected than ever (*Europa*, 2009). Therefore, the European countries are not all equally relevant to the purpose of this research. The most relevant countries are actually those with fewer frontiers and whose citizens share enhanced collaborations and expectations in Europe, i.e. the members of the EU and the non-members with close connections to the Union.

To ensure that the relevant countries were represented in the sample, a stratification procedure was undertaken to divide the population of interest in groups and subgroups, prior to sample selection. According to Bowling (2002), dividing the population in strata and sampling from each stratum avoids under or over representation of certain groups of the population. Stratification assures the researcher that there will be sufficient numbers in each group to enable comparisons, avoiding inadequate representations of the population (Smith *et al.*, 2008).

The 49 European countries (population of interest) were initially divided in the classic 2 groups: members of the EU (group 1) and non-members of the EU (group 2). The members of the EU were ordered by population (Figure 2.2) and these were further divided in 3 subgroups, of 9 countries each, according to their population (Table 2.1). The population of interest is generally stratified according to the variables believed to be important to the study objectives (Smith *et al.*, 2008).

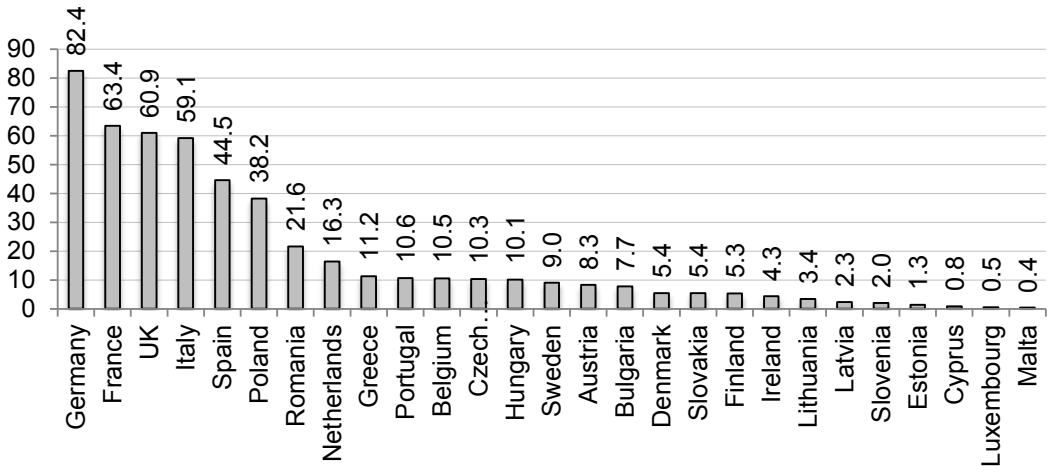

Figure 2.2 Population (in millions) per member state of the EU in 2007 (adapted from *Europa*, 2008).

Table 2.1 Members of the EU divided in 3 subgroups according to their population (the countries selected were underlined).

Subgroup 1	Subgroup 2	Subgroup 3
Germany	Portugal	Finland
France	Belgium	Ireland
UK	Czech Republic	Lithuania
Italy	Hungary	Latvia
Spain	Sweden	Slovenia
Poland	Austria	Estonia
Romania	Bulgaria	Cyprus
Netherlands	Denmark	Luxembourg
Greece	Slovakia	Malta

In a study that aims to identify the most frequently dispensed oral compounded medicines in Europe, the determinant variable is the population and not the size of the country or its geographical location. For this reason, the stratification procedure was carried out considering the population per country. The resulting 3 subgroups reflect the diversity of the population within the EU, from the most populated to the least populated countries (Table 2.1). Stratification is particularly useful in ensuring that samples are representative (Smith, 2005). In order to get the best coverage of Europe, sampling was then carried out in each subgroup. A larger sample fraction was taken from subgroup 1 (more populated countries) to provide results that represent the majority of the EU population. Thereafter, two identical sample fractions were taken from subgroups 2 and 3, so that the different subgroups of the population were all represented in the sample. The method adopted at this stage was convenience sampling and a total of 10 members of the EU were selected, which are underlined in Table 2.1.

At last, considering the non-members of the EU (group 2), one country was selected from this strata and the method adopted was an opportunistic sampling[12] procedure.

[12]Opportunistic samples share features of convenience samples in terms of the selection procedure but may also be representative of the population of interest (Smith, 2002).

In fact, Switzerland was not only the most convenient country from this group but also the one that shares more relations with the Union (ergo opportunistic sample). Over 900,000 EU citizens live and work in Switzerland, and many more cross the borders or transit the country on a regular basis (EEAS, 2011). For these reasons, Switzerland was the non-member of the EU considered in this research. The stratification and sampling of European countries are shown in Figure 2.3.

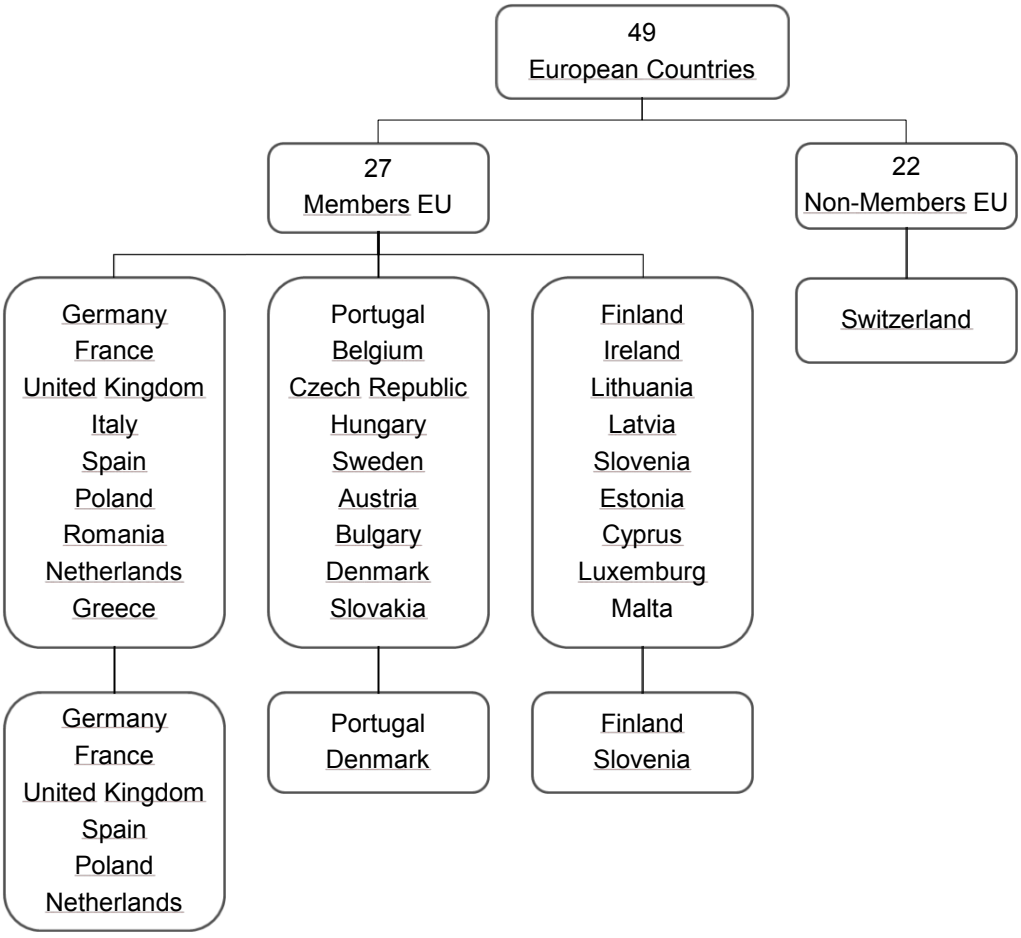

Figure 2.3 Stratification and sampling of European countries.

In summary, the international survey was undertaken on sample of 11 European countries, namely: Germany, France, UK, Spain, Poland, Netherlands, Portugal, Denmark, Finland, Slovenia and Switzerland (Figure 2.4). These include Eastern and Western, Mediterranean and Scandinavian European countries, in a total of 10 members and 1 non-member of the EU.

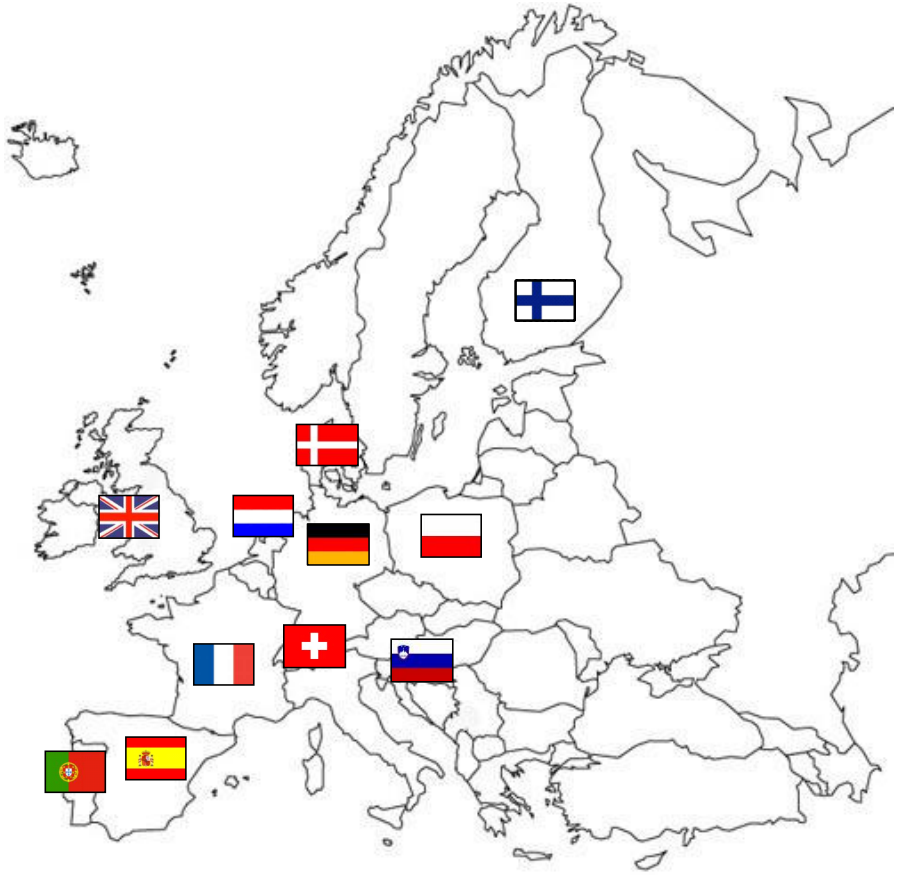

Figure 2.4 European countries included in the international survey.

2.2.2 **Sample of hospital pharmacies**

Sampling theory assumes a random sample and, in general, the representativeness of the study population is enhanced by the use of random sampling methods (Bowling, 2002). However, this is not always the case as, for instance, in studies that aim to select individuals or settings with a particular characteristic within the population of interest. In a study that aims to identify the most frequently dispensed oral compounded medicines in Europe, hospital pharmacies that dispense a few, or no oral compounded medicines at all, might be selected in a random sampling method, whilst hospital pharmacies that dispense the most might be omitted. This sampling method would negatively impact the outcome of the research. The procedure in which the researcher purposively identifies and selects the individuals or settings expected to present the study characteristic is called purposive sampling (Smith, 2005). Therefore, the method adopted to sample the hospital pharmacies in each European country was a purposive sampling

procedure, which is a deliberately non-random method of sampling that aims to sample a group of people or settings with a particular characteristic (Bowling, 2002). In this research, the hospital pharmacies that most frequently dispense oral compounded medicines are the ones that present the study characteristic. Consequently, the purposive sample in each European country corresponded to those hospital pharmacies that most frequently dispense oral compounded medicines in that country. Identifying the purposive samples was not straightforward and, for some countries, it involved seeking the expert opinion of several national stakeholders on pharmaceutical compounding.

Sampling is always liable to be affected by errors, which cannot be eliminated but should be reduced to an acceptable level (Bowling, 2002). In order to minimise sampling error in this research, purposive samples were regularly checked and more hospital pharmacies were added to the initial lists, when appropriate. For every European country, the goal was to identify all relevant hospital pharmacies so that if the study were to be conducted by another researcher, the purposive samples would be equivalent.

It is important to highlight that the size of the purposive samples varied considerably within the European countries since it corresponded to the number of hospital pharmacies that most frequently dispense oral compounded medicines in that country. This study characteristic is not necessarily proportional to the population in the country, nor its size, and it can only be estimated following a deep understanding of the compounding practices in each country. Additionally, it is not possible to anticipate if all paediatric hospitals across Europe would be relevant to this research and it should not be assumed that the majority of oral compounded medicines are dispensed in these specialist hospitals. In conclusion, the size and nature of the purposive samples are country-specific and these will be discussed in the respective chapters.

In summary, a multi-stage sampling procedure was adopted to identify the hospital pharmacies that most frequently dispense oral compounded medicines, per country, as follows:

On a 1st stage, the European countries were stratified and a convenience sample of members of the EU was selected plus an opportunistic sample of non-members of the EU. On a 2nd stage, a purposive sample of hospital pharmacies was selected, per European country. Altogether, the sample selected may be described as a stratified purposive sample.

The European countries included in the research will be described in chronological order, per individual chapter, followed by an overview and discussion of compounding in Europe.

2.3 **Data collection**

A systematic process of data collection was undertaken, which included a structured literature review and a detailed register of the views of external stakeholders, experts and country-specific representatives. A wide-ranging and time-consuming process of data collection was performed for each European country, in order to meet the objectives of the study, as follows:

- Identification and understanding of the official concept of compounded medicines (types and definitions); national regulations and legal requirements for the practice of compounding.
- Identification of the most relevant professional organisations and information sources on compounding.
- Identification of existing knowledge on the practice of compounding.

The literature review was undertaken for each European country considered, including both national and international information sources, in English and in the following official languages: Danish, Dutch, Finnish, French, German, Portuguese, Polish, Slovenian and Spanish. The assistance of national stakeholders and the staff at the UCL (University College London) School of Pharmacy with selected translations was very helpful at this stage. The literature review included academic journals and databases; conference presentations and abstracts; professional journals, databases, newsletters and websites; legal and policy documents; pharmacopoeias; official and non-official formularies and textbooks.

As part of the process of data collection, selected external stakeholders, experts and country-specific representatives were contacted and their views

were registered in detail. For each European country, if relevant data on hospital compounding practices had recently been collected by other researchers or organisations, the need for conducting the national survey was revised at this stage. Relevant data were identified in the UK, France and Germany, which will be addressed in the respective chapters.

So that information was easily accessed and updated, a robust data organisation system was developed for filling large quantities of data. Information was archived for each country and, within each, data from the hospital pharmacies was registered, in detail, in individual portfolios. Considerable effort was required to encourage the selected European hospitals to collaborate with data collection. For many hospital pharmacies, gathering the required data was an arduous and time consuming process and, therefore, data collection was not finalised until the very end of the research. For each European country, data collection procedures will be thoroughly addressed in the respective chapters.

2.4 **Data processing and analysis**

European hospitals were divided in 3 categories: participant, non-participant and non-respondent hospitals.

Participant hospitals contributed the required data but to variable extents. The majority of hospitals provided quantitative datasets but some provided semi-quantitative and qualitative data, as well as incomplete datasets, which were processed and analysed accordingly. Data from hospital pharmacies were provided in variable formats, from completed questionnaires provided by the researcher to their own formats, either manually or electronically. Hospital pharmacies were frequently contacted to confirm the interpretation of the datasets, in particular with regards to the quantities of the different dosage forms dispensed. For each dataset, data entries were checked in detail and transcribed to a national database (in Microsoft Excel). Incomplete or not clearly identified data entries were checked with the hospital pharmacy staff. Non-valid data entries were excluded from the processed database (Section 2.4.1).

Non-participant hospitals did not contribute data and the reasons appointed for not participating were grouped together and assigned codes. The coding frame was developed considering the actual responses (Smith, 2005) as shown in Table 2.2. In code A, compounded medicines were not dispensed at all by the hospital pharmacy (A1) or, alternatively, compounded medicines were dispensed but none for oral administration (A2). In code B, compounded medicines were dispensed by the hospital pharmacy but data was not provided because of the following reasons: only few compounded medicines were dispensed (B1); only few oral compounded medicines were dispensed (B2); the required data was not readily accessible (B3); there were no compounding records at the hospital pharmacy (B4); or the required data was deemed confidential (B5). In code C, no reason was appointed by hospital pharmacies for not participating in the research.

Table 2.2 The coding frame for the reasons appointed by hospital pharmacies for not participating in the research.

A	**Not dispensed**	A1	Compounded medicines
		A2	Oral compounded medicines
B	**Dispensed**	B1	Few compounded medicines
		B2	Few oral compounded medicines
		B3	No readily accessible data
		B4	No records
		B5	Confidential data
C	**Non-participant**	No reason appointed	

Participant hospitals that did not contribute complete, quantitative datasets were also assigned a code (Table 2.2). The reasons for not contributing the required data were not always clear and hospital pharmacies were frequently contacted for confirmation of their reasons. This approach occasionally resulted in receiving the required data afterwards, increasing the number of participant hospitals contributing complete and quantitative datasets.

Following data processing, data entries were analysed to determine the therapeutic category of the corresponding compounded medicines.

Initially, it was though that the BNF (British National Formulary, Section 4.2.2) would be the appropriate reference for categorising the compounded medicines dispensed Europe-wide. The BNF is divided in 15 chapters, each of which is related to a particular system of the body or to an aspect of medical care, and active substances are distributed per therapeutic indications (Joint Formulary Committee, 2008). The BNF was used for data analysis in Portugal, UK and Poland. However, it was then concluded that many active substances dispensed abroad were actually not included in the BNF.

Therefore, in a second approach to data analysis, an international reference was selected to categorise the compounded medicines dispensed Europe-wide. The anatomical therapeutic chemical (ATC) classification system was thought to be the appropriate reference since the WHO (World Health Organization) recommends it for international comparisons. In this system, substances are divided in groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties (WHO Collaborating Centre for Drug Statistics Methodology, 2008). This system was used for data analysis in Portugal, UK, Poland and France. However, the ATC classification includes only substances for which an ATC code was requested (by manufacturers, regulatory agencies or researchers) and, in fact, several active substances dispensed in Europe did not have such a code. In addition, many active substances were included in more than one therapeutic group[13], which added ambiguity to data analysis since it was not possible to determine the actual therapeutic indication for every compounded medicine dispensed. Therefore, at this stage, it was concluded that the ATC classification system was not the appropriate reference source to categorise the compounded medicines dispensed Europe-wide.

[13]Dexamethasone, for instance, was attributed the following ATC codes (not all inclusive): A01AC02 (Alimentary tract and metabolism); C05AA09 (Cardiovascular system); D07AB19 (Dermatologicals); M02AB02 (Systemic hormonal preparations) and R01AD03 (Respiratory system) (WHO Collaborating Centre for Drug Statistics Methodology, 2008).

In a third approach to data analysis, “Martindale: The Complete Drug Reference” (*Martindale 35*, 2007) was concluded to be the reference of choice since it is based on published information and includes substances and medicines currently in use throughout the world. It contains over 5,500 monographs arranged in 54 chapters, which bring together substances and groups of substances that have similar uses or actions. Active substances are included in one therapeutic group (only) that reflects the uses of the substances being described (*Martindale 35*, 2007). For comparative purposes, this unambiguous classification of active substances is the ideal system. Nevertheless, as indicated previously, it was not possible to determine the actual therapeutic indication for any dispensed product in this study and, therefore, the therapeutic groups assigned to active substances are regarded as the best estimate of the therapeutic indications of the compounded medicines dispensed. Another important feature of *Martindale 35* (2007) is the information on proprietary medicines, which covers a wide range of countries, and proved to be very helpful as European hospitals also reported proprietary medicines being used in pharmaceutical compounding. Data entries reporting proprietary medicines used in the preparation of the compounded medicines were processed and transcribed to the corresponding active substances, which were then categorised according to *Martindale 35* (2007). “Synonyms” was another helpful feature in Martindale as European hospitals frequently reported active substances using equivalent or shortened designations (e.g. butylscopolamine bromide instead of hyoscine butylbromide).

Included in the data analysis was the identification of Narrow Therapeutic Index (NTI) drugs dispensed in European hospitals. NTI drugs may be broadly defined as critical-dose substances for which small changes in systemic concentration can lead to significant changes in pharmacodynamic response, resulting in potentially toxic effects or subtherapeutic effects (Burns, 1999; Pope, 2009). An official definition and list of NTI drugs has not yet been published in Europe and, as a result, the official list published in Brazil by the national agency of sanitary vigilance - *Agência Nacional de*

Vigilância Sanitária (ANVISA, 2007) - was adopted for data analysis in this research. This is shown in Appendix 1.

2.4.1 **Exclusion criteria**

Not included in the definition and practice of compounding were: off-label use (of proprietary medicines); reconstitution, repackaging and handling of medicines, as explained in Section 1.1.2.4. Consequently, these activities were excluded from the survey. Veterinary compounding was excluded as well and all hospitals considered were for human patients only.

Also excluded from this research were:

- Sterile compounded medicines.
- Non-sterile, non-oral dosage forms (Section 2.1.3).
- Data entries corresponding to vehicles, for instance, Simple Syrup BP (British Pharmacopoeia) (see compounding formulary in Appendix 2).
- Data entries in which the name of the active substance(s) could not be clearly identified or checked with hospital pharmacy staff.
- Data entries in which the number of times dispensed corresponded to “0”.

For all data entries in which the respective dosage form or number of times dispensed could not be clearly identified or checked with the hospital pharmacy staff, these were included in the research as qualitative data entries.

3. **Compounding in Portugal**

Portugal joined the EU in 1986 and its official language is Portuguese (*Europa*, 2009). Portugal is constituted by the mainland and the archipelagos of *Madeira* and *Açores*. The mainland is situated in the South-westernmost point of continental Europe and the archipelagos in the Atlantic Ocean (INE, 2009). Portugal occupies an area of 91,900 Km^2 and is the 10^{th} most populated country in the EU, with a population of 10.6 million in 2007 (Figure 2.2) (*Europa*, 2008). The distribution of the population across the country is not homogeneous, but is strongly concentrated on the coast, particularly between the cities of *Viana do Castelo* and *Setúbal*, with higher incidence in the metropolitan areas of Lisbon (capital) and *Porto* (second largest city) (INE, 2009).

In 2005, there were 204 hospitals in Portugal (ratio of 1.93 hospitals per 100,000 population) and, in 2006, there were a total of 36,563 hospital beds (ratio of 345.44 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2005, there were 10,320 pharmacists in Portugal (ratio of 97.83 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4) and, according to the Portuguese statistical data, there were 738 pharmacists working in the hospital sector in 2008 (OF, 2008). Considering the total of 198 Portuguese hospitals (INE, 2009), there was a ratio of 3.7 pharmacists per hospital. Nevertheless, in 2005 more than 20 Portuguese hospitals had only 1 hospital pharmacist, which has been suggested to not be sufficient for the 24 hours a day support that is required in hospitals (Machado and Silva, 2005).

In Portugal, hospital pharmacy (also known as pharmaceutical services) corresponds to a department within the hospital that has technical and scientific autonomy and is usually directed by a hospital pharmacist, who reports to the administration board of the hospital. Pharmaceutical compounding is one of the activities undertaken in the hospital pharmacy and, for the majority of hospitals, it is the pharmacy's responsibility to prepare cytotoxics, parenteral nutrition fluids and other medicines for intravenous

administration, in aseptic preparation facilities that have greatly improved over recent years. For economic reasons, other compounded medicines are sometimes prepared in centralised hospital pharmacies (Feio, 2008). The preparation of quality compounded medicines is a big concern for Portuguese hospital pharmacists and QC groups have been set up in many hospitals to ensure that these medicines are prepared and dispensed in conformity with the standards (Machado and Silva, 2005). Nevertheless, in December 2009, six patients who were admitted for eye surgery in one of the largest hospitals in Portugal were left blind due to a compounding error. The eye preparations were compounded with the wrong active substance and the QC group did not identify the mistake (Mesquita, 2009).

Pharmaceutical compounding in hospital and community pharmacy is currently a common practice in Portugal. Non-sterile compounding occurs in both settings, whereas sterile compounding is almost restricted to hospital pharmacy (Carvalho *et al.*, 2008). Compounded medicines have always been prepared and dispensed in Portugal, and since the foundation of a national compounding information centre, in 1999, that pharmaceutical compounding has begun a process of reformation and modernisation (Section 3.2.1). More initiatives have occurred subsequently, which have contributed to the promotion of pharmaceutical compounding in Portugal as, for instance, the publication of a contemporary formulary and the approval of up-to-date legislation. Portuguese pharmacists no longer consider compounded medicines an activity of the past but, instead, an opportunity for the future (ANF, 2008a) and pharmaceutical compounding is now recognised as a valuable therapeutic option in Portugal.

There are very few published studies regarding the practice of pharmaceutical compounding in Portugal. Barros and Almeida (2008) identified the oral compounded medicines dispensed to paediatric patients in a convenience sample of 6 hospital pharmacies in Lisbon. They reported a total of 52 different oral compounded medicines, dispensed during a 2-month period in 2004. The most frequently dispensed oral dosage form was sachets and the most frequent therapeutic group was cardiovascular drugs. The most common active substances were: folic acid, ursodeoxycholic acid and

phenobarbital (oral powders); chloral hydrate, trimethoprim and midazolam (oral liquids). Paediatric and university hospitals largely compounded oral powders whereas general hospitals mainly compounded oral liquids. Rosa *et al.* (2006), from the hospital pharmacy at *Hospital de Dona Estefânia,* a maternity and children's Portuguese hospital in Lisbon, reported that there is a lack of appropriate formulations for paediatrics. According to the authors, pharmaceutical compounding is one of the solutions to this problem and it is common practice to prepare sachets and oral liquids, starting from the respective proprietary medicines, in order to obtain medicines adapted for the paediatric population. A particularly valuable contribution to pharmaceutical compounding in Portugal was the Masters' project by Pinto (2006). The researcher developed a universal vehicle for the easy and rapid preparation of oral suspensions with assured quality and appropriate characteristics for oral administration. The monograph for this vehicle was included in the *Formulário Galénico Português* (FGP) (Section 3.2.2) - Portuguese galenic formulary - and it was the basis for the development of further monographs for oral suspensions, containing different active substances, which were also included in the FGP.

3.1 **Legislation**

The first legislation regarding pharmaceutical compounding was published in 1991 and remained in force until 2004, despite the fact that it became obsolete over the intervening years (e.g. the price of compounded medicines was not updated), and was contributing to a generalised lack of interest in compounded medicines in Portugal. Eventually, legislation appropriate for current practices was published in 2004 and this has contributed to a boosting of pharmaceutical compounding throughout the country. This is the current legislation and comprises a large set of legal documents concerning the practice of pharmaceutical compounding in community and hospital pharmacies.

In Portugal, compounded medicines correspond to *Medicamentos Manipulados* and include any *Fórmula Magistral* (magistral formula) or *Preparado Oficinal* (officinal preparation) prepared and dispensed under the responsibility of a pharmacist. *Fórmula Magistral* corresponds to a medicine

prepared in a hospital or community pharmacy according to a doctor's prescription that specifies the patient for whom the medicine is intended. *Preparado Oficinal* corresponds to any medicine prepared according to the indications of a compendium, a pharmacopoeia or a formulary in a hospital or community pharmacy, and is intended to be directly dispensed to the patients assisted by that pharmacy (Ministério da Saúde, 2004a). All monographs included in the FGP correspond to *Preparados Oficinais* since the FGP has been recognised by the *Autoridade Nacional do Medicamento e Produtos de Saúde* (INFARMED), the national authority of medicines and health products (INFARMED, 2004a; CETMED, 2005).

Compounded medicines in Portugal may technically be prepared in advance provided that these are multidose preparations (packaged in single-dose containers) and are part of a list that as yet has not been published (Ministério da Saúde, 2004a). Hence, in practice, the advanced preparation of compounded medicines is not allowed in Portugal.

The price of compounded medicines is specified by law and it is determined in accordance with the cost of the staff's salary, the cost of raw materials and the cost of packaging materials (Ministérios da Economia e da Saúde, 2004). Before this regulation the price of compounded medicines was low and pharmacists were discouraged to prepare these medicines. Nowadays, pharmaceutical compounding is cost-effective and more and more pharmacists are investing in new facilities and modern equipment for compounding (Carvalho, 2005).

It was established by law (Ministério da Saúde, 2004b) that the government would subsidise 50% of the cost of the compounded medicines included in a list, proposed by INFARMED, but this list was published only towards the end of 2010. This fact was criticised by the president of the national association of pharmacies (ANF) (Section 3.2.1) at the launching of the FGP 3rd edition (edn.) (ANF, 2008a). Before the publication of this list, the compounded medicines subsidised were the ones included in the Portuguese Pharmacopoeia 9 and in the National Galenic Formulary (Section 3.2.2) (Gabinete da Secretária de Estado da Saúde, 2005). This recently published list includes almost 90 entries of one or more active substances, and the

respective dosage forms, and these medicines are reimbursed for 30% of their cost. Further compounded medicines may be included in this list provided that one of the following conditions is met: nonexistence of proprietary medicines with the same active substance and in the same dosage form; existence of a therapeutic need with regards to the proprietary medicines available; need for adjustments of strengths or dosage forms to the therapeutic needs of specific populations, as for paediatrics or geriatrics. Prescriptions including a reference to proprietary medicines or other products are not subsidised in Portugal (Ministério da Saúde, 2010).

With regards to raw materials, all substances included in compounded medicines must be part of the Portuguese Pharmacopoeia, or another scientific compendium, and must not be included in the list of substances that cannot be used in the prescription and preparation of compounded medicines (Ministério da Saúde, 2004a). This negative list determines that the following substances cannot be used in pharmaceutical compounding: animal organ extracts; active substances (for internal use) in a dosage higher than that authorised for proprietary medicines; active substances included in medicines that were suspended or repealed; and finally, a set of active substances, including: clobenzorex (and other anorectics); levothyroxine (and similar substances); fluoxetine and other substances (INFARMED, 2004b). Anti-obesity drugs are included in this negative list in order to avoid their misuse by means of pharmaceutical compounding. Levothyroxine is also included in the list because of a compounding error in the past including this active substance. In addition, there is a specific regulation for the suppliers of raw materials that specifies the conditions that these must meet (INFARMED, 2004c).

When preparing a compounded medicine, the pharmacist must assure the quality of the preparation by following good compounding practices (GCP) in community and hospital pharmacies – "*Boas práticas a observar na preparação de medicamentos manipulados em farmácia de oficina e hospitalar*" – established by law (Ministério da Saúde, 2004c). These guidelines are constituted by a set of 8 norms, as follows: personnel; facilities and equipment; documentation; raw-materials; packaging materials;

compounding; QC and labelling. In Portugal, QC must be performed for all compounded medicines prepared and the QC tests are specified by law. The verification of organoleptic characteristics, final weight/volume, pH (solutions), uniformity of weight (solids) are some of the tests specified in the Portuguese GCP.

If a hospital does not meet the necessary conditions for the preparation of specific compounded medicines, these may be prepared by an authorised body provided that the medicines required are for the exclusive use of the hospital (INFARMED, 2004d).

With regards to community pharmacies, although compounding-specialist pharmacies are not found in Portugal, every community pharmacy must have a compounding laboratory and its dimensions are specified by law (INFARMED, 2007; Carvalho *et al.*, 2008). Moreover, there is a list of the minimum compounding equipment that is required in a pharmacy, for instance, glass and porcelain mortars; balance (capable of weighing milligram quantities); measuring cylinders and pipettes (INFARMED, 2004e).

3.2 **Professional organisations and information sources**

3.2.1 **Portuguese professional organisations**

- *Associação Nacional das Farmácias* (ANF): is the national association of pharmacies, a non-governmental organisation that represents and supports 97% of Portuguese community pharmacies. The ANF is constituted by several organisations, each focused on a particular pharmaceutical activity (ANF, 2008b). The two ANF organisations relevant on pharmaceutical compounding are described below.

i. *Centro Tecnológico do Medicamento* (CETMED): was the pharmaceutical technology department of ANF, a department created in 1999 to promote and develop pharmaceutical compounding by community pharmacies (and also hospital pharmacies) in Portugal, directed by Carlos Maurício Barbosa (Associate Professor at the Faculty of Pharmacy, University of Porto). From 1999 to 2003, CETMED provided 160 consultations on pharmaceutical compounding to a total of 45 Portuguese hospital pharmacies (Barbosa *et al.*, 2003). The practice of pharmaceutical compounding resurged in Portugal as

pharmacists were encouraged and supported by CETMED to prepare and dispense compounded medicines. CETMED was closed down by ANF in 2005 and its services were integrated in the *Laboratório de Estudos Farmacêuticos*.

ii. *Laboratório de Estudos Farmacêuticos* (LEF): is the laboratory of pharmaceutical studies, the organisation from ANF that incorporated CETMED in 2005. The LEF, amongst other services, provides a compounding information centre that offers technical and scientific information services to all health care professionals. The LEF also develops monographs for the FGP and offers training courses on pharmaceutical compounding (LEF, 2006), the same services that were initiated by CETMED.

- *Associação Portuguesa de Farmacêuticos Hospitalares* (APFH): is the Portuguese association of hospital pharmacists, an organisation that represents and supports Portuguese hospital pharmacists. The mission of APFH is to assist hospital pharmacists enable people to use medicines better (APFH, 2010). APFH organises a congress every 3 years and an annual symposium between (Batista, 2008). Pharmaceutical compounding in hospital pharmacy is usually one of the subjects discussed at the APFH events; in 2004, at the 5th congress of the APFH, there was a workshop entirely dedicated to compounding (Gouveia, 2005). APFH is a full member of the EAHP (Batista, 2008).

3.2.2 **Portuguese information sources**

- *Formulário Galénico Português* (FGP): is the Portuguese galenic formulary, a national reference for pharmaceutical compounding initiated by CETMED. It was first published in 2001 aiming to contribute to the quality of the compounded medicines prepared and dispensed in the Portuguese pharmacies; and also to contribute to the standardisation of pharmaceutical compounding in Portugal (CETMED, 2001). The FGP was developed based on a comparative study of formularies from selected EU countries, Switzerland, Norway and also USA (Barbosa and Pinto, 2001). A second and much larger edition of the FGP was published in 2005, including a total of 133 monographs for (liquid and semi-solid) compounded medicines, current

legislation relevant for pharmaceutical compounding, technical information and recommendations, and also standard operating procedures (CETMED, 2005). Monographs for compounded medicines are very comprehensive, including a total of 15 different sections (for most medicines): formula, method of preparation (manual and mechanical), description of the medicine, packaging, labelling, QC, beyond-use-date and storage conditions, clarifications, therapeutic indications, administration and usual dosages, secondary effects, precautions and contra-indications, interactions, intoxication symptoms and treatment and, finally, bibliography. All monographs are complemented with the respective work sheets. An example of a monograph from the FGP 2005 - Phenobarbital 1% Oral Suspension - is shown in Appendix 5. The current 3rd edition of the FGP was published in 2007 and is very different from the previous editions, as a result of the integration of CETMED in LEF. The current edition is focused on Paediatrics and includes a total of 98 monographs for compounded medicines, exclusively oral liquids (solutions and suspensions) (LEF, 2007; ANF, 2008a).

- *Farmacopeia Portuguesa* (FP): is the Portuguese Pharmacopoeia, which includes monographs for compounded medicines, though the number of monographs has been gradually reduced throughout the years (Barbosa and Pinto, 2001). The current edition is the FP 9 and includes only 5 monographs for compounded medicines, namely: *unguentum picis mineralis cum zinci oxydi et amylum*; *unguentum picis mineralis*; *suppositoria glyceroli*; *tincture picis mineralis*; and *sirupus ipecacuanhae* (Comissão da FP, 2008). Since the number of monographs for compounded medicines included in the FP 9 is very limited, Portuguese pharmacists in community and hospital pharmacies frequently use the FP IV (1946), which includes around 350 monographs for compounded medicines (*Farmacopeia Portuguesa IV*, 1946; Barbosa and Pinto, 2001).
- *Formulário Galénico Nacional* (FGN): is the national galenic formulary, the Portuguese official formulary that is still in force today. It was published in 1969 and has not been updated since (Comissão Permanente da FP, 1969; Barbosa and Pinto, 2001).

- *Formulario Officinal e Magistral*: although dating from 1915, the *Formulário Veiga* (after the author Joaquim Urbano da Veiga) is another formulary that is commonly used by Portuguese pharmacists (Veiga *et al.*, 1915; Barbosa and Pinto, 2001).
- *Tecnologia Farmacêutica*: are the Portuguese textbooks of reference in pharmaceutical technology, edited in 3 volumes, which provide the basics for the practice of pharmaceutical compounding. This set of books is currently used in academia and in pharmacy practice in Portugal (Prista *et al.*, 1995; 1996a; 1996b; Barbosa and Pinto, 2001).

3.3 **Methods**

Portugal was the first European country included in the research. It was the most convenient country to start with because of the practice and expertise of Maria Carvalho (MC) in the field of pharmaceutical compounding in her home country; the easy access and proximity of MC to Portuguese hospital pharmacies; and the common language shared with all professionals.

The research project in this country was initiated in 2006 by consulting Portuguese stakeholders, namely: Carlos Maurício Barbosa (Director of CETMED and Associate Professor at the Faculty of Pharmacy, University of Porto) and Jorge Brochado (President of the APFH and chief hospital pharmacist at the *Hospital de Santo António*), who contributed with their knowledge and experience to planning the research. Their recommendations and advice were particularly important in the initial stages of the research, namely in the design of the template questionnaire (Section 3.3.1) and in identifying the purposive sample of Portuguese hospitals (Section 3.3.2).

It was concluded that the template questionnaire should be piloted in selected hospitals pharmacies before being distributed to the purposive sample of hospitals. A convenience sample[14] of 3 hospitals was then established in 3 regions of Portugal, in order to even out possible geographical idiosyncrasies in the practice of pharmaceutical compounding. The pilot study was initiated at the beginning of 2007 with a visit to the

[14]Convenience samples are useful in preliminary fieldwork and pilot studies (Smith, 2005).

following hospitals: *Hospital Geral de Santo António*, in *Porto*; *Hospital de São Pedro*, in *Vila Real*; and *Hospital de Santa Maria*, in Lisbon.

The contents of the template questionnaire were carefully evaluated during the hospital visits. Data from the compounding records of each hospital was inserted in the template questionnaire to test its adequacy and, at the same time, to initiate data collection in Portugal. As a result of the pilot study, the contents of the template questionnaire were further tailored to the current hospital compounding practices and, at last, a first version of the Portuguese questionnaire was obtained.

3.3.1 **Country-specific questionnaire**

Although the aim of the project was to identify and characterise the extemporaneously compounded oral medicines most frequently dispensed in European hospital pharmacies, it was initially decided to include only the oral liquid compounded medicines in the research. At that time, it was considered that collecting data regarding other dosage forms would unnecessarily increase the time and length of a Europe-wide project.

The research instrument developed to collect information regarding oral liquid compounded medicines was a self-completion questionnaire, designed to include all oral liquids dispensed by the hospital pharmacy in 2006. In an Excel table, for each oral liquid dispensed, the questionnaire addressed the following information: name of the active substance; strength; dosage form; volume; and number of times dispensed per month, from January to December 2006. The units of strength and volume were also required. Under dosage form was “solution / emulsion / suspension” so that it was clear which dosage forms were considered oral liquids. The first entry on the Excel table was an example including “Captopril, 1 mg/mL, solution, 100 mL, 24 (total times dispensed)”. Directions were included above the table, as the following: “Please fill in the following table with only the ORAL LIQUID compounded medicines dispensed by the hospital pharmacy in the year 2006”. It was decided that the questionnaire should address the compounded medicines dispensed instead of the compounded medicines prepared by the hospital pharmacy. This distinction is crucial, particularly in a Europe-wide project, as

not all compounded medicines dispensed in hospitals are necessarily prepared in the respective hospital pharmacies (Section 2.1.2). The Excel table is shown in Appendix 6 and the main heading in Figure 3.1.

In order to estimate the importance of oral liquids in comparison to other dosage forms dispensed by the hospital pharmacy, 2 closed questions[15] were added to the questionnaire:

1 - "Which was the main DOSAGE FORM dispensed by the hospital pharmacy in the year 2006?" The range of responses was: "Sachets, Capsules, Suppositories, Ointments/Creams, Solutions/Suspensions".

2 - "Considering all dosage forms, what is the average TOTAL number of compounded medicines dispensed by the hospital pharmacy in the year 2006?" The range of responses was: "[< 100] … [> 2000]".

It is common practice to allow comments towards the end of the questionnaire (Smith, 2005). Hence, a few lines were added under the heading "Comments", immediately after the 2 questions. Altogether, questions and comments were included in the questionnaire as a separate Excel sheet (Appendix 7).

So that information was complete, an initial sheet with a brief introduction to the research project was also added to the questionnaire (Appendix 8). As a result, the template questionnaire was made in the format of a 3-sheet Excel document, including the following: an initial sheet with a brief introduction, 1 table and a final sheet with questions and comments.

In the initial stages of data collection, it was concluded that relevant data on oral compounded medicines was being left out by limiting the request to oral liquids only. In fact, several Portuguese hospitals dispensed only a few oral liquids when compared to other oral dosage forms. This situation was considered likely to occur throughout Europe and, therefore, the aim of the project was revised at this stage.

[15]Closed questions limit the range of responses and, therefore, are preferable in self-completion questionnaires since these questions are easier and quicker to respond (Smith, 2005).

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PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

INDICAÇÕES Por favor preencha a seguinte tabela apenas com os Medicamentos Manipulados ORAIS LÍQUIDOS dispensados pelos Serviços Farmacêuticos no ano de 2006

Substância Activa	Dosagem unidades	Forma Farmacêutica Solução / Emulsão / Suspensão	Volume unidade	Número de vezes dispensado em 2006 Jan	Fev	Mar	Abr	Maio	Jun	Jul	Ago	Set	Out	Nov	Dez	TOTAL
EXEMPLO	Captopril	1mg/mL	Solução	100mL	0	2	5	1	3	5	2	1	2	2	0	1	24
																	0
																	0

Figure 3.1 Country-specific questionnaire (Portugal) (version 1).

Although the inclusion of all oral dosage forms in the research would considerably increase the time and length of the project, it was decided that it would definitely raise the challenge and impact of a Europe-wide comparative study on pharmaceutical compounding.

It was also found that not all hospital pharmacies kept compounding records for each month but, instead, per year. Therefore, the table was modified in order to include just the (total) number of times each compounded medicine was dispensed over the 12-month period. Moreover, the request for all oral liquid compounded medicines was contributing to a generalised delay in the process of data collection, as pharmacists were required to go through all compounding records which, for many pharmacies, corresponded to hundreds of pages of information. In order to optimise this process and to enhance response rates, the request for all oral liquids was substituted by the request for the most frequently dispensed oral compounded medicines. In order to identify and characterise the most frequently dispensed oral compounded medicines per country, it was concluded that data regarding the top 40 (if applicable) oral compounded medicines dispensed should be collected, per selected hospital, as the following: name of the active substance; strength; dosage form; quantity; and number of times dispensed in 2006. Finally, 3 more examples were included in the table, so that other dosage forms were also highlighted (Figure 3.2).

In order to facilitate the process of data collection, the quantities in the examples were now given in intervals and not individual quantities (which was time-consuming for most pharmacies to provide). In addition, a distinction was made with regards to the quantities of oral liquid and oral solid dosage forms. Oral liquids were expected to be reported by number of multidose containers whereas oral solids were expected to be reported by number of packs (of unidose containers) dispensed. For comparative purposes, 1 multidose oral liquid is not equivalent to 1 unidose oral solid and, therefore, it was decided to make this distinction clear. The Excel table (version 2) is shown in Appendix 9 and the main heading in Figure 3.2.

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PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

Por favor preencha a seguinte tabela considerando os MEDICAMENTOS MANIPULADOS ORAIS mais frequentemente dispensados pelos Serviços Farmacêuticos em 2006

	Substância Activa	Dosagem	Forma Farmacêutica	Quantidade	Número de vezes dispensado em 2006
Exemplos	Captopril	1 mg / mL	Solução	50 - 250 mL	75
	Nitrofurantoína	5 mg / mL	Suspensão	100 - 300 mL	67
	Bicarbonato de Sódio	500 mg	Cápsulas	30 - 300 caps	45
	Fenobarbital	7 mg	Papéis medicamentosos	20 - 40 pp	41
1					
2					
3					

Figure 3.2 Country-specific questionnaire (Portugal) (version 2).

At this stage, it was acknowledged that both multidose oral liquids and packs of unidose oral solids do not necessarily correspond to the treatment for 1 single patient. In fact, compounded medicines may be prepared at the hospital pharmacy for a group of patients or even for an entire ward.

With the purpose of estimating the importance of the most frequently dispensed oral compounded medicines in comparison to all oral compounded medicines dispensed by the hospital pharmacy, the following question was added to the questionnaire: 1 - “Please estimate the TOTAL number of ORAL COMPOUNDED MEDICINES dispensed by the hospital pharmacy in 2006.”

Moreover, it was concluded that it would be interesting to find out how many pharmacists and technicians were part of the hospital pharmacy in 2006, so that the size of the pharmacy staff would be compared to the compounding activity in the pharmacy. Therefore a second question was added to the questionnaire, as follows: 2 - “Please indicate the number of PHARMACISTS and the number of TECHNICIANS working in the hospital pharmacy in 2006.”

These 2 questions substituted the previous 2 closed questions in the template questionnaire (version 1). The “Comments” were kept at the end of the research instrument, as shown in Appendix 10. In conclusion, the template questionnaire (version 2) corresponded to a 3-sheet Excel document, including the following: an initial sheet with a brief introduction, one table (optimised) and a final sheet with questions and comments (optimised).

Later in the process of data collection it was considered that if the questionnaire was even more simplified, response rates would probably be maximised. For this reason, the initial sheet with a brief introduction was removed from the Excel document and converted into a separate portable document format (PDF). Consequently, the Portuguese questionnaire resulted in a 2-sheet Excel document, which was complemented with a separate PDF introduction.

Further on the process of data collection (Section 3.3.3), the questionnaire was even more simplified so that non-respondents were encouraged to

collaborate by providing key data. Hence, email reminders were sent to the majority of the hospitals including just the table.

At this stage, it was decided that the introduction was not essential since all hospital pharmacists had been explained the project by telephone. Moreover, although it would be interesting to estimate the size of the pharmacy staff, this information was not essential to the aim of the project and, therefore, it was excluded from the research. Finally, in the course of data collection, it was concluded that hospital pharmacies not always had the 2006 (specifically) data available.

Moreover, because data collection was undertaken for more than 1 year, it was decided that the questionnaire should address the previous year, instead of 2006, so that the latest available data were collected. Hospital pharmacists were then requested to provide data for the previous year or, alternatively, the latest available year at the pharmacy. For comparative purposes, it was concluded that it would be more relevant to compare the latest available data than data regarding one specific year, as there were no relevant changes in the practice of pharmaceutical compounding for the years included in the research.

3.3.2 **Purposive sample of hospitals**

The purposive sample of Portuguese hospitals was established considering the complete list of hospitals that had contacted CETMED from 1999 to 2005 (Section 3.1.1). Therefore, it was postulated that the hospital pharmacies that prepared and dispensed compounded medicines in Portugal would have contacted CETMED for its consultancy services at least once during its period of activity (1999-2005). The complete list of hospitals was provided by Carlos Maurício Barbosa and included a total of 60 Portuguese hospitals, distributed throughout the mainland and archipelagos, including the cities of: *Almada*, *Amadora, Barcelos, Barreiro, Beja, Braga, Bragança*, *Chaves, Coimbra, Faro, Figueira da Foz, Funchal, Guarda, Guimarães, Horta, Lamego, Leiria,* Lisbon (capital)*, Oeiras, Ovar, Penafiel, Porto, Santarém, Santa Maria da Feira, Santo Tirso, São João da Madeira, Setúbal, Tomar, Torres Vedras, Trofa, Viana do Castelo, Vila Nova de Famalicão, Vila Nova*

de Gaia, Vila Real and *Viseu.* A total of 14 hospitals were from Lisbon and 9 hospitals from *Porto*. Figure 3.3 displays the purposive sample of hospitals in the mainland only as the 2 archipelagos are not included in the map. The purposive sample of hospitals was concentrated on the coast, including Lisbon and *Porto*, which reflects the heterogeneous distribution of the population across the country (INE, 2009).

Figure 3.3 Map of Portugal (mainland) adapted from National Geographic Society (1998a); indicating the location of the purposive sample of hospitals (●).

3.3.3 **Data collection**

The purposive sample in Portugal was provided as a list of 60 hospitals including only the name of the hospitals. Because the contact details of the chief pharmacists were not available at the hospital's websites and none of the pharmaceutical bodies in Portugal were willing to share any of their details (not even their names), the telephone number of each hospital was searched online and each hospital pharmacy was contacted by telephone by MC. The individual discussions with hospital pharmacists were important for a personalised explanation of the research project and encouragement for collaboration. If pharmacists were willing to collaborate with data, their email addresses were requested at this stage so that they would receive the questionnaire attached to a brief introductory email. Only 1 hospital

pharmacist requested the questionnaire to be sent by post instead of email. Non-respondents were sent periodical email reminders, which were interspersed with telephone reminders, throughout the years of 2007, 2008 and beginning of 2009. Persistent non-respondents who seemed available for a visit were suggested that data collection would be undertaken by MC directly at their pharmacies. A total of 5 Portuguese hospitals accepted the suggestion and data were collected during the hospitals visits: 1 hospital was visited in 2008 and 3 hospitals were visited in 2009 (at the very last stage of data collection in Portugal). In total, the research project in Portugal included the visit to 8 hospitals across the country and throughout the years of 2007, 2008 and 2009. The hospital visits and the persistent email and telephone reminders were essential for a good response rate from such a large purposive sample of hospitals.

3.4 **Results and discussion**

In Portugal, 60 hospitals were contacted to participate in the research project and a response rate of 93% was obtained. Out of the 56 respondents, 39 hospitals contributed with data regarding the oral compounded medicines most frequently dispensed by their pharmacies and 17 hospitals were non-participants (Figure 3.4). Out of the 39 participant hospitals, almost 80% provided quantitative and complete datasets. All other replies were distributed as follows: 3 hospitals provided quantitative but incomplete datasets; 2 hospitals provided semi-quantitative data; and, finally, 3 hospitals provided qualitative data only. The main reasons stated by these hospitals for not sharing complete datasets were that data was not readily accessible and that no records were kept with regards to specific data.

Over 50% of the participant hospitals submitted data in the questionnaire provided. The majority of the questionnaires were received by email and only 1 questionnaire was received by post and another one by fax; 3 additional hospitals provided the required data by telephone. The participant hospitals shared data regarding different years which, in most cases, corresponded to the latest available year at the pharmacy, namely: 2006 (53%); 2007 (31%); 2008 (14%); 2006 and 2007 (2 hospitals); and, finally, 2005 (1 hospital).

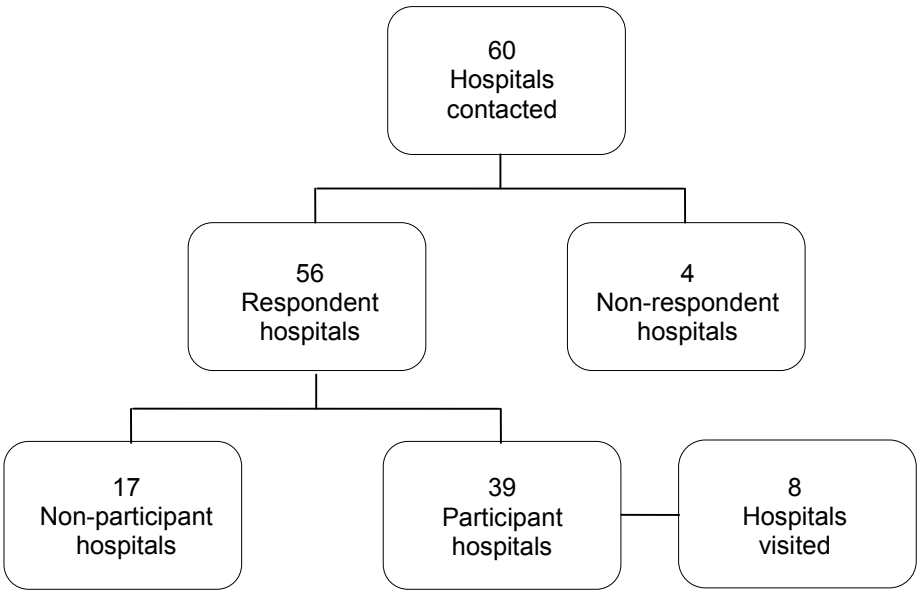


Figure 3.4 Purposive sample showing respondent, participant and visited hospitals.

The reasons stated by hospital pharmacies for not providing data were: 47% (n=8) of the non-participants did not dispense oral compounded medicines, in particular; 3 hospitals did not keep records of the compounded medicines dispensed; 2 hospitals did not dispense any compounded medicines at all (oral/non-oral); 1 hospital dispensed only a few compounded medicines; 1 hospital dispensed oral compounded medicines but data was not readily accessible; 1 hospital dispensed oral compounded medicines but data was considered confidential. Only 1 hospital did not provide any reason for not participating in the research.

Contacting such a large purposive sample of hospitals was a complex and time-consuming process, particularly because hospital pharmacists in Portugal were not readily accessible even by telephone. In most cases, more than 1 telephone call to the hospital pharmacy was necessary to reach the chief pharmacist or the person responsible for the pharmaceutical compounding department. Moreover, several pharmacists required an authorisation from the board of directors of the hospital prior to sharing any data, which complicated the process of data collection even more. A total of 189 telephone calls were made to Portuguese hospital pharmacies (mean >3 telephone calls per hospital) and a total of 127 emails were sent with requests for collaboration. During the telephone discussions, 29% of

respondents stated that they requested compounded medicines from other hospitals and/or community pharmacies, mainly because their facilities did not meet the minimum requirements for the preparation of certain compounded medicines, and/or they did not have enough staff for a pharmaceutical compounding department. Only 1 hospital pharmacy stated that they prepared compounded medicines for other hospitals. An example of a prescription for a compounded medicine request to a community pharmacy by a Portuguese hospital is show in Figure 1.2.

3.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral compounded medicines in Portugal is shown in Table 3.1. All active substances reported were included in *Martindale 35* (2007) and these were grouped according to the respective therapeutic classification, giving a total of 175 different active substances and 33 therapeutic groups. Cardiovascular drugs was the group with the greatest number of different active substances (n=26), followed by nutritional agents and vitamins (n=24) and antibacterials (n=16). Although these active substances were all reported as oral compounded medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: dermatological drugs and sunscreens (Appendix 11); disinfectants and preservatives (Appendix 12); paraffins and similar bases (Appendix 13); stabilising and suspending agents (Appendix 14); and supplementary drugs and other substances (Appendix 15). The active substances included in these groups were described in the respective appendixes.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 8 NTI drugs were reported and these are underlined in Table 3.1.

The active substances dispensed by most hospitals were: captopril and trimethoprim (n>25); ranitidine (n=21-25); chloral hydrate, furosemide, nystatin and spironolactone (n=16-20); aspirin, caffeine citrate, folic acid, hydrochlorothiazide, hydrocortisone, iodine and potassium iodide (Lugol's Solution, see below), magnesium sulfate, omeprazole, phenobarbital, propranolol HCl, pyrazinamide and ursodeoxycholic acid (n=10-15).

Table 3.1 Active substances most frequently dispensed as oral compounded medicines in Portugal (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aminophenazone, aspirin, codeine, indometacin, methadone HCl, morphine, morphine HCl, morphine sulfate, sodium salicylate

Antibacterials
Amoxicillin, cefuroxime, chloramphenicol, ciprofloxacin, clindamycin, doxycycline, ethambutol HCl, isoniazid, neomycin, nitrofurantoin, pyrazinamide, rifampicin, spiramycin, sulfadiazine, trimethoprim, vancomycin

Antidepressants
Fluoxetine HCl

Antiepileptics
Gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, primidone, stiripentol, topiramate, vigabatrin

Antifungals
Amphotericin B, nystatin, terbinafine, voriconazole

Antigout drugs
Allopurinol

Antimalarials
Hydroxychloroquine sulfate, mefloquine HCl, pyrimethamine, quinine

Antimyasthenics
Pyridostigmine bromide

Antiparkinsonian drugs
Carbidopa, levodopa, selegiline HCl, trihexyphenidyl HCl

Antiprotozoals
Metronidazole, metronidazole benzoate

Antivirals
Aciclovir, didanosine, ganciclovir, tenofovir, valganciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Chloral hydrate, cyamemazine, midazolam, risperidone

Bronchodilators and anti-asthma drugs
Aminophylline, caffeine, caffeine citrate

Cardiovascular drugs
Acenocoumarol, amiloride HCl, amiodarone, amlodipine besilate, bosentan, captopril, clonidine, colestyramine, diazoxide, digoxin, dipyridamole, enalapril, flecainide acetate, furosemide, hydrochlorothiazide, losartan potassium, metolazone, metoprolol, minoxidil, nifedipine, pravastatin sodium, propranolol HCl, ramipril, simvastatin, spironolactone, warfarin sodium

Contrast media
Barium sulfate

Corticosteroids
Dexamethasone, fludrocortisone acetate, hydrocortisone, prednisolone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Acetylcysteine

Dermatological drugs and sunscreens
Salicylic acid, urea

Disinfectants and preservatives
Chlorhexidine, sodium benzoate

Electrolytes
Calcium chloride, magnesium sulfate, potassium chloride, potassium sodium hydrogen citrate, sodium bicarbonate, sodium chloride, sodium citrate, sodium phosphate

GI drugs
Calcium carbonate, ispaghula, omeprazole, pantoprazole, ranitidine, senna, sodium sulfate, sucralfate, sulfasalazine

General anaesthetics
Ketamine HCl

Immunosuppressants
Tacrolimus

Local anaesthetics
Cocaine, lidocaine, tetracaine

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide

Muscle relaxants
Baclofen

Nutritional agents and vitamins
Arginine, arginine HCl, ascorbic acid, biotin, calcium folinate, folic acid, folinic acid, glucose, isoleucine, lactose, leucine, medium-chain triglycerides, pyridoxine HCl, riboflavin, sodium fluoride, sorbitol, sucrose, thiamine, tocopherol, valine, vitamin A, vitamin E, zinc acetate, zinc sulfate

Paraffins and similar bases
Cholesterol

Prostaglandins
Misoprostol

Stabilising and suspending agents
Carmellose, ceratonia, methylcellulose

Supplementary drugs and other substances
Betaine, borax, boric acid, citric acid, creatine, fluorescein, glycerol, indigo carmine, methacholine chloride, miglustat, pancreatin, strychnine nitrate, ubidecarenone, ursodeoxycholic acid, xylose

Thyroid and antithyroid drugs
Iodine, levothyroxine sodium, potassium iodide, potassium perchlorate, sodium perchlorate

Urological drugs
Oxybutynin, sildenafil citrate

The compounded medicines reported included just 1 active substance (single-drug) in most cases, or a maximum of 2 active substances in combination (excluding the oromucosal preparations for CIOM, Section 3.4.4). The active substances reported in combination (multi-drug) were the following:

- Oral liquids: ceratonia and sorbitol; hydrochlorothiazide and spironolactone; iodine and potassium iodide (Lugol's Solution, see below); levodopa and carbidopa; and sodium citrate and citric acid (Shohl's Solution, see below).
- Oral powders: hydrochlorothiazide and amiloride HCl; hydrochlorothiazide and spironolactone; and ispaghula and senna (Agiolax, see below).

Apart from compounded medicines including active substances, 1 hospital also reported placebo capsules, in a total of 1,400 units.

Compounded medicines were also reported by the given titles (non-proprietary names) which they are commonly known for, as follows: Lugol's Solution (10 hospitals); Shohl's Solution (2 hospitals); and *Poção de Todd* (1 hospital). These 3 compounded medicines correspond to oral liquids and were dispensed in a total of 585 multidose containers. A formulary for the compounded medicines reported by given title is shown in Appendix 16.

The compounded medicines dispensed were reported either by the respective active substance(s), their given titles or by the proprietary medicines used in their preparation.

In total, 10 proprietary medicines were reported by 4 hospitals, namely: Fungizone (amphotericin B); Lasix (furosemide) and Mycostatin (nystatin), as almost 300 multidose oral liquids; Agiolax (ispaghula and senna), Aptamil (infant feed), Eoprotin (infant feed), Protifar (nutritional protein supplement), Renilon (preparation for enteral nutrition), Resical (cation-exchange resin) and Uralyt-U (potassium sodium hydrogen citrate), as over 2,000 unidose oral powders. Although Resical was reported by only 1 hospital, it is likely that more hospitals might have used this proprietary medicine since a total of 3 hospitals reported “cation-exchange resin” as part of the oral compounded medicines dispensed. Furthermore, other proprietary medicines might have been used in the preparation of the compounded medicines reported. However, this information is rarely part of the registry details of the compounded medicines dispensed and, therefore, it is not readily accessible by the majority of the hospital pharmacies.

In addition, 3 hospitals reported nutritional supplements as part of the oral compounded medicines most frequently dispensed by their pharmacies. Although the exact composition of the supplements was rarely detailed, the majority of these were either glucose or protein-based. All nutritional supplements were dispensed as sachets (oral powders), in a sum of almost 4,000 units. Two active substances reported were not permitted legally in pharmaceutical compounding in Portugal, namely: levothyroxine sodium (2 hospitals) and fluoxetine HCl (1 hospital). Although not allowed, there may be a therapeutic need for compounded medicines including the active substances considered in the Portuguese negative list (Section 3.1). As a result, it is not surprising that Portuguese pharmacists use “forbidden” active substances in pharmaceutical compounding since, in these situations, compounded medicines may be the only therapeutic option available.

The active substances were dispensed as oral solid dosage forms, oral liquid dosage forms and/or oromucosal preparations. These are discussed separately below.

3.4.2 **Oral solids**

Oral solid dosage forms were reported by 87% (n=34) of participant hospitals and included oral powders (33 hospitals) and capsules (8 hospitals). In total, 29 hospitals shared complete information with regards to the oral solids dispensed, whereas 3 hospitals disclosed only qualitative information and 2 hospitals were not able to provide any information since they did not keep the records of the oral solids dispensed; qualitative data was processed and analysed accordingly (Section 2.4). The quantities of oral solids were provided as the number of packs and/or the number of individual units dispensed, which are shown separately below (Figure 3.5). A total of 16 hospitals provided both figures whereas 7 hospitals provided the number of packs and 6 hospitals provided the number of individual units only.

Oral powders were dispensed in larger quantities than capsules both in number of packs and in number of units dispensed. A total of 3,900 packs (99.5%) and 50,917 units (72.9%) of oral powders were reported but these figures are not directly comparable as 5 hospitals did not provide the number of packs and 7 hospitals did not provide the number of units of oral powders dispensed. Hence, both figures are considered together for analysis.

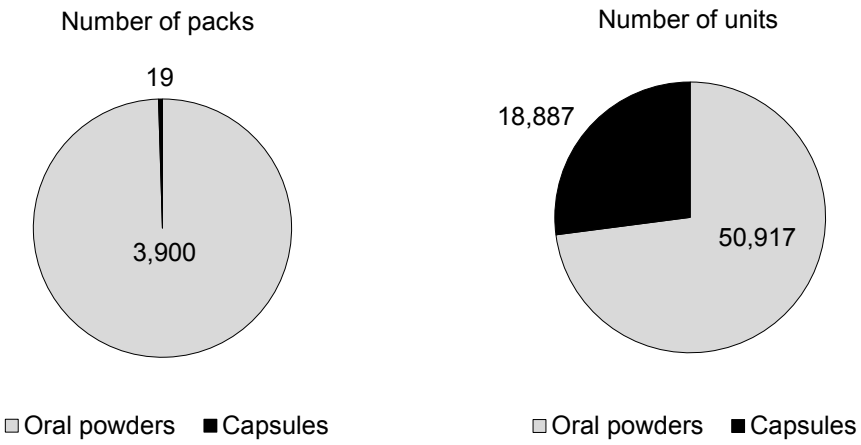
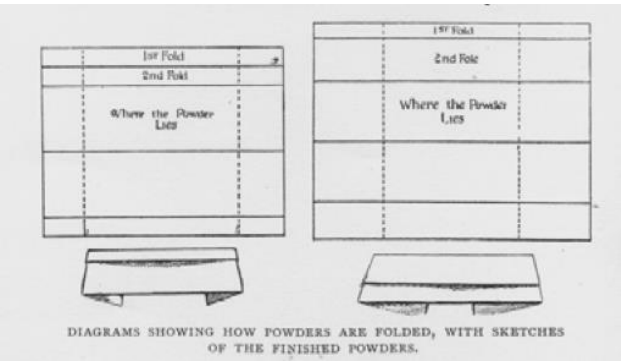


Figure 3.5 Oral solids dispensed per number of packs and number of individual units.

A total of 19 packs and 18,887 units of capsules were reported but, again, these figures are not directly comparable as, although all hospitals provided the number of units dispensed, 4 hospitals did not provide the number of

packs dispensed. For this reason, the number of units of capsules dispensed is considered individually for analysis.

Oral powders were reported mainly as sachets (Figure 3.6) and only a few were dispensed in envelopes and flasks. These 2 containers (envelopes and flasks) are usually reserved for larger quantities of powders.



DIAGRAMS SHOWING HOW POWDERS ARE FOLDED, WITH SKETCHES OF THE FINISHED POWDERS.

Figure 3.6 Individual powders folded in sachets (adapted from RPS, 2002b).

The top 15 active substances dispensed as oral powders are listed in Figure 3.7. This list includes the top 10 active substances ranked by number of packs and also the top 10 active substances ranked by number of individual units. A total of 5 active substances are common to both rankings, namely: magnesium sulfate, sodium chloride, calcium carbonate, phenobarbital and folic acid. Magnesium sulfate (30 mg - 40 g) was dispensed as oral powders by 13 hospitals, in a sum of 343 packs and 4,893 units. The pack sizes varied from 1 to 53 sachets and the quantity dispensed by most hospitals was 30 g. Oral doses of 5 g to 10 g of magnesium sulfate in 250 mL of water are given for rapid bowel evacuation (*Martindale 35*, 2007) and, therefore, it is likely that the 30 g corresponded to powders for oral liquids[16]. Phenobarbital was the second most frequently dispensed active substance, by number of packs (n=276), and it was reported in 18 different strengths (1.25-50 mg) by a total of 10 hospitals. Sodium chloride, on the other hand, was dispensed by only 2 hospitals, in strengths of 1 g, 1.5 g, 3 g and 5 g, in a sum of 236 packs and 4,349 units.

[16]Powders (and granules) for oral solutions and suspensions, which were abbreviated to powders for oral liquids, generally conform to the definition of oral powders (Section 2.1.3).

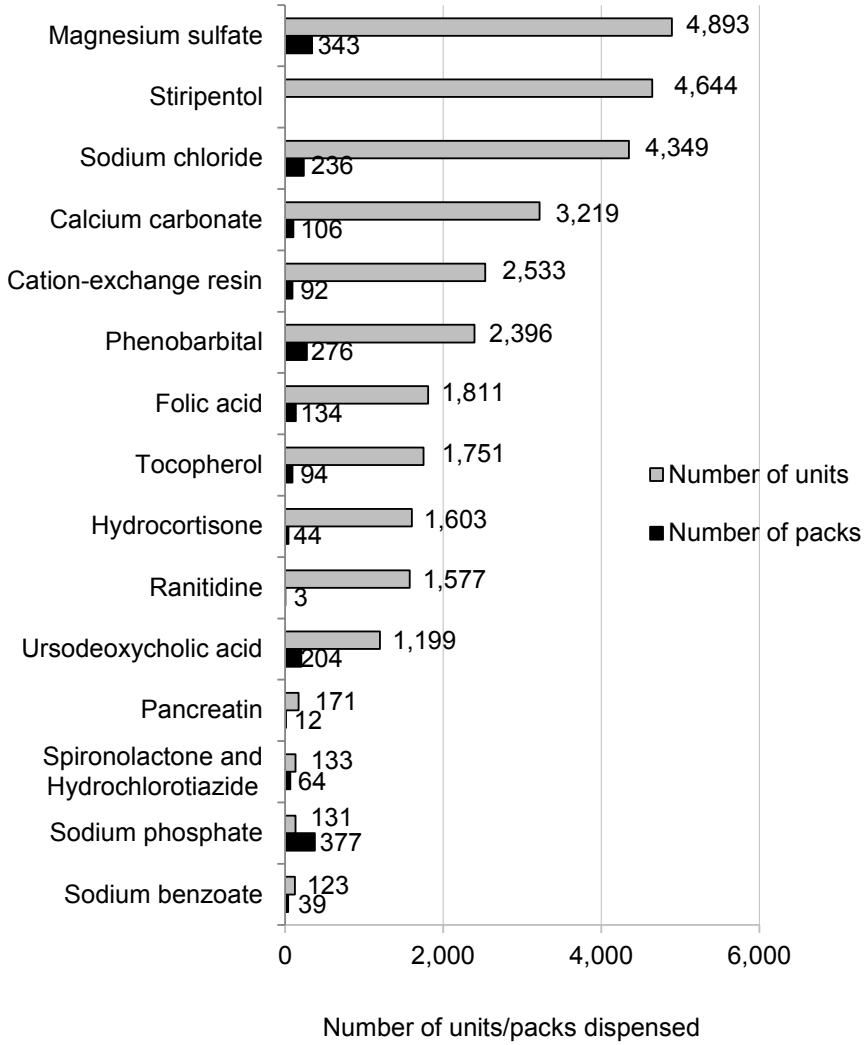


Figure 3.7 Top 15 active substances dispensed as oral powders per number of units/packs.

The pack size of oral powders varied within hospitals and active substances but it is possible to estimate an average pack size by considering the 16 hospitals that provided both number of packs and number of individual units. According to these data, an average of 13 oral powders (sachets) per pack were dispensed by the participant hospitals, which was adopted for the purposes of overall data comparison. This figure indicates that, in general, oral powders are prepared in Portuguese hospitals for individual patients, which also explains the wide range of strengths reported for the majority of the active substances dispensed as oral powders. The most frequent therapeutic groups were “electrolytes” and “nutritional agents and vitamins”. The therapeutic group represented by more active substances was

cardiovascular drugs, which included 23 active substances dispensed as oral powders.

Capsules were dispensed in Portugal by only 21% (n=8) of the participant hospitals and only 10 different active substances were reported (Figure 3.8). Zinc sulfate was the most frequently dispensed active substance, reported in 3 strengths (220 mg, 250 mg and 300 mg) by a total of 4 hospitals; 3 hospitals provided the quantities dispensed by number of units only, whereas 1 hospital provided both quantities, as follows: 5 packs of 300 capsules of zinc sulfate each, corresponding to a total of 1,500 units dispensed.

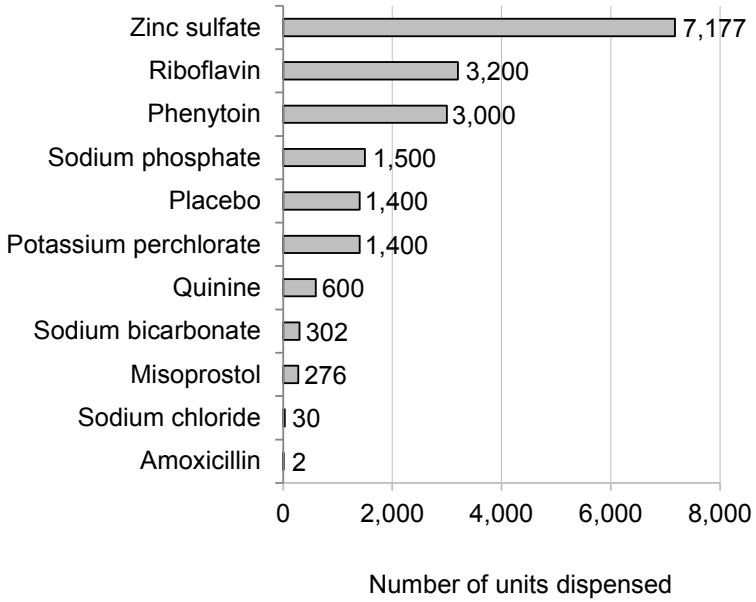


Figure 3.8 Active substances dispensed as capsules, per number of units.

The pack sizes varied greatly within hospitals and active substances. For instance, phenytoin was dispensed in one pack of 3,000 units whereas sodium chloride was dispensed in packs of 30 units (Figure 3.8). These figures indicate that capsules are prepared by hospital pharmacies in Portugal either as a batch (for stock or to be dispensed to the wards) or individually (to be dispensed directly to patients).

Placebo was also reported as capsules (Section 3.3.1). The most frequent therapeutic group was nutritional agents and vitamins and included zinc sulfate and riboflavin. The therapeutic group represented by more active

substances was electrolytes and included sodium phosphate, sodium bicarbonate and sodium chloride.

One of the hospitals visited stated that they prepared capsules instead of sachets because capsules were less time-consuming to prepare, considering that manual (or semi-automatic) capsule machines enable the preparation of 50-100 (maximum 300) units of capsules at a time (Section 2.1.3). Nevertheless, capsules had to be opened before administration to paediatric patients and their contents added to liquids or food.

3.4.3 **Oral liquids**

Oral liquid dosage forms were reported by all participant hospitals and included solutions (54%), suspensions (31%) and syrups[17] (9.3%). It is likely that the classification of some oral liquids by the hospital pharmacies was not accurate and, therefore, some solutions may have corresponded to suspensions/syrups (and vice-versa). Only 6% of the oral liquid dosage forms dispensed were classified simply as oral liquids (Figure 3.9). None of the hospitals reported unidose containers and it was assumed that all oral liquids dispensed were, indeed, multidose. The volumes dispensed ranged from 10 mL to 5,100 mL, per individual container. All hospitals reported the volumes dispensed per container, with the exception of 1 hospital that reported total volumes instead.

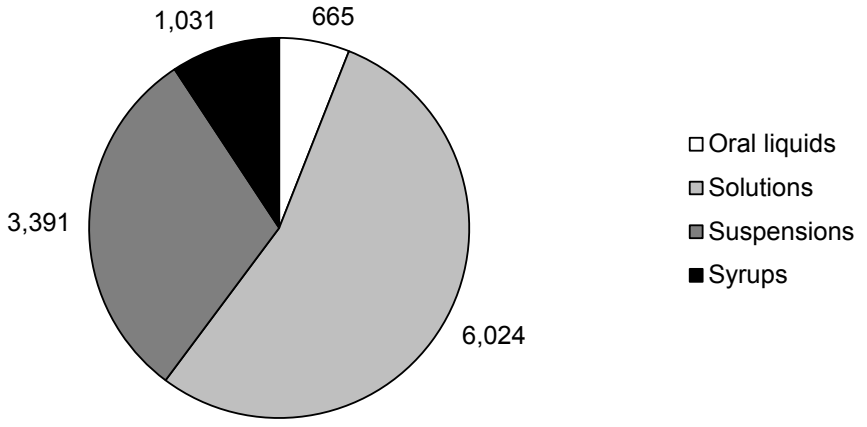


Figure 3.9 Oral liquid dosage forms dispensed, per dosage form.

[17]Syrups are aqueous preparations characterised by a sweet taste and viscous consistency. These may contain sucrose at a concentration of at least 45% (*m/m*) but the sweet taste may also be obtained by using other polyols or sweetening agents (EDQM, 2007).

Almost 14,000 units of oral liquids were reported. Some may have corresponded, instead, to mouthwashes for radiotherapy and chemotherapy patients (Section 3.4.4). If these mouthwashes were excluded, the oral liquids dispensed were slightly greater than 11,000 units. All volumes dispensed over 2,000 mL corresponded to the mouthwashes for radiotherapy and chemotherapy patients. It may then be concluded that these mouthwashes were prepared in large scale to be dispensed to the wards and not directly to individual patients.

Oral liquids, solutions and suspensions were dispensed in a sum of 10,080 units (90.7%) (excluding the mouthwashes) (Figure 3.9) and by 92% of the hospitals. The top 10 active substances dispensed were: morphine, trimethoprim, captopril, ranitidine and chloral hydrate (shown in Table 3.2.); sucrose, codeine, furosemide, sodium bicarbonate and omeprazole.

Morphine was the most frequently dispensed active substance and it was reported by 5 hospitals in a sum of 1,186 units of 50 mL to 2,000 mL. The wide range of volumes dispensed indicated that morphine was prepared both in large scale to be dispensed to the wards and also in small scale to be dispensed directly to individual patients. This active substance was reported as morphine and morphine HCl, in 6 different strengths, from 0.2 mg/mL to 20 mg/mL. The most frequently dispensed strengths were 10 mg/mL and 20 mg/mL.

Table 3.2 Oral liquids most frequently dispensed in Portugal.

Active substances	Number of strengths (most frequent)	Range of volumes	Number of hospitals	Number of units dispensed
Morphine	6 (10 and 20 mg/mL)	50-2,000 mL	5	1,186
Trimethoprim	3 (10 mg/mL)	10-250 mL	18	1,055
Captopril	4 (1 mg/mL)	25-500 mL	24	622
Ranitidine	5 (15 and 2.5 mg/mL)	10-360 mL	20	562
Chloral hydrate	4 (50 and 100 mg/mL)	20-500 mL	10	498

The next most frequently dispensed active substances were: trimethoprim, captopril, ranitidine and chloral hydrate. All these active substances have a monograph for an oral liquid compounded medicine in the FGP, either the FGP 2005 (CETMED) or the FGP 2007 (LEF) (Section 3.2.2). The most standardised active substance was trimethoprim that, although reported by 18 hospitals, was dispensed only in 3 different strengths and in the volumes of just 10 mL to 250 mL. An example of a Portuguese prescription for trimethoprim 1% is shown in Figure 1.2. The most frequent strength was 10 mg/mL, which corresponds to the strength indicated in the FGP monograph. Captopril was the active substance dispensed by most hospitals and, although dispensed in 4 different strengths, the 1 mg/mL corresponded to 99% of all strengths dispensed, which is also the strength indicated in the FGP monograph. As a whole, the most frequent strengths of the oral liquid compounded medicines dispensed were those indicated in the respective monographs of the FGP, which suggests that an official national formulary was a key contribute to the standardisation of pharmaceutical compounding nation-wide.

The active substances dispensed as oral liquids, solutions and suspensions were classified with reference to *Martindale 35* (2007) (Figure 3.10) and the most frequent therapeutic groups were: cardiovascular drugs, which included 2 of the top 10 active substances (captopril and furosemide); analgesics, anti-inflammatory drugs and antipyretics, which also included 2 of the top 10 active substances (morphine and codeine); and antibacterials, which included trimethoprim, the second most frequently dispensed active substance.

The top 3 therapeutic groups represented 51% of all oral liquids, solutions and suspensions dispensed and the top 10 active substances accounted for almost 60% of these, which indicates the focused nature of pharmaceutical compounding in Portugal.

Syrups corresponded to only 9.3% of all oral liquids dispensed (Figure 3.9) and were reported by a total of 20 hospitals. As mentioned before, it is likely that the classification of some oral liquids was not accurate and, therefore, part of the solutions/suspensions might have corresponded to syrups (and

vice-versa) (Section 2.1.3). In any case, syrups were dispensed in much lesser quantities than the solutions or suspensions, as shown in Figure 3.9.

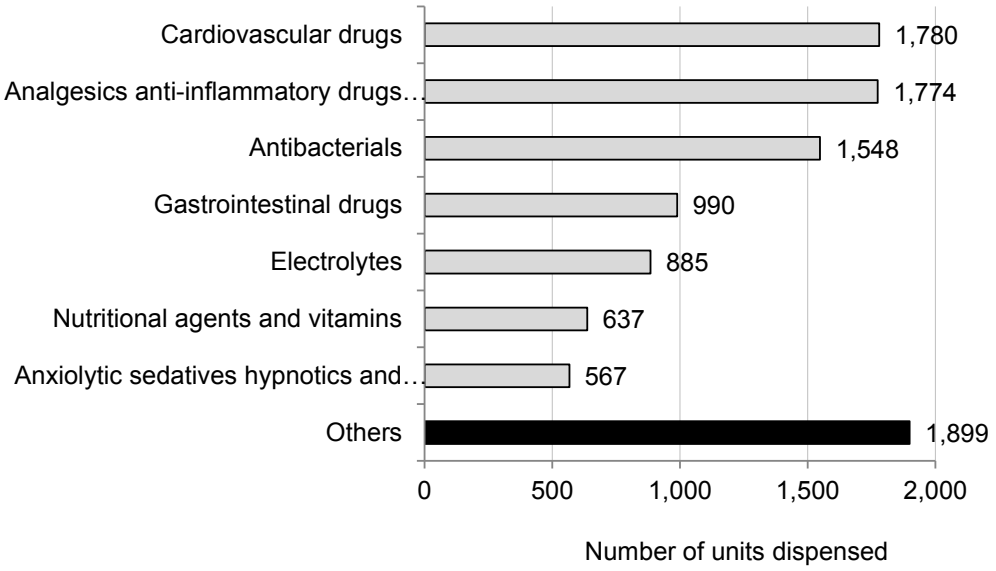


Figure 3.10 Oral liquids, solutions and suspensions, per number of units and by therapeutic groups.

The top 10 active substances dispensed as syrups were: chloral hydrate, trimethoprim, caffeine citrate, furosemide, sucrose, captopril, spironolactone, omeprazole, propranolol HCl and ranitidine. When compared to the top 10 of oral liquids, solutions and suspensions (mentioned above), only the following 3 active substances were not included: caffeine citrate, which was reported by 6 hospitals in the strengths of 2% and 1.5 mg/mL (30-100 mL); spironolactone, which was reported by only 2 hospitals, in the strengths of 2.5 mg/mL and 0.2% (50 mL and 60 mL); and propranolol HCl, which was reported by only 1 hospital and in the single strength of 1 mg/mL (80-320 mL).

The most frequently dispensed syrups were chloral hydrate (40-200 mg/mL; 9 hospitals; 392 units) and trimethoprim (10 mg/mL; 8 hospitals; 208 units), which accounted for 58% of all syrups dispensed by the participant hospitals. When the oral liquid dosage forms are considered altogether, the top 5 active substances were: trimethoprim (1,263 units), morphine (1,206 units), chloral hydrate (890 units), captopril (665 units) and ranitidine (585 units).

Considering just the oral compounded medicines, liquid dosage forms (syrups, solutions and suspensions, excluding the mouthwashes) were dispensed in a total sum of 11,111 multidose containers and solid dosage forms (oral powders and capsules) were dispensed in a total sum of 69,804 individual units. However, the number of units dispensed for the oral powders is not complete since a total of 12 additional hospitals dispensed oral powders but did not share the number of individual units dispensed. Therefore, the total sum of oral powders dispensed is much higher than 69,804 units. It is not possible to accurately determine the ratio of oral solid dosage forms vs (versus) oral liquid dosage forms but it is likely that oral solids were more frequently dispensed than oral liquids. Nevertheless, more hospitals reported dispensing oral liquid dosage forms (n=39) than solid dosage forms (n=34) and only 2 hospitals reported all dosage forms (oromucosal preparations, syrups, solutions, suspensions, oral powders and capsules). These findings are in accordance with Rosa *et al.* (2006) who stated that is common practice to prepare both sachets and oral liquids in hospital pharmacy. According to Barros and Almeida (2008), oral powders (sachets) were the most frequently dispensed dosage form in a sample of 6 Portuguese hospitals. However, this study was undertaken in 2004, before the publication of the FGP 2005 (CETMED) / FGP 2007 (LEF), which contributed to a change of practices in pharmaceutical compounding in Portugal, as the conversion of many sachets into liquid dosage forms. The most frequently dispensed active substances identified by the authors - folic acid, ursodeoxycholic acid and phenobarbital (oral powders) - are included in the top 15 listed in Figure 3.7, and two of their most frequently dispensed oral liquids - trimethoprim and chloral hydrate - are also part of the top 10 listed above. Cardiovascular drugs, the most frequent therapeutic group identified by the authors, was also the most frequent group with regards to oral liquids, solutions and suspensions. Although the size of the studies is very different, this comparison shows that the oral compounded medicines dispensed in Portugal changed only slightly from 2004 to 2008.

3.4.4 **Oromucosal preparations**

Although the aim of the research was to identify and characterise the most frequently dispensed oral compounded medicines, some hospital pharmacies also shared data regarding oromucosal preparations. These medicines were either specifically classified by the hospital pharmacies as oromucosal or, alternatively, the additional comments relating to their use clearly suggested that these were not oral compounded medicines per se but instead oromucosal preparations.

Oromucosal preparations are solid, semi-solid or liquid preparations containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect. Several categories of oromucosal preparations may be distinguished as, for example: mouthwashes; oromucosal solutions and oromucosal suspensions; semi-solid oromucosal preparations (e.g. oromucosal gel, oromucosal paste); and gargles. For many oromucosal preparations, it is likely that some proportion of the active substance(s) is swallowed and absorbed in the GI tract (EDQM, 2007). The distinction between oral and oromucosal compounded medicines is not always clear and, therefore, it was decided to include the oromucosal preparations reported by the hospital pharmacies for data processing and analysis. At this stage, oromucosal preparations were then removed from the exclusion criteria of the research (Section 2.4.1).

A total of 11 hospitals reported oromucosal preparations as part of the oral compounded medicines most frequently dispensed by their pharmacies, which represented 28% of all participant hospitals. However, more Portuguese hospitals might have dispensed oromucosal preparations but excluded this information from the dataset since the request for data specifically referred oral compounded medicines only. The most frequently dispensed oromucosal preparation was a mouthwash[18] for aphthous ulcers (mucositis) in patients undergoing radiotherapy and chemotherapy, commonly known as chemo-induced oral mucositis (CIOM) (Chan and Ignoffo, 2005; McElhiney, 2011). The composition of this mouthwash varied

[18]Mouthwashes are aqueous solutions intended for use in contact with the mucous membrane of the oral cavity and are not meant to be swallowed (EDQM, 2007).

slightly within hospitals and it corresponded to a sodium bicarbonate solution (in most cases) including one or more of the following active substances: amphotericin B and nystatin (antifungals); aciclovir (antivirals); chlorhexidine (disinfectants and preservatives) and lidocaine (local anaesthetics). More than 16,000 multidose containers of this mouthwash were reported as oromucosal preparations, in volumes of 50 mL to 560 mL. Furthermore, similar combinations of the active substances identified above were reported as oral liquids by 10 additional Portuguese hospitals and it is likely that these oral liquids corresponded, instead, to the mouthwashes for CIOM. Altogether, the oromucosal preparations and oral liquids including the active substances mentioned above were dispensed in a sum of over 19,000 multidose containers. Apart from these mouthwashes, two additional oromucosal preparations were reported by the participant hospitals, namely: sodium fluoride gel[19] (20 g) in a total of 156 units (1 hospital); and artificial saliva[20] (100-1,000 mL) in a total of 602 units (4 hospitals).

Although oromucosal preparations were not part of the aim of the research, Portuguese hospitals reported more oromucosal preparations than oral compounded medicines. The most frequently dispensed compounded medicines were, indeed, mouthwashes for CIOM, which is consistent with the fact that cancer is one of the major causes of discharge from all Portuguese hospitals (including through death) (Figure 3.11).

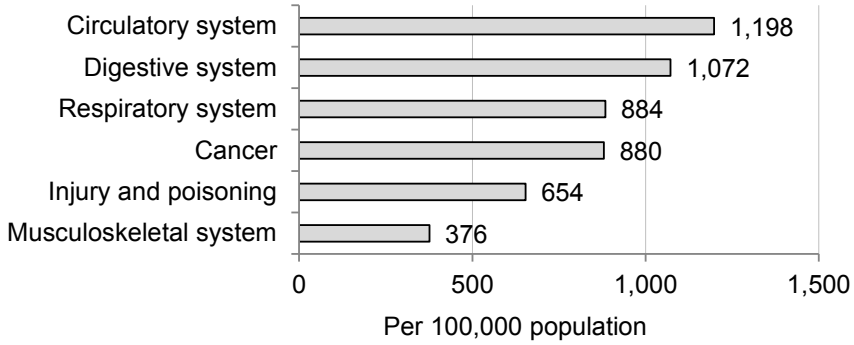


Figure 3.11 Number of patients per 100,000 population discharged from all hospitals (including through death) in Portugal during 2006 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

[19]Semi-solid oromucosal preparations are hydrophilic gels or pastes intended for administration to the oral cavity or to a specific part of the oral cavity (EDQM, 2007).
[20]Oromucosal solutions and oromucosal suspensions are liquid preparations intended for administration to the oral cavity by means of a suitable applicator (EDQM, 2007).

3.5 **Summary**

- The foundation of CETMED, the development of the FGP and the approval of up-to-date legislation contributed to the modernisation of compounding practices in Portugal.
- A purposive sample of 60 hospitals was included in the research (8 hospitals were visited) and a response rate of 93% was obtained. A total of 175 different active substances (including 8 NTI drugs) were reported corresponding to 33 different therapeutic groups. The top 3 therapeutic groups were: cardiovascular drugs (n=26), nutritional agents and vitamins (n=24) and antibacterials (n=16). Placebo was dispensed in a total sum of 1,400 units of capsules (n=1).
- Oral solid dosage forms were reported by 87% of all participant hospitals and included oral powders and capsules. Oral powders (mainly sachets) were dispensed in a total sum of 3,900 packs (99.5%) and 50,917 units (72.9%) and the top 5 active substances common to both rankings were: magnesium sulfate, sodium chloride, calcium carbonate, phenobarbital and folic acid. Capsules were dispensed in a total sum of 19 packs and 18,887 units and the top 5 active substances were: zinc sulfate, riboflavin, phenytoin, sodium phosphate and potassium perchlorate.
- Oral liquid dosage forms were reported by all participant hospitals and included solutions, suspensions and syrups. Oral liquids (excluding mouthwashes) were dispensed in a total sum of 11,111 containers and the top 5 active substances were: trimethoprim, morphine, chloral hydrate, captopril and ranitidine. Oral liquids, solutions and suspensions were dispensed in a total of 10,080 multidose containers (90.7%) whereas syrups were dispensed in a total of 1,031 multidose containers (9.3%). It is likely that oral solids were more frequently dispensed than oral liquids.
- Oromucosal preparations were reported by 28% of hospitals but over 19,000 multidose containers were dispensed, particularly mouthwashes for CIOM, which represented the most frequently dispensed compounded medicines in Portugal.

4. **Compounding in the UK**

The United Kingdom of Great Britain and Northern Ireland (UK) joined the EU in 1973 and its official language is English (*Europa*, 2009). The UK is an archipelago located in the North Atlantic Ocean that is linked to continental Europe by the channel tunnel. The UK comprises Great Britain (England, Scotland and Wales) and Northern Ireland (Carr, 2011). It is the third most populated country in the EU, with a population of 60.9 million in 2007 (Figure 2.2), but is physically only the 8th largest EU country, occupying a surface area of 243,800 Km^2 (*Europa*, 2008).

In 2007, there were 2,312 hospitals in the UK (ratio of 3.79 hospitals per 100,000 population) and a total of 167,019 hospital beds (ratio of 370 hospital beds per 100,000 population) (HOPE, 2009). Since the European health for all database (HFA-DB) does not include up-to-date information regarding the UK (WHO Regional Office for Europe, 2010) (Appendixes 3 and 4), this information was obtained from the European Hospital and Healthcare Federation (HOPE, 2009).

In 2007, there were 47,962 pharmacists registered with the Royal Pharmaceutical Society of Great Britain (RPSGB) (Section 4.2.1). Considering the UK population in the same year, there was a ratio of 78.66 pharmacists per 100,000 population (Seston *et al.*, 2007; HOPE, 2009). The average number of pharmacists per UK hospital could not be obtained from the EAHP (2005) as, although the UK participated in the 2005 survey, the response rate (3%) was too low to be included in their results. Therefore, considering that 21.7% of the pharmacists registered with the RPSGB in 2005 were working for the hospital sector, in a total of 10,068 pharmacists, the UK average is 4.4 pharmacists per hospital[21], which is slightly lower than the European average of 4.7 pharmacists per European hospital (EAHP, 2005; HOPE, 2009; Douglas, 2011).

Pharmaceutical compounding in the UK corresponds to the extemporaneous preparation of medicines in community and hospital pharmacies and also to

[21]A total of 2,312 UK hospitals (HOPE, 2009) were considered in determining the average of pharmacists per hospital in the UK.

the manufacture of specials by licensed hospital manufacturing units and pharmaceutical industries (Section 4.1). The extemporaneous preparation of medicines, in particular, is becoming less common in the UK (Marriott *et al.*, 2010) and it has been considerably replaced by the use of specials (Tuleu *et al.*, 2003). A widely reported compounding mistake in a UK community pharmacy, which led to the death of an infant, contributed to the general decline of this practice (Anonymous, 2000a; Carvalho *et al.*, 2008). Rennison and Portlock (2003) even suggested that the extemporaneous preparation of medicines was no longer appropriate in the community setting. Likewise, in the hospital setting, this practice is no longer common as the majority of pharmacy departments dispense specials instead of preparing extemporaneously compounded medicines (Horton, 2006; Jackson and Lowey, 2010). On average, less than 2 extemporaneously compounded medicines are prepared on a daily basis per paediatric hospital in England (Tuleu *et al.*, 2003; Yeung e*t al.*, 2004). Extemporaneous preparations are still considered a necessary and important alternative to proprietary medicines, particularly for children (Nunn, 2003), and there are still circumstances in which such medicines are required (Jackson and Lowey, 2010). For example, captopril and nifedipine are 2 cardiovascular drugs frequently used for children, but there is no licensed liquid dosage form available in the UK (Tuleu *et al.*, 2005; Mulla *et al.*, 2007; Joint Formulary Committee, 2008). Indeed, the majority of cardiovascular drugs used in children are unlicensed medicines (Standing and Tuleu, 2005). Pharmaceutical compounding is, therefore, the alternative of choice to treat children who are unable to swallow licensed solid dosage forms. The lack of licensed liquids in the UK has been confirmed by Yeung *et al.* (2004) who concluded that 76% of the non-sterile extemporaneously compounded medicines prepared in 7 paediatric hospitals in England (for 12 months) were liquid dosage forms. According to their results, a total of 3,728 extemporaneous preparations were reported by the participant hospitals and the most frequently dispensed active substances were potassium chloride, midazolam and vancomycin. A complete list of the top 20 active substances dispensed is shown in Appendix 17. Tuleu *et al.* (2003) concluded that out of the 672 extemporaneously compounded medicines prepared in an English

paediatric hospital, 45% were oral liquids and 13% were powders for reconstitution into liquid dosage forms. In relation to the therapeutic indications, 30% of these extemporaneous preparations were for metabolic disorders; 19% for CNS disorders; 11% were antivirals; and 10% were indicated for electrolytes disorders (Tuleu *et al.,* 2003). Turner *et al.* (1996) studied prospectively unlicensed drug use in another English paediatric hospital (for 4 months) and concluded that the most frequently dispensed oral unlicensed medicines (including "off-label" indications) were: chloral hydrate, sucralfate and amiloride (oral liquids).

In the UK, the lack of standardisation in pharmaceutical compounding has been raised by Mulla *et al.* (2007) who highlighted the fact that captopril formulations vary considerably throughout the country. According to their findings, 4 hospitals dispensed captopril tablets (intended to be crushed and dissolved in water before administration) and 22 hospitals dispensed 9 different oral liquids containing captopril. Nevertheless, despite the fact that different hospitals prepare different formulations, these are used interchangeably by patients without the assurance of therapeutic equivalence (Mulla *et al.*, 2007). The need for improving the quality and formulation of unlicensed medicines in the UK was also recognised by the National Advisory Board for the Manufacture of Pharmaceuticals in the NHS (National Health Service) who funded a research project undertaken by the Pharmacy Department at the Leeds Teaching Hospitals NHS Trust. The aim of this project was to improve the quality of oral unlicensed medicines prepared in the NHS by developing standardised and validated formulations for the 50 most frequently dispensed extemporaneous preparations (Lowey and Jackson, 2007). The authors (Lowey and Jackson, 2008) emailed a questionnaire to a convenience sample of NHS Trusts in the regions of Yorkshire, the North-East and London, in order to collect data regarding the top 20 oral liquid extemporaneous preparations dispensed over 12 months (2005-2006); 51 Trusts participated in the research and a total of 117 different extemporaneous preparations were dispensed as oral liquids, corresponding to an average of 10.3 different extemporaneous preparations per individual Trust. The most frequently dispensed dosage forms were

suspensions (66.2%) and solutions (22.2%). Oral powders were occasionally dispensed (4.3%) and capsules were only rarely dispensed (0.2%). According to the authors, more capsules are now produced by specials manufacturers instead of being extemporaneously compounded in hospital pharmacies. The top 5 extemporaneously compounded medicines were: levothyroxine, clobazam, clozapine, sodium chloride and morphine sulfate. A complete list of the top 50 extemporaneous preparations dispensed is shown in Appendix 18. Lowey and Jackson (2008) consider the practice of extemporaneous preparation a "manufacturing burden" on NHS hospitals and predicted that the "unnecessary use" of these medicines will decrease with time in the UK since the development of the "Pro-File" database, which allows NHS staff to identify and outsource specials effectively (NHS, no date).

4.1 **Legislation**

In the UK, medicinal products must be granted a Marketing Authorisation (formerly known as Product Licence) to be placed on the market or to be distributed by way of wholesale dealing (unless in accordance with any exception or exemption) (DHSS, 1994). Pharmaceutical compounding is included in the exemptions for medicines licensing, and pharmacists are allowed to prepare and dispense "unlicensed medicinal products" to fill a special need (MHRA, 2008). This exemption is conferred to pharmacists under Section 10 of the Medicines Act 1968 (DHSS, 1986).

According to the definition of unlicensed medicines stated in the respective BP general monograph (BP Commission, 2008a), an unlicensed medicine is "one which is prepared, at the request of an authorised health care professional, to address patient medical requirements, unmet by current licensed medicines". Unlicensed medicines may be either manufactured under a manufacturing specials licence (known as specials) or prepared extemporaneously under the supervision of a pharmacist (known as extemporaneous preparations). In addition, specials are usually produced in batches whereas extemporaneous preparations are considered one-off preparations only. In the UK, compounded medicines correspond then to

"unlicensed medicinal products" and include both specials and extemporaneous preparations.

A licensed specials manufacturer operates in accordance with GMP and is subject to regular inspections from the MHRA (Medicines and Healthcare products Regulatory Agency) (Jackson and Lowey, 2010). Therefore, specials are manufactured according to GMP, whereas extemporaneous preparations may be prepared in a hospital or community pharmacy in accordance with less strict standards. Although both unlicensed, specials are then regarded as a quality assured alternative to extemporaneous preparations. For this reason, over the last few years, specials have been increasingly used in place of extemporaneously prepared medicines in the UK (RPSGB, 2010a). Nevertheless, specials are almost never supported by bioavailability and stability data (Tuleu *et al.*, 2003) and, therefore, their quality and safety is not always guaranteed. Only licensed medicinal products with a Marketing Authorisation have their quality, safety and efficacy assured.

Hence, in the UK, a medicinal product that does not have a Marketing Authorisation may be produced by a specials manufacturer (hospital manufacturing unit or pharmaceutical industry); prepared extemporaneously in a community or hospital pharmacy; or, alternatively, obtained from abroad (imported) (Paediatric Formulary Committee, 2008).

The first agreed and detailed guidelines for pharmaceutical compounding in the UK were edited by Fenton-May (2002) in the format of a "Guide to the preparation of non sterile extemporaneous products in NHS hospitals" (Jackson and Lowey, 2010). This guide was intended for use as a reference in community and hospital pharmacies, which were not licensed as specials manufacturers, and included important guidelines on risk management; personnel and training; documentation; raw materials; facilities, equipment and processes; cleaning, disinfection and hygiene; monitoring and audit; and formulation and stability (Fenton-May, 2002). This guide was recently updated by Jackson and Lowey (2010), in the format of a book - Handbook of Extemporaneous Preparation - that also includes a formulary with 50 technical monographs (Jackson and Lowey, 2010).

4.2 **Professional organisations and information sources**

4.2.1 **English professional organisations**

- Royal Pharmaceutical Society of Great Britain (RPSGB)[22]: is the dedicated professional leadership body for pharmacists and pharmacy in England, Scotland and Wales. The mission of the RPSGB is to promote and represent the professional interests of its members. Pharmaceutical compounding is included in the Society's support and development activities. Several events related with compounding have been organised by the RPSGB (2008; 2009) and several documents and information sheets have also been published by the Society (RPS, 2002a; 2002b; 2004). The "Medicines, Ethics & Practice: A guide for pharmacists and pharmacy technicians", for example, sets professional standards and provides guidance applicable to all pharmacists; it was first published by the RPSGB in 1988 (RPSGB, 2010b). The principles included in Section 2 - "Code of Ethics for Pharmacists and Pharmacy Technicians" - (RPSGB, 2007) were further expanded on a document named "Professional Standards and Guidance for the Sale and Supply of Medicines" that included a list of standards for the "Extemporaneous Preparation or Compounding (4.)" (Donnelly *et al.*, 2008) as, for example: "*If you wish to be involved in extemporaneous preparation you must ensure that: 4.1 a product is extemporaneously prepared only when there is no product with a Marketing Authorisation available and where you are able to prepare the product in compliance with accepted standards...*" (Anonymous, 2000b; RPSGB, no date).
- The Association of Commercial Specials Manufacturers (ACSM): represent the specials manufacturers in the UK and, to date, includes a total of 14 member companies. The ACSM works closely with pharmacists, regulators and other governmental/professional bodies and aims to educate and ensure the standards and the future of specials in the UK. According to the ACSM, specials are made "individually or in very small batches" and represent less than 1% of all prescriptions in the UK (ACSM, 2010).

[22]Currently corresponds to the Royal Pharmaceutical Society (RPS) (RPSGB, 2011).

- UK paediatric organisations: such as the Centre for Paediatric Pharmacy Research (CPPR) and the Neonatal and Paediatric Pharmacists Group (NPPG) are also involved in pharmaceutical compounding, to a certain extent, although their focus is paediatric pharmacy and care in general (NPPG, 2010; CPPR, 2011).

4.2.2 **English information sources**

- British Pharmacopoeia (BP): is the UK's official and authoritative collection of standards for medicinal and pharmaceutical substances and also formulated preparations (finished dosage forms). Since 1864, the BP has made an important contribution to protecting public health by setting publicly available standards for the quality of medicines (Breckenridge, 2008). The BP is updated every year and, in 2008, an important step was given towards the quality of unlicensed medicines in the UK. The BP 2008 edition introduced a general monograph and 9 individual monographs for unlicensed formulations (Appendix 19) with which compliance is mandatory (BP Commission, 2008a). The individual monographs are intended for those formulations manufactured under a specials licence and also those prepared extemporaneously under the supervision of a pharmacist (BP Commission, 2008b). Hence, all medicinal products sold or supplied in the UK must comply with the respective BP monographs (Lee, 2010). The BP 2008 also included a revised "Supplementary Chapter V", which provides guidance on the legal requirements, ethical considerations, labelling and standards for the preparation and manufacture of unlicensed medicines (BP Commission, 2008c). The following BP editions (2009, 2010 and 2011) introduced further individual monographs for unlicensed medicines, which gives a total of 36 monographs published since 2008 (Appendix 19) (Lee, 2010). An example of a BP monograph (Paediatric Phenobarbital Oral Solution) is shown in Appendix 20.
- British Pharmaceutical Codex (BPC): was first published in 1907 by the Pharmaceutical Society of Great Britain in order to fulfil the need for an official reference that included information about commonly used medicines that were not part of the BP (Marriott *et al.*, 2010). Subsequent revisions of the BPC were published throughout the years until 1973 (10th edition) and

1976 (Supplement to the BPC 1973). Part 6 of BPC 1973 includes a formulary with monographs for compounded medicines, from aerosol inhalations to waters aromatic, in a total of 55 different dosage forms / (traditional) pharmaceutical preparations (Council of the Pharmaceutical Society of Great Britain, 1973; 1976).

- British National Formulary (BNF): is a therapeutic formulary that is published twice a year by the British Medical Association and the RPSGB. It includes important and up-to-date information regarding the selection, prescribing, dispensing and administration of medicines in the UK. Although pharmaceutical compounding is not the focus of the BNF, this formulary includes compounded medicines described in the BP and BPC (e.g. Liquid Paraffin Oral Emulsion, BP). It also includes important information regarding the availability of specials (e.g. spironolactone is available from Rosemont as "special order") and labelling (cautionary and advisory labels for dispensed medicines are in respective appendixes) (Joint Formulary Committee, 2008).
- BNF for children (BNFC): is also a therapeutic formulary, corresponding to the BNF but for paediatric patients, that is published once a year by the British Medical Association, the RPSGB, the Royal College of Paediatrics and Child Health, and the NPPG. The BNFC includes important advice regarding the use of unlicensed medicines and the "off-label" use of licensed medicines in children (Paediatric Formulary Committee, 2008).
- UCLH (University College London Hospitals) Formulary: is an example of a hospital formulary that includes information regarding the availability of compounded medicines for different therapeutic indications. These therapeutic formularies aim to ensure a safe, effective and economic use of medicines within the Trusts (Beresford, 2002).
- Pharmaceutical Compounding and Dispensing: is a reference in the UK for pharmacy students and practitioners involved in the practice of compounding. It includes an historical perspective of pharmacy and compounding; tutorials on the skills and techniques necessary for compounding the majority of the dosage forms; and a wide range of formulae for compounded medicines. This book was first published in 2006 and it is now on the 2nd edition (Marriott *et al.*, 2010).

- Handbook of Extemporaneous Preparation: this book consists on an update of the "Guide to the Preparation of Non Sterile Extemporaneous Products in NHS hospitals" (Fenton-May, 2002) and also includes a formulary with 50 monographs of extemporaneous preparations. It was written to be implemented as the standard for the extemporaneous preparation of medicines in the NHS hospitals across UK (Jackson and Lowey, 2010).

4.3 **Methods**

The UK was the second European country included in the research. It was the most convenient country, after Portugal, since the research project was based at the UCL School of Pharmacy, in London. The easy access and proximity of MC to UK hospitals allowed the first visits to be taken in 2006, to Great Ormond Street Hospital for Children (NHS Trust) and University College Hospital (UCLH NHS Foundation Trust). The discussions with the stakeholders in both hospitals, Ann Horton[23] and Tony Murphy[24], were very important at this initial stage for a clear insight on the practice of extemporaneous preparations in the UK. Also in 2006, 2 further visits were undertaken in Leeds, namely:

- Rosemont, a licensed specials manufacturer, for a better understanding of the concept of specials in the UK.
- Leeds Teaching Hospitals NHS Trust, for a meeting with Andrew Lowey[25], who contributed important guidance and advice to the set up of the research, based on his involvement in the project: The Quality and Formulation of Unlicensed, Non-Sterile, Oral Medicines Prepared in the NHS (Section 4) (Lowey and Jackson, 2007).

At a second visit to UCLH, Tony Murphy contributed with his expert opinion on the layout and wording of the UK questionnaire. His guidance and advice were decisive in the achievement of a clear and straightforward questionnaire, adapted to the compounding practices in the UK.

[23]Dispensary manager (2006), Great Ormond Street Hospital for Children NHS Trust.
[24]Pharmacy manufacturing (2006), UCLH NHS Foundation Trust.
[25]QA / research pharmacist (2006), Leeds Teaching Hospitals NHS Trust.

The fieldwork in this country was complete after the visit to 2 additional London hospitals, namely: “St Thomas’ Hospital (Guy’s and St Thomas’ NHS Foundation Trust)” (2007) and “St Bartholomew’s Hospital (Barts and The London NHS Trust)” (2008). In total, the research project in the UK included the visit to 5 hospitals and 1 licensed specials manufacturer (2006-2008).

At the start of the project, Lowey and Jackson (2007) had already completed their research on “The Quality and Formulation of Unlicensed, Non-Sterile, Oral Medicines Prepared in the NHS” but, since their data collection referred to oral liquid extemporaneous preparations only (all other oral dosage forms and specials were excluded) and hospitals were selected by convenience, the project in the UK was designed to build on their results and discussion.

4.3.1 **Country-specific questionnaire**

The research instrument developed to collect information regarding oral compounded medicines most frequently dispensed in UK hospital pharmacies was a self-completion questionnaire, based on the template established for Portugal (version 2, Section 3.3.1) and adapted to the practice of pharmaceutical compounding in the UK. The fieldwork and discussions with stakeholders contributed to the design of a UK-specific questionnaire, similar to the Portuguese template, but including all necessary adjustments to avoid misunderstandings. For instance, in Portugal, the concept of compounded medicines refers to extemporaneous preparations only whereas, in the UK, compounded medicines correspond to unlicensed medicines and include both extemporaneous preparations and specials. As a result, the UK questionnaire was initially formatted as a 4-sheet Excel document, including: an initial sheet with a brief introduction (Appendix 21) and a final sheet with 2 questions (Appendix 22), like the Portuguese template. However, instead of 1 individual table for unlicensed medicines, the UK questionnaire included 1 table for extemporaneous preparations and a second table for specials. The main headings of both tables are shown in Figure 4.1 and Figure 4.2.

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

UNLICENSED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

UNITED KINGDOM

Please fill in the following information (up to 40):

Considering the ORAL EXTEMPORANEOUS PREPARATIONS most frequently dispensed by your Pharmacy in 2006

EXTEMPORANEOUS PREPARATIONS are defined for the purpose of this study as unlicensed medicines prepared by the hospital pharmacy (under the Section 10 exemption)

	Active Substance	Strength	Dosage Form	Pack Size	Number of times dispensed in 2006
Examples	Captopril	1 mg / mL	Solution	50 - 250 mL	75
	Nitrofurantoin	5 mg / mL	Suspension	100 - 300 mL	67
	Sodium Bicarbonate	500 mg	Capsules	30 - 300 caps	45
1					
2					
3					

Figure 4.1 Country-specific questionnaire (UK): Table 1 (extemporaneous preparations).

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

UNLICENSED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

UNITED KINGDOM

Please fill in the following information (up to 40):

Considering the ORAL SPECIALS most frequently dispensed by your Pharmacy in 2006

SPECIALS are defined for the purpose of this study as unlicensed medicines prepared by a hospital manufacturing unit or commercial manufacturer (holding a "Specials" Manufacturing Licence)

	Active Substance	Strength	Dosage Form	Pack Size	Manufacturer	Number of times dispensed in 2006
Examples	Furosemide	5 mg / 5 mL	Solution	150 mL	Rosemont Pharmaceuticals	75
	Spironolactone	10 mg / 5 mL	Suspension	125 mL	Rosemont Pharmaceuticals	67
	Magnesium Carbonate	500 mg	Capsules	100 caps	Hospital Manufacturing Unit	45
1						
2						
3						

Figure 4.2 Country-specific questionnaire (UK): Table 2 (specials).

In table 1, extemporaneous preparations were defined as “unlicensed medicines prepared by the hospital pharmacy (under the Section 10 exemption)” whereas, in table 2, specials were defined as “unlicensed medicines prepared by a hospital manufacturing unit or commercial manufacturer (holding a “Specials” Manufacturing Licence)”. Both definitions were adapted from the BP official definitions (Section 4.1). Since data collection in the UK was undertaken during 2007, the questionnaire addressed information relating to 2006. Furthermore, in the final sheet with questions, instead of a request for the overall total number of unlicensed medicines, pharmacists were requested the overall total number of both oral extemporaneous preparations and oral specials (Appendix 22). So that the UK questionnaire was not too extensive, the initial introductory sheet was also removed from the Excel document and converted into a separate PDF. Consequently, the UK questionnaire resulted in a 3-sheet Excel document, which was complemented with a separate PDF introduction.

4.3.2 **Purposive sample of hospitals**

In the UK, specials are usually produced in batches whereas extemporaneous preparations are considered one-off preparations only. The purposive sample of hospitals included the complete list of licensed hospital manufacturing units described in the BNF 52 (Joint Formulary Committee, 2006), which was further updated with 8 additional hospitals from the BNFC 2007 (Paediatric Formulary Committee, 2007) (Appendix 23).

In relation to extemporaneous preparations, it was considered likely that the paediatric hospitals were the hospitals that dispensed the largest quantities of extemporaneous preparations in the UK, due to the importance of pharmaceutical compounding to this patient population (Section 1.1.5.1). For this reason, the purposive sample of hospitals in the UK also included the complete list of paediatric hospitals provided by Yeung *et al.* (2004) (Appendix 24). Furthermore, 4 additional hospitals were added to the list, as a result of professional contacts established in the course of the project, which gave a purposive sample of 36 hospitals.

4.3.3 **Data collection**

All hospitals in the purposive sample were contacted by email during 2007 in order to collect data regarding both extemporaneous preparations and specials most frequently dispensed in 2006. The email was sent to hospital pharmacists including the UK questionnaire attached, together with a separate PDF introduction. Non-respondents were sent periodical email reminders, up to a maximum of 5 email reminders per hospital. A few hospital pharmacists were also contacted by MC in person and by telephone.

4.4 **Results and discussion**

In the UK, 36 hospitals were contacted to participate in the research project, including 7 paediatric hospitals, 25 licensed specials manufacturers plus 4 additional hospitals. In total, 20 hospitals responded to the request for collaboration (56% response rate) and 16 hospitals were non-respondents. The 20 respondent hospitals were located across England and Wales, as follows: Birmingham (n=1), Cardiff (n=1), Colchester (n=1), Huddersfield (n=1), London (n=8), Newcastle upon Tyne (n=3), Preston (n=1), Sheffield (n=1), Stockport (n=1), Stoke-on-Trent (n=1) and Surrey (n=1) (Figure 4.3).

Figure 4.3 Map of the UK adapted from National Geographic Society (1998b); indicating the location of the respondent hospitals (●).

From the 20 respondents, 15 hospitals contributed data regarding oral unlicensed medicines most frequently dispensed in 2006 and 5 hospitals were non-participants (Figure 4.4).

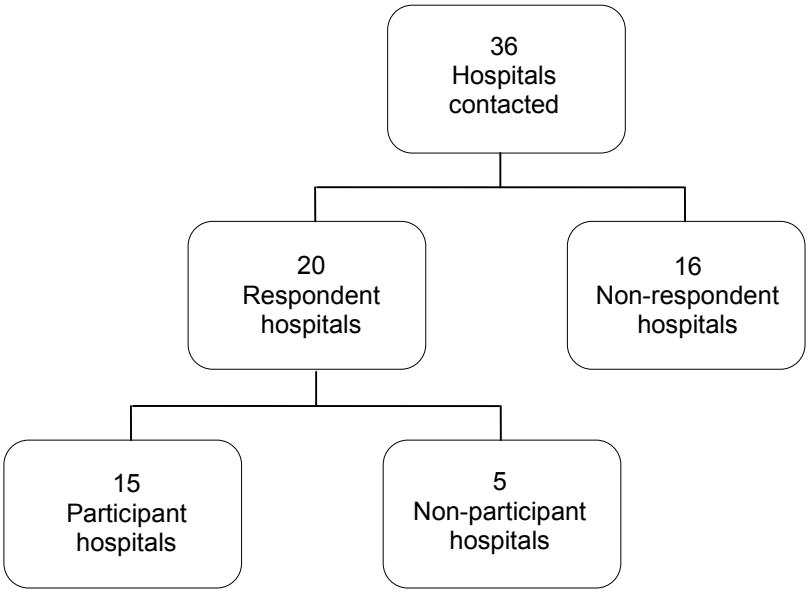


Figure 4.4 Purposive sample distributed by respondent and participant hospitals.

All participant hospitals shared complete datasets, including the oral extemporaneous preparations and/or specials dispensed. In total, 8 hospitals contributed data regarding both extemporaneous preparations and specials; 6 hospitals contributed data on extemporaneous preparations and 1 hospital on specials only.

With reference to the coding frame in Table 2.2, the 5 non-participant hospitals did not contribute data for the following reasons: 3 hospitals dispensed oral unlicensed medicines but data were not readily accessible and 2 hospitals dispensed oral unlicensed medicines but data were classified as confidential. The disclosure of information regarding specials, in particular, represented a problem for some hospitals, either because data were not readily accessible: "*we cannot pull off the information from our current antiquated computer system* (paediatric hospital, in West Midlands); *unfortunately I was unable to get any information about the oral specials"* (licensed hospital manufacturing unit, in London); or, alternatively, because data were classified as confidential (particularly in the case of licensed specials manufacturers): "*I have been told the Trust does not favour sharing*

this information; as a commercially focused manufacturer I cannot release confidential information regarding quantities we produce" (licensed hospital manufacturing units, in London). The oral specials reported by the UK hospitals were prepared in their own manufacturing units and/or bought from other specials manufacturers. In total, 18 different specials manufacturers were reported by the participant hospitals.

A total of 4 UK hospitals were visited by MC with the purpose of collecting data and visiting the preparation/manufacturing areas (Section 4.3). Although all 4 hospitals contributed to the research project, none of these provided data during the visit but provided it later. The hospital visits were undertaken between 2006 and 2008 but all datasets referred specifically to 2006, for comparative purposes. All UK hospitals sent the required data by email; 10 hospitals supplied data in the questionnaire provided and 5 hospitals in their own formats. A total of 7 hospitals provided datasets including non-oral unlicensed medicines (e.g. enemas, nasal drops and topical solutions), which were excluded accordingly (Section 2.4.1). After data processing, the UK database included a total of 489 data entries, corresponding to the datasets of 15 hospitals.

4.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral unlicensed medicines in the UK is shown in Table 4.1. Active substances were grouped according to the respective therapeutic classification (*Martindale 35*, 2007), giving a total of 159 different active substances and 36 therapeutic groups. Cardiovascular drugs was the group with the greatest number of different active substances (n=21), followed by antibacterials (n=15) and electrolytes (n=14). Although these active substances were all reported as oral unlicensed medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: dermatological drugs and sunscreens (Appendix 11); disinfectants and preservatives (Appendix 12); paraffins and similar bases (Appendix 13); and supplementary drugs and other substances (Appendix 15). The active substances included in these groups are described in the respective appendixes.

Table 4.1 Active substances most frequently dispensed as oral unlicensed medicines in the UK (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Diclofenac, indometacin, methadone HCl, morphine, morphine HCl, morphine sulfate, naproxen, paracetamol

Antibacterials
Benzylpenicillin, clindamycin, clindamycin HCl, colistin sulfate, ethambutol HCl, gentamicin sulfate, isoniazid, neomycin, oxytetracycline, pyrazinamide, rifabutin, sulfadiazine, tetracycline, vancomycin, vancomycin HCl

Antidepressants
Amitriptyline, dosulepin HCl, imipramine

Antidiabetics
Gliclazide, metformin HCl

Antiepileptics
Clobazam, clonazepam, gabapentin, phenobarbital, phenobarbital sodium, primidone

Antifungals
Amphotericin B, griseofulvin

Antigout drugs
Allopurinol, probenecid

Antihistamines
Cyclizine

Antimalarials
Hydroxychloroquine sulfate, primaquine phosphate, quinine dihydrochloride, quinine sulfate

Antimyasthenics
Pyridostigmine bromide

Antineoplastics
Aminolevulinic acid HCl, busulfan, cyclophosphamide, hydroxycarbamide, mercaptopurine, methotrexate, tioguanine

Antiparkinsonian drugs
Carbidopa, levodopa, trihexyphenidyl HCl

Antivirals
Didanosine, valaciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Chlordiazepoxide, chloral hydrate, clozapine, levomepromazine, lorazepam, midazolam, midazolam maleate, secobarbital, zuclopenthixol

Blood products, plasma expanders and haemostatics
Tranexamic acid

Bronchodilators and anti-asthma drugs
Caffeine, caffeine citrate

Cardiovascular drugs
Amiodarone, amlodipine besilate, captopril, chlorothiazide, clonidine, diazoxide, diltiazem HCl, doxazosin mesilate, enalapril, flecainide acetate, furosemide, hydralazine HCl, labetalol HCl, lisinopril, metoprolol, metoprolol tartrate, prazosin HCl, propranolol HCl, spironolactone, verapamil HCl, warfarin sodium

Chelators, antidotes and antagonists
Calcium polystyrene sulfonate, mesna (sodium 2-mercaptoethanesulphonate), methionine, naltrexone

Contrast media
Meglumine amidotrizoate, sodium amidotrizoate

Corticosteroids
Dexamethasone, fludrocortisone acetate, hydrocortisone, prednisolone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Acetylcysteine, ammonium chloride

Dermatological drugs and sunscreens
Acitretin

Disinfectants and preservatives
Sodium benzoate, sodium metabisulfite

Electrolytes
Calcium gluconate, magnesium chloride, magnesium glycerophosphate, magnesium sulfate, monobasic potassium phosphate, monobasic sodium phosphate, phosphate, potassium chloride, potassium citrate, potassium phosphate, sodium bicarbonate, sodium

chloride, sodium citrate, sodium phosphate

GI drugs
Calcium carbonate, hyoscine butylbromide, hyoscine hydrobromide, loperamide HCl, omeprazole, propantheline bromide

General anaesthetics
Chloroform, ketamine HCl

Hypothalamic and pituitary hormones
Desmopressin

Immunosuppressants
Azathioprine, tacrolimus

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide

Muscle relaxants
Dantrolene sodium, tizanidine HCl

Nutritional agents and vitamins
Arginine, calcium folinate, citrulline, ergocalciferol, folinic acid, glucose, glycine, lactose, menadiol sodium phosphate, pyridoxine HCl, thiamine, vitamin D

Paraffins and similar bases
Cholesterol

Stimulants and anorectics
Methylphenidate HCl

Supplementary drugs and other substances
Citric acid, glycerol, glycopyrronium bromide, macrogols, manuka, monosodium glutamate, sodium phenylbutyrate, tetrabenazine, xylose

Thyroid and antithyroid drugs
Levothyroxine sodium, potassium iodide, potassium perchlorate

Urological drugs
Sildenafil citrate

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 7 NTI drugs were dispensed as oral compounded medicines (underlined in Table 4.1).

The active substances dispensed by most hospitals were: ethambutol HCl (n=10); clobazam and sodium chloride (n=9); pyrazinamide and pyridoxine HCl (n=7).

All active substances reported were included in *Martindale 35* (2007), with the exception of nickel sulfate that was dispensed by 1 hospital as 11.2 mg capsules (Appendix 26). Since nickel sulfate is the most common cause of contact allergy, it is likely that it was indicated for oral hyposensitization therapy or allergy testing (Tammaro *et al.*, 2009).

Almost all compounded medicines included just 1 active substance (single-drug) in their composition. In fact, only 4 compounded medicines included more than 1 active substance, namely: aminoacids in combination (named as aminoacid formula B); co-careldopa (carbidopa and levodopa); Gastrografin (meglumine amidotrizoate and sodium amidotrizoate) and tricitrate oral

solution (sodium citrate, potassium citrate and citric acid monohydrate). Apart from compounded medicines including active substances, 2 hospitals also reported compounded medicines including placebo, which was dispensed both as capsules and oral powders, in a total of 392 units of oral solids.

UK hospitals reported a number of compounded medicines by their given titles as, for instance: Albright's Solution (2 hospitals), Joulie's Solution (2 hospitals), Knox Mouthwash (1 hospital), Peppermint Water (3 hospitals), Simple Linctus Paediatric[26] (1 hospital) and St Mark's Powders (1 hospital). These compounded medicines were added to the given titles formulary (Appendix 16). Peppermint Water (Concentrated) and Simple Linctus Paediatric are official formulae since these are included in official texts, namely the BP and BPC (Marriott *et al.*, 2010).

Almost all compounded medicines were reported by active substances and only 2 were reported by the respective proprietary names, as follows: Calcium Resonium (calcium polystyrene sulfonate) and Gastrografin (meglumine amidotrizoate and sodium amidotrizoate). These were reported by only 1 hospital and, although named as the proprietary medicines that were likely used in their preparation, both were reported specifically as specials and not as one-off extemporaneous preparations. Because specials are usually prepared in large scale, these should preferably include raw materials in bulk instead (Section 1.1.2.2). Finally, 2 hospitals reported capsules including "radio-opaque pellets". These pellets[27] are used as faecal markers for faecal fat estimation in the diagnosis and control of malabsorption (Simpson *et al.*, 1979).

The UK participant hospitals reported both oral (liquids and solids) and oromucosal unlicensed medicines, which are discussed separately below. The most frequently dispensed dosage forms were oral liquids. A total of 50,571 unidose and multidose oral liquids were reported, which represented

[26]Although linctuses are not an official PhEur dosage form, these are subject of an individual monograph in the BP (Oral Liquids of the BP) and correspond to viscous oral liquids containing 1 or more active substances dissolved in a vehicle that usually contains a high proportion of sucrose, other sugars or a suitable polyhydric alcohol or alcohols. Linctuses are intended for use in the treatment or relief of cough (BP Commission, 2008a).
[27]Pellets correspond to small cylinders (about 3.2 mm in diameter by 8 mm in length) of an active substance (Rudnic and Schwartz, 2005).

over 95% of all unlicensed medicines dispensed (both extemporaneous preparations and specials). Only 4% of the medicines dispensed corresponded to oral solids. Oromucosal preparations accounted for less than 1% of the unlicensed medicines reported, as shown in Figure 4.5.

4.4.2 **Oral solids**

Oral solid dosage forms were dispensed by 10 hospitals (67% of all participants) and included both oral powders and capsules. In total, 2,256 packs of oral solids were reported, which represented only 4.3% of all unlicensed medicines dispensed (Figure 4.5).

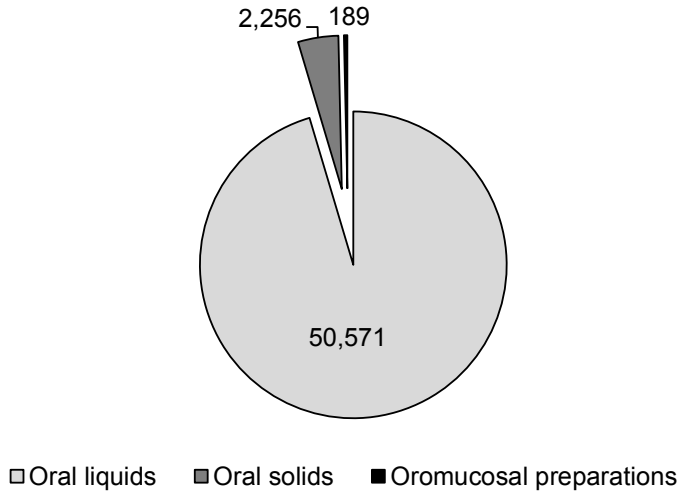


Figure 4.5 Oral and oromucosal unlicensed medicines dispensed per number of units/packs.

The most frequently dispensed oral solid dosage forms were oral powders, which were dispensed by a total of 5 hospitals, in a sum of 2,120 packs, representing 94% of all oral solids. Out of the 2,120 packs of oral powders, 91% were specials and only 9% were extemporaneous preparations. Specials were dispensed by only 1 hospital, which suggests that this is a particular "type" of hospital. A total of 3 different active substances were dispensed as specials, namely: glucose, dispensed both as specials and extemporaneous preparations, in packs of 14.6 g and 75 g (n=934); manuka dispensed as specials only, in packs of 80 g (n=800); and calcium polystyrene sulfonate, dispensed as specials only, in packs of 15 g (n=200).

The top 5 active substances dispensed as extemporaneous preparations were: lactose (n=70); glucose, sodium citrate and sodium chloride (St Mark's

Powders) (n=23); and xylose (n=18). Placebo was also reported as extemporaneous preparations, in a total of 10 packs of oral powders and dispensed by only 1 hospital. In general, specials were dispensed in much larger quantities than extemporaneous preparations.

Capsules were so dispensed by 7 hospitals, in a sum of 136 packs, which represented only 6% of all oral solids. Although capsules were reported by more hospitals, in comparison with extemporaneous preparations, capsules were dispensed in much lesser quantity probably because these were not dispensed as specials but only as extemporaneous preparations. The most frequently dispensed capsules were radio-opaque pellets (2 hospitals), followed by potassium iodide (65 mg; 1 hospital) and potassium perchlorate (200 mg; 1 hospital). Placebo capsules were also reported by 1 hospital.

4.4.3 **Oral liquids**

Oral liquid dosage forms were dispensed by all participant hospitals and included solutions, suspensions, mixtures[28] and syrups. Oral liquids represented 95.4% of all unlicensed medicines dispensed (Figure 4.5).

The strengths of oral liquids were frequently reported per dosing unit (e.g. 100 mg/5 mL and 3 mg/10 mL) and not just per mL. In order to avoid administration errors, the pharmacist when labelling a compounded medicine must carefully decide whether to indicate the strength of an oral liquid per dosing unit or just per mL, as this interchange is likely to confuse patients (Jackson and Lowey, 2010). The volumes reported ranged from 4 mL to 1,000 mL. Although none of the hospitals distinguished unidose from multidose containers, it was assumed that quantities <10 mL corresponded to unidose whereas quantities ≥10 mL corresponded to multidose containers (Section 2.1.3). On this basis only 2 hospitals dispensed unidose oral liquids and, in total, only 3 active substances were dispensed as unidose, namely: midazolam (10 mg/mL), midazolam maleate (12.5 mg/5 mL) and mesna (100 mg/mL). The 3 unidose oral liquids were dispensed as unlicensed solutions,

[28]Although mixtures are not an official PhEur dosage form, these are subject of an individual monograph in the BP (Oral Liquids of the BP) and correspond to an oral liquid containing 1 or more active substances dissolved, suspended or dispersed in a suitable vehicle (BP Commission, 2008a).

in a total of 371 units; midazolam and midazolam maleate were dispensed as oral specials.

Multidose containers were dispensed in much larger quantities; 50,200 multidose oral liquids. The quantities of multidose oral liquids, per dosage form, were reported as follows: solutions and suspensions (n=49,578), mixtures (n=142) and syrups (n=88). In addition, a total of 316 multidose oral liquids were not classified with regards to the dosage form and 76 were classified generally as oral liquids.

Solutions and suspensions were specifically reported by all participant hospitals, in a sum of 49,578 multidose units, which corresponded to almost 99% of all multidose oral liquids dispensed. The majority of the solutions and suspensions reported were described as specials (n=44,137), which represented 89% of all multidose solutions and suspensions dispensed. The top 5 active substances are shown in Table 4.2.

Paracetamol was the most frequently dispensed active substance. It was reported as an oral special by only 1 hospital, a licensed specials manufacturer, in the single strength of 1g/10 mL and in a sum of 14,500 multidose units. Batch sizes varied from 500 to 2,500 multidose units of 200 mL each.

Table 4.2 Oral unlicensed medicines most frequently dispensed as multidose solutions and suspensions.

Active substances	Strengths	Volumes	Number of hospitals	Number of units dispensed	
				Extemporaneous preparations	Specials
Paracetamol	1 g/10 mL	200 mL	1	_____	14,500
Sodium bicarbonate	1 mmol/mL (8.4%)	50-200 mL	4	28	5,348
Peppermint Water		100 mL 200 mL	4	23	3,009
Phenobarbital sodium	50 mg/5 mL	15-200 mL	2	14	2,492
Diclofenac	50 mg/5 mL	150 mL	1	_____	2,040

Paracetamol oral liquid is licensed in the UK both as an oral suspension of 120 mg/5 mL and another of 250 mg/5 mL which corresponds to 240 mg/10

mL and 500 mg/10 mL, respectively (Joint Formulary Committee, 2008). The special dispensed by the UK hospital is twice the strength of the highest strength licensed suspension, which indicates that there is a need for a licensed paracetamol oral liquid for adults. Nevertheless, specials are unlicensed medicines and, therefore, these should only be prescribed in exceptional situations. Paracetamol 1 g/10 mL (14,500 multidose units) represented 29% of all multidose solutions and suspensions dispensed by the UK hospitals, which is not consistent with the concept of compounded medicines (Section 1.1.4) nor with the "individual or small batch production" claimed by specials manufacturers (Section 4.2.1). Sodium bicarbonate was the next most frequently dispensed active substance, which was dispensed both as extemporaneous preparations (n=28) and specials (n=5,348) by a total of 4 hospitals and in the single strength of 1 mmol/mL (equivalent to 8.4%). As stated in the BNF 56: "*Oral solutions of sodium bicarbonate are required occasionally; these need to be obtained on special order and the strength of sodium bicarbonate should be stated on the prescription*" (Joint Formulary Committee, 2008). The next most frequently dispensed active substances were, in decreasing order, *Peppermint Water*, phenobarbital sodium and diclofenac (Table 4.2). For the top 5 active substances reported and, in general, specials were dispensed in much larger quantities than extemporaneous preparations. In fact, out of the 50,200 multidose oral liquids, 88% corresponded to specials and only 12% to extemporaneous preparations. Although extemporaneous preparations are associated with more risks than specials, the evident large scale production of specials is of concern since these medicines are unlicensed and, therefore, their quality, safety and efficacy has not been accessed by the MHRA.

The active substances dispensed as multidose solutions and suspensions were classified with reference to *Martindale 35* (2007) and the most frequent therapeutic groups were: analgesics, anti-inflammatory drugs and antipyretics, which represented 36% of all therapeutic groups and included paracetamol and diclofenac; electrolytes (20%), which included sodium bicarbonate; and gastrointestinal drugs (7%), which included *Peppermint Water* (Figure 4.6). Whereas the leading therapeutic group with regards to

unlicensed medicines dispensed in hospitals was analgesics, anti-inflammatory drugs and antipyretics, the leading therapeutic group in terms of prescription items dispensed in the community in England (2006-2007) was cardiovascular drugs (NHS, 2008).

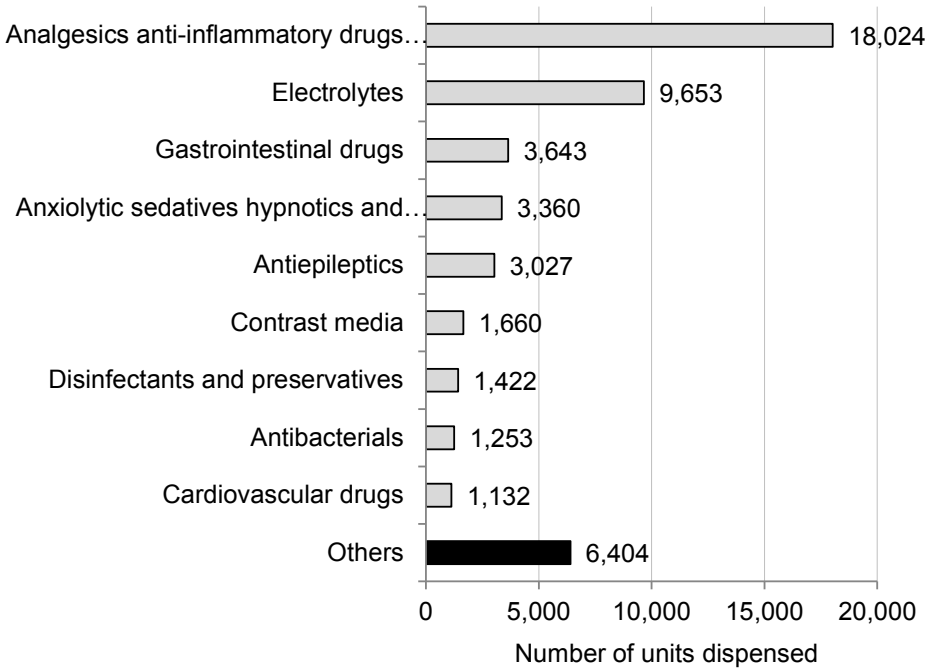


Figure 4.6 Solutions and suspensions (multidose) dispensed by number of units and classified by therapeutic groups.

As part of the multidose oral liquids, mixtures were reported by 4 hospitals in a sum of 142 (0.3%) units. Only 7 active substances were reported as mixtures and these were (in decreasing order): magnesium chloride, chloral hydrate, magnesium sulfate, caffeine citrate, phosphate, sodium benzoate and hydralazine HCl. Only caffeine citrate was reported as a special.

Also part of the multidose oral liquids, syrups were reported by 3 hospitals, in a sum of 88 (0.2%) units. The most frequently dispensed syrup was chloral hydrate (500 mg/5 mL), which was reported as a special only. Chloral hydrate and glycerol were the only active substances reported as syrups. Nevertheless, it is likely that more active substances were dispensed as syrups but these might have been classified by the hospital pharmacies as solutions, suspensions or even mixtures. The ambiguity of the dosage forms classification is well represented in the chloral hydrate that was reported as a syrup, mixture and solution. In the UK, the BPC (Section 4.2.2) describes a

Chloral Hydrate Mixture that contains 20% of syrup and a Chloral Hydrate Elixir Paediatric[29], in which syrup is the main vehicle (Council of the Pharmaceutical Society of Great Britain, 1973) (Appendix 2). Yet, both mixture and elixir described in the BPC are classified in the BNF 56 as an oral solution (Joint Formulary Committee, 2008). Moreover, chloral hydrate in syrup is classified in the international literature as an oral liquid (in general) (Appendix 2) (Allen, 2006c). In practice, pharmacists face the ambiguity of the dosage forms classification on a daily basis and, in case of uncertainty, oral liquid compounded medicines should be classified as liquid preparations for oral use (EDQM, 2011).

The multidose oral liquids (solutions, suspensions, mixtures and syrups), both specials and extemporaneous preparations, were dispensed in a variety of strengths. The active substances dispensed in the greatest range of strengths are shown in Table 4.3. In general, extemporaneous preparations were dispensed in a greater range of strengths than specials. This was expected since specials are produced in batches and, therefore, in order to optimise costs, specials manufacturers are interested in producing selected strengths only. Nevertheless, the purpose of pharmaceutical compounding is to offer a customised therapeutic alternative to patients and the standardisation of strengths is not consistent with individualised therapy.

Table 4.3 Active substances dispensed in the greatest range of strengths.

Active substances	Number of strengths		
	Total (range)	Extemporaneous preparations	Specials
Levothyroxine sodium	8 (25-200 µg/5 mL)	8	3
Clonidine	6 (25 µg-50 mg/5 mL)	5	2
Ethambutol HCL	6 (100-600 mg/5 mL)	5	3

Although it may be argued that the standardisation of strengths leads to fewer compounding errors, nowadays, with the computerisation and a

[29]Although elixirs are not an official PhEur dosage form, these are subject of an individual monograph in the BP (Oral Liquids of the BP) and correspond to clear and flavoured oral liquids containing 1 or more active substances dissolved in a vehicle that usually contains a high proportion of sucrose, or a suitable polyhydric alcohol or alcohols, and may also contain ethanol (96% or diluted) (BP Commission, 2008a).

QA/QC (quality assurance / quality control) system in hospitals and community pharmacies, the quality of compounded medicines may be assured.

The top 10 active substances dispensed as extemporaneous preparations is shown in Table 4.4. Whereas the top 3 unlicensed medicines dispensed were specials and corresponded to paracetamol (n=14,500), sodium bicarbonate (n=5,348) and Peppermint Water (n=3,009); the top 3 extemporaneous preparations were dispensed in much lesser quantities and corresponded to clozapine (n=701), midazolam (n=632) and Albright's Solution (n=444).

Table 4.4 Top 10 active substances dispensed as extemporaneous preparations, per number of units.

Active substances	Units dispensed
1. Clozapine	701
2. Midazolam	632
3. *Albright's Solution*	444
4. *Joulie's Solution*	420
5. Glycopyrronium bromide	309
6. Levothyroxine sodium	253
7. Morphine sulfate	238
8. Clonidine	213
9. Omeprazole	193
10. Sodium chloride	84

Considering both oral solids and liquids, the top 10 extemporaneous preparations dispensed by the UK hospitals corresponded to oral liquids only, which is in accordance with Brion *et al.* (2003), Tuleu *et al.* (2003) and Yeung *et al.* (2004), who concluded that the most frequently dispensed dosage forms in the UK were oral liquid dosage forms. With reference to the top 20 active substances described by Yeung *et al.* (2004) (Appendix 17), only midazolam, clonidine and sodium chloride were included in their list. On the other hand, the top 50 extemporaneous preparations dispensed by a convenience sample[30] of NHS hospitals (Lowey and Jackson, 2008)

[30]Convenience samples are those in which the researcher selects the individuals that are more readily accessible and willing to participate in the research, despite the fact that these may not be representative (Smith, 2005).

(Appendix 18) included the majority of the active substances described in Table 4.4. In fact, only *Albright's Solution* and glycopyrronium bromide were not included in their list. In comparison, clozapine was dispensed in very similar quantities whereas midazolam, *Joulie's Solution* and omeprazole were reported in much larger quantities than the NHS sample by Lowey and Jackson (2008).

4.4.4 **Oromucosal preparations**

In the UK, oromucosal preparations were reported by 6 hospitals (40% of all participant hospitals) and only 5 different active substances were dispensed, as follows:

- Tranexamic acid: is an antifibrinolytic agent that is used in the prophylaxis and treatment of haemorrhage associated with excessive fibrinolysis. Tranexamic acid solutions have been widely used as mouthwashes, particularly in the NHS (*Martindale 35*, 2007; Lowey and Jackson, 2008). This active substance was reported by 5 hospitals in the single strength of 50 mg/mL and in a sum of 104 multidose units (100-500 mL).
- *Knox Mouthwash*: according to Jackson and Lowey (2010) there are several formulae for this mouthwash, including different active substances and in different strengths. Typically, it includes triamcinolone acetonide (500 µg/mL = 2.5 mg/5 mL) and erythromycin ethyl succinate (47.5 mg/mL = 237.5 mg/5 mL) (Appendix 16) (Jackson and Lowey, 2010). *Knox Mouthwash* was the only special reported by the participant hospitals; it was dispensed in a sum of 83 multidose units (100-300 mL) and by only 1 hospital. The strengths reported for the active substances were 2.5 mg/5 mL and 250 mg/5 mL, which are very similar to the formula mentioned above.
- Folinic acid: is the active form of folic acid and it is given as calcium or sodium folinate (*Martindale 35*, 2007). It was dispensed as an oromucosal preparation in the strength of 3 mg/10 mL (200 mL) and by only 1 hospital.
- Tetracycline: is an antibacterial with a wide spectrum of activity (*Martindale 35*, 2007). It was dispensed as an oromucosal preparation in the strength of 5% (200 mL), by only 1 hospital.

A total sum of 189 multidose units of oromucosal preparations were reported, which accounted for less than 1% of all unlicensed medicines dispensed (Figure 4.5). Out of the 189 oromucosal preparations, 56% (n=106) were extemporaneous preparations and 44% (n=83) were specials.

4.5 **Summary**

- Compounded medicines in the UK correspond to unlicensed medicinal products and include both specials and extemporaneous preparations. Specials are manufactured according to GMP in licensed hospital manufacturing units or pharmaceutical industries.
- To date, there is no professional organisation specifically dedicated to pharmaceutical compounding, nor an official and up-to-date compounding formulary in the UK. The BP includes a general monograph and also individual monographs for unlicensed medicines.
- A purposive sample of 36 hospitals was included in the research (5 hospitals and 1 licensed specials manufacturer were visited) and a response rate of 56% was obtained. A total of 159 different active substances (including 7 NTI drugs) were reported corresponding to 36 different therapeutic groups. The top 3 therapeutic groups were cardiovascular drugs (n=21), antibacterials (n=15) and electrolytes (n=14). Placebo was dispensed as capsules and oral powders in a sum of 392 units (n=2).
- Oral solid dosage forms were reported by 67% of all participant hospitals and included oral powders and capsules. Oral powders were dispensed in a sum of 2,120 packs and the top 3 active substances were: glucose, manuka and calcium polystyrene sulfonate. Capsules were dispensed in a sum of 136 packs and the top 3 active substances were: radio-opaque pellets, potassium iodide and potassium perchlorate.
- Oral liquid dosage forms were reported by all participant hospitals and included solutions, suspensions, mixtures and syrups; the respective strengths were frequently reported per dosing unit. Oral liquids were dispensed in a total sum of 50,571 containers and the top 5 active substances were: paracetamol, sodium bicarbonate, *Peppermint Water*, phenobarbital sodium and diclofenac. Solutions and suspensions were dispensed in a total of 49,578 multidose containers (98.8%) whereas mixtures and syrups were dispensed in a total of 142 and 88 multidose containers (0.5%). Oral liquids were more frequently dispensed than oral solids. In general, specials were dispensed in much larger quantities than extemporaneous preparations but these were reported in a greater range of strengths.
- Oromucosal preparations were reported by 40% of hospitals, in a sum of 189 multidose containers, and the active substances dispensed were: tranexamic acid, *Knox Mouthwash*, folinic acid and tetracycline.

5. **Compounding in Switzerland**

Switzerland was the only non-member of the EU that was included in the international survey. It is considered the non-member with the greatest relations with the EU and was included in the research because of these close interconnections (Section 2.2.1). Switzerland is centrally located in Europe, bordering France in the West, Germany in the North, Austria and the principality of Liechtenstein in the East, and Italy in the South (Switzerland Tourism, 2010a). Switzerland occupies an area of 41,290 Km^2 and has a population of 7.6 million (*Europa*, 2009). The largest Swiss cities are (in decreasing order): Zurich, Geneva, Basel, Bern and Lucerne. This country is administratively divided into 26 cantons and has 4 official languages (traditionally spoken in different regions of the country), as follows: Swiss (German) (64%), French (20%), Italian (7%) and Rumantsch (1%) (Switzerland Tourism, 2010a; 2010b).

In 2005, there were 337 hospitals in Switzerland (ratio of 4.53 hospitals per 100,000 population) and a total of 41,196 hospital beds (ratio of 553.92 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2006, there were 4,269 pharmacists in Switzerland (ratio of 57.04 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4). According to the EAHP survey, the average number of pharmacists in Swiss hospitals is 4.1, compared to the European average of 4.7 pharmacists per European hospital. Nevertheless, Swiss hospitals have an average of 6.7 qualified pharmacy technicians/assistants per hospital, compared to the European average of 6. Switzerland also has an average of 2.2 non-qualified pharmacy assistants per hospital (EAHP, 2005; Hartmann, 2010).

Hospital pharmacists in Switzerland are reported to make an important contribution to the safe, correct and economic use of medicines (Grünig, 2006) and, according to Zelger[31] (2006), the practice of pharmaceutical compounding is considered to reinforce the presence and importance of

[31]Georges Zelger is the president of the GSASA (Section 5.2.1).

hospital pharmacists in Switzerland. Postgraduate education in hospital pharmacy has been officially recognised and Swiss pharmacists now have the opportunity of being awarded the professional qualification of "Hospital Pharmacist FPH (*Foederatio Pharmaceutica Helvetiae* - Swiss Pharmaceutical Federation)". This specialisation includes 5 areas of expertise and pharmaceutical manufacture is one of these areas (Grünig, 2006; Zelger, 2006).

Because Switzerland is not a member of the EU, the movement of goods across borders is limited and, in the case of urgent need, it may be difficult to get medicines from other countries. In addition, Switzerland is a small country with a limited market for medicines and, therefore, important pharmaceutical formulations (e.g. isoniazid, quinine, hydromorphone and hydrocodone for injection) have been removed from the market by pharmaceutical industries for purely economic reasons (Martinelli, 2006). As a result, pharmaceutical compounding plays an increasingly important role in this country.

In Switzerland, compounded medicines may be prepared individually or in batches of small quantities. The practice of pharmaceutical compounding is subject to many legal constraints and, therefore, only a limited number of Swiss hospitals are able to prepare and dispense compounded medicines (Surber *et al.*, 2006). The preparation of compounded medicines in small quantities must comply with the Swiss "GMP for the production of compounded medicines in small quantities", which is particularly intended for non-sterile compounding (Martinelli, 2006) (Section 5.1). However, there is not yet a definition for "small quantity" and, according to Zelger (2006), this will have a huge impact on hospital compounding once it is established. In addition, the preparation of compounded medicines in small quantities is restricted to the formulas included in officially recognised references. In Switzerland, the only authorised reference is the Swiss Pharmacopoeia (PhHelv, Section 5.2.2) which, according to Martinelli (2006), does not include many essential pharmaceutical formulations. This situation reduces the flexibility of the hospitals in meeting patients' needs and, ultimately, the patient health may suffer (Martinelli, 2006).

In a study by Di Paolo *et al.* (2006), conducted prospectively in a Swiss paediatric university hospital, the use of unlicensed and off-label medicines in children was a common practice. Of the 483 prescriptions analysed over 6 months (2001/2002), 24% were for unlicensed medicines and the majority of these were prepared by the hospital pharmacy "in-house" either as batch preparations (e.g. chloral hydrate, caffeine citrate and morphine solutions) or as individualised preparations (e.g. captopril, furosemide, hydrochlorothiazide and spironolactone capsules, solutions and suspensions). The oral unlicensed medicines included in the top 10 (unlicensed and off-label) were: spironolactone oral suspension 5 mg/mL, hydrochlorothiazide oral suspension 5 mg/mL and captopril oral capsules (Di Paolo *et al.*, 2006).

As the country is administratively divided in 26 cantons, the Swiss health care system does not operate on a national level. Instead, every canton has its own health care services and laws (Zelger, 2006). For this reason, there are differences in pharmaceutical compounding practices and regulations throughout Switzerland.

5.1 **Legislation**

According to Swiss legislation, medicines must be authorised by Swissmedic (Section 5.2.1) to be placed on the market. Compounded medicines are included in the exemptions to this authorisation and are classified into 3 categories, as follows:

1. *Formule Magistrale* (magistral formulae): correspond to the medicines prepared according to a medical prescription in a community pharmacy or hospital pharmacy or, by request of these, in a establishment which is a holder of a manufacturing authorisation, and which are intended for use by one person or a specific group of people (L'Assemblée Fédérale de la Confédération Suisse, 2000).
2. *Formule Officinale* (officinal formulae): correspond to the medicines prepared in small quantities in a community pharmacy, hospital pharmacy, drugstore or in another establishment which is a holder of a manufacturing authorisation, and in accordance with a special monograph of the PhHelv (Section 5.2.2), another pharmacopoeia, or a formulary recognised by

Swissmedic (Section 5.2.1), and which are intended to be dispensed to the customers of that establishment (L'Assemblée Fédérale de la Confédération Suisse, 2000). So far, Swissmedic (Section 5.2.1) has not recognised any national or international formularies (Gosdschan, 2008). Thus, only the monographs included in the pharmacopoeias belong to this category of officinal formulae.

3. *Formule Propre* (own formulae): correspond to the medicines prepared in small quantities in a community pharmacy, hospital pharmacy, drugstore or in another establishment which is a holder a manufacturing authorisation, in accordance with a formula of that particular establishment (L'Assemblée Fédérale de la Confédération Suisse, 2000). A hospital's individual formulae belong to this category of own formulae (Gosdschan, 2008).

In Switzerland, compounded medicines prepared in small quantities are subject to GMP - *Règles de Bonnes Pratiques de Fabrication de Médicaments en Petites Quantités* - which are part of the PhHelv (Section 5.2.2) (Swissmedic, 2006a; Zelger, 2006). These guidelines encompass a set of 9 norms, namely: quality management; personnel; facilities and equipment; documents; production; QC; outsourcing production; claims and product withdrawals; and autoinspection. These GMP requirements are part of a QA system, which guarantees that compounded medicines are consistently prepared with appropriate quality.

5.2 **Professional organisations and information sources**

5.2.1 **Swiss professional organisations**

- Swiss Agency for Therapeutic Products (Swissmedic): is the Swiss agency for the authorisation and supervision of therapeutic products and aims to ensure that authorised therapeutic products are of high quality, effective and safe; it is responsible for the PhHelv (Section 5.2.2). Companies that manufacture or distribute medicinal products in Switzerland require a licence granted by Swissmedic (Swissmedic, 2009; 2010). Swissmedic is an independent body responsible for developing and enforcing medicines legislation and regulations (Zelger, 2006).

- *Société Suisse des Pharmaciens* (pharmaSuisse): is the Swiss society of pharmacists, which has departments of “Politics and Economy”, “Science, Education and Quality” and “Communication and Marketing”. In 2009, there were 1,353 (78.2%) pharmacies and 5,528 individual members of pharmaSuisse (no date). The pharmaSuisse is the entity responsible for the *Formularium Helveticum*, a non-official Swiss formulary (Section 5.2.2) (Riedl, 2008).
- Swiss Society of Public Health Administration and Hospital Pharmacists (GSASA): is a small professional group, comprising mainly hospital pharmacists, that has an important and active role in the Swiss health care system. The GSASA has several departments, linked to specific working groups, including the departments of drug manufacturing, risk management and quality. The GSASA created its own professional quality referencing system: Quality Referential for Swiss Hospital Pharmacies (QRHP) (Zelger, 2006; GSASA, 2010; Weidemeier *et al.*, no date). In 1999, GSASA introduced the postgraduate education in Swiss hospital pharmacy (Grünig, 2006).

5.2.2 **Swiss information sources**

Switzerland has not published an official formulary for pharmaceutical compounding. Instead, there are 2 non-official formularies that have not been updated recently and are considered largely obsolete: *Formularium Helveticum*, published in 1991 by pharmaSuisse; and *Formularium Clinicum,* published in 1996 by GSASA (Barbosa and Pinto, 2001). According to Martinelli (2006), no professional organisation has been appointed so far for financing and/or developing an officially recognised formulary. As a result, the only official reference source in Switzerland with monographs for compounded medicines is the PhHelv.

- *Pharmacopoea Helvetica* (PhHelv): is the Swiss Pharmacopoeia that, in association with the PhEur, constitutes the official pharmacopoeia in Switzerland. The PhHelv 10, published in 2006, includes 134 (official) monographs, almost half of which are for pharmaceutical preparations. The 10th edition introduced, among others, GMP for cytotoxic medicines (in small quantities) and also an (official) monograph for Methadone HCl 10 mg/mL

Oral Solution (Appendix 2). A monograph for methadone oral solution was already included in the *Formularium Helveticum* but it was a non-official formula. The monographs for pharmaceutical preparations included in the PhHelv correspond to standardised quality preparations (Swissmedic, 2006a; 2006b; 2009). However, the PhHelv does not include all pharmaceutical preparations and there is a general lack of official monographs for compounded medicines in Switzerland (Martinelli, 2006). Swissmedic does not have sufficient resources to include all the necessary pharmaceutical preparations in the PhHelv and, therefore, there is a gap between the officinal formulae that are needed and the official monographs that are published in Switzerland (Gosdschan, 2008).

- E-Drug Compounding: is a website that contains compounding information collected by a medium sized Swiss hospital pharmacy for over 30 years and which aims to support the practice of pharmaceutical compounding, particularly in developing countries (*E-Drug Compounding*, 2011a). It includes a long list of free downloadable monographs for ophthalmic preparations; oral dosage forms (27 compounded medicines and 6 vehicles); parenteral forms; suppositories; topical preparations; other pharmaceutical preparations; and cosmetic preparations (*E-Drug Compounding*, 2011b).

5.3 **Methods**

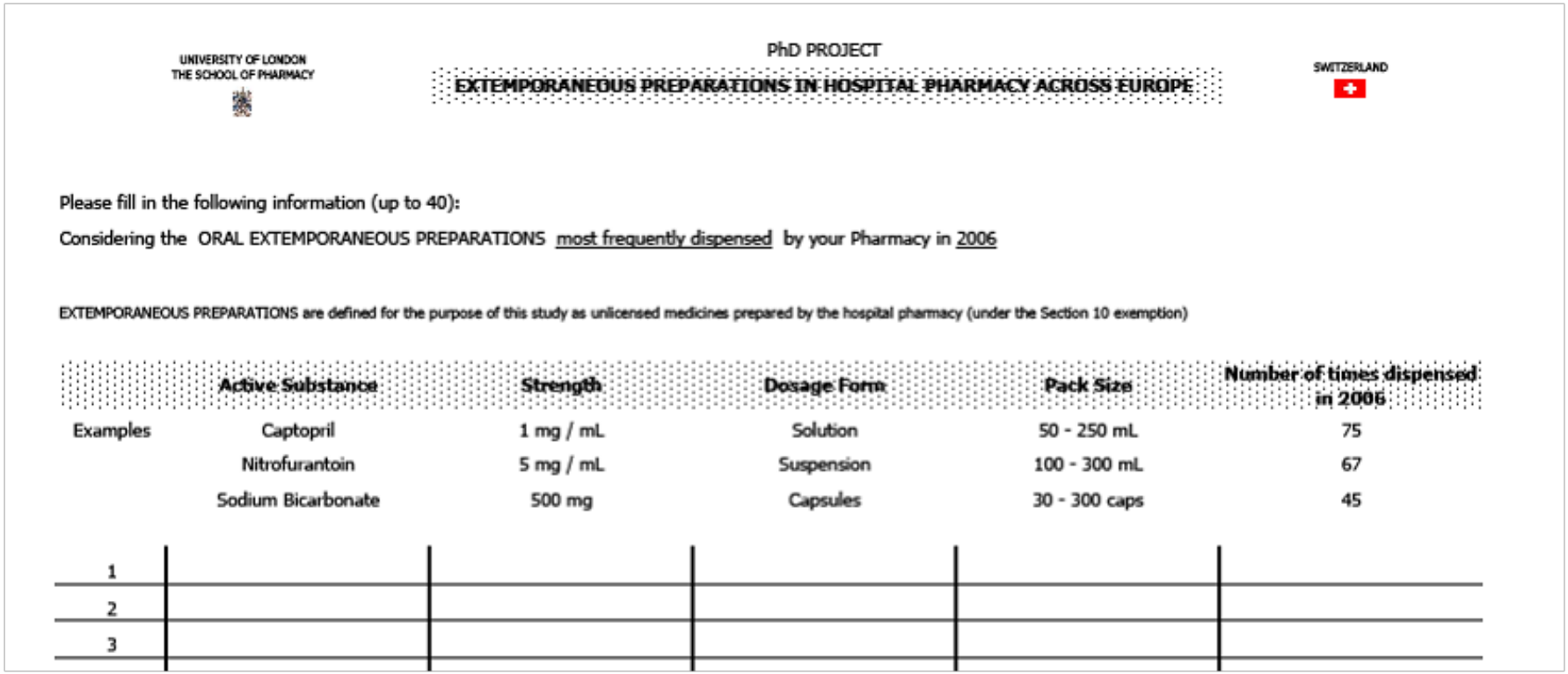
Switzerland was the first European country included in the research in which information regarding the practice of pharmaceutical compounding was not readily accessible and, therefore, there was a need for an international collaboration with Swiss stakeholders. Hans Stötter (clinical reviewer and head of the working group on paediatrics at Swissmedic, Section 5.2.1) was contacted in July 2007 and the Swiss questionnaire was discussed at this stage. The questionnaire was developed in English and comprised a detailed introduction, as suggested by the stakeholder, 1 Excel table and 2 additional questions, as the Portuguese and UK questionnaires.

In January 2008, it was decided that Bettina Gasser (Masters' student at Swissmedic) would contribute to the research as part of her thesis on "Drug safety in Paediatrics" (Gasser, 2008). Therefore, MC visited Swissmedic to set up the research but, in the meantime, the Masters' student had already

contacted part of the Swiss hospital pharmacies, by telephone and email, with the request for oral compounded medicines most frequently dispensed to paediatrics (only). The Swiss questionnaire (main heading in Figure 5.1) was sent to hospital pharmacies, despite the fact that it was incomplete (i.e. the definition of compounded medicines corresponded to the UK definition of extemporaneous preparations - Section 4.3.1).

However, since the Masters' student explained the purpose of the research to each participant, the questionnaire was regarded by hospital pharmacies just as a table for data collection. Furthermore, the questionnaire was initiated in 2007 and, therefore, it addressed information relating to 2006, despite the fact that data collection was undertaken in 2008. For these reasons, data collected in Switzerland referred to oral compounded medicines dispensed to paediatrics (only) and in the year 2006.

The purposive sample of hospitals was established by the stakeholder and the Masters' student; and it included 33 hospitals (1 per city), distributed throughout the country. The hospital in Bern was visited by MC and, although only 1 hospital was included in fieldwork, several discussions with national stakeholders took place in Bern, which contributed to a better understanding of the practice of pharmaceutical compounding in Switzerland.



UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

EXTEMPORANEOUS PREPARATIONS IN HOSPITAL PHARMACY ACROSS EUROPE

SWITZERLAND

Please fill in the following information (up to 40):

Considering the ORAL EXTEMPORANEOUS PREPARATIONS most frequently dispensed by your Pharmacy in 2006

EXTEMPORANEOUS PREPARATIONS are defined for the purpose of this study as unlicensed medicines prepared by the hospital pharmacy (under the Section 10 exemption)

	Active Substance	Strength	Dosage Form	Pack Size	Number of times dispensed in 2006
Examples	Captopril	1 mg / mL	Solution	50 - 250 mL	75
	Nitrofurantoin	5 mg / mL	Suspension	100 - 300 mL	67
	Sodium Bicarbonate	500 mg	Capsules	30 - 300 caps	45
1					
2					
3					

Figure 5.1 Country-specific questionnaire (Switzerland).

5.4 **Results and discussion**

Following the visit to Swissmedic, a total of 15 datasets were returned to MC by email, which corresponded to the oral compounded medicines most frequently dispensed to paediatric patients in 15 Swiss hospital pharmacies (45% response rate of 33 pharmacies). The participant hospitals were located across the country, in the cities of: *Basel*, Bern (capital), *Biel*, *Chur*, *Fribourg, Geneva, La Chaux de Fonds*, *Lausanne*, *Lugano, Lucern, Munsterlingen, Neuchatel*, *Sion, Winterthur* and *Zurich* (Figure 5.2), corresponding to a total of 12 cantons and including the largest Swiss cities.

Figure 5.2 Map of Switzerland adapted from National Geographic Society (1998c); indicating the location of the participant hospitals (●).

The majority of non-participant hospitals stated that they had not dispensed any compounded medicines to paediatric patients, which does not necessarily mean that they had not dispensed any compounded medicines at all. If all oral compounded medicines had been requested (instead of for paediatrics only), more hospitals may have contributed with data to the research.

A total of 12 hospital pharmacies shared data in the questionnaire provided and 3 (20%) hospitals shared data in their own format. A total of 5 hospitals provided datasets including non-oral compounded medicines (e.g. IV and eye

preparations; topical and rectal compounded medicines), which were excluded accordingly (Section 2.4.1). After data processing, the Swiss database included a total of 469 data entries, corresponding to the datasets of 15 hospitals.

5.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral compounded medicines in Switzerland (for paediatric patients) is shown in Table 5.1. Active substances were grouped according to the respective therapeutic classification (*Martindale 35*, 2007), giving a total of 142 different active substances and 31 therapeutic groups. Cardiovascular drugs was the group with the greatest number of different active substances (n=29), followed by electrolytes (n=14) and antibacterials (n=12). Although these active substances were all reported as oral compounded medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: disinfectants and preservatives (Appendix 12); and paraffins and similar bases (Appendix 13). The active substances included in these groups are described in the respective appendixes.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 3 NTI drugs were dispensed as oral compounded medicines (underlined in Table 5.1)

The active substances dispensed by most hospitals were: spironolactone (n=12), phenobarbital (n=11) and captopril (n=10).

All active substances reported were included in *Martindale 35* (2007) with the exception of cystamine dihydrochloride, which was dispensed by 1 hospital as 150 mg capsules (Appendix 26). Cystamine is considered a potential candidate for the treatment of the neurodegenerative disorder Huntington disease (Borrell-Pagès *et al.*, 2006).

The majority (93%) of compounded medicines dispensed included just 1 active substance and only 7% included 2 or more active substances.

Table 5.1 Active substances most frequently dispensed as oral compounded medicines in Switzerland (for paediatric patients) (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aspirin, codeine, codeine phosphate, hydromorphone HCl, indometacin, methadone HCl, morphine, morphine HCl, opium

Anthelmintics
Levamisole

Antibacterials
Dapsone, flucloxacillin sodium, isoniazid, neomycin, neomycin sulfate, polymyxin B sulfate, pyrazinamide, rifabutin, rifampicin, sulfadoxine, spiramycin, trimethoprim

Antidepressants
Fluoxetine HCl, oxitriptan

Antiepileptics
Clobazam, ethosuximide, mesuximide, phenobarbital, phenytoin, primidone, topiramate, vigabatrin

Antimalarials
Primaquine phosphate, pyrimethamine

Antineoplastics
Busulfan, etoposide, hydroxycarbamide, mercaptopurine

Antiparkinsonian drugs
Levodopa, carbidopa

Antiprotozoals
Metronidazole

Antivirals
Ganciclovir, nevirapine, valganciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Chloral hydrate, diazepam, midazolam

Bronchodilators and anti-asthma drugs
Caffeine, caffeine citrate

Cardiovascular drugs
Acenocoumarol, amiodarone, amiodarone HCl, amlodipine besilate, atropine sulfate, captopril, carvedilol, clonidine HCl, diazoxide, dihydralazine sulfate, dipyridamole, enalapril, enalapril maleate, flecainide acetate, fluvastatin sodium, furosemide, hydrochlorothiazide, labetalol HCl, losartan potassium, metoprolol, metoprolol tartrate, nifedipine, phenoxybenzamine HCl, phenprocoumon, propafenone HCl, propranolol HCl, sotalol HCl, spironolactone, valsartan

Chelators, antidotes and antagonists
Activated charcoal, deferiprone

Corticosteroids
Dexamethasone, fludrocortisone acetate, hydrocortisone, prednisone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Ipecacuanha, naphazoline

Disinfectants and preservatives
Chlorhexidine, sodium benzoate

Electrolytes
Calcium glycerophosphate, calcium hydrogen phosphate, calcium phosphate, dibasic potassium phosphate, dibasic sodium phosphate, magnesium gluconate, magnesium sulfate, monobasic potassium phosphate, potassium chloride, potassium citrate, potassium gluconate, sodium bicarbonate, sodium chloride, sodium citrate

GI drugs
Calcium carbonate, cisapride, hyoscine butylbromide, mesalazine, omeprazole, ranitidine, ranitidine HCl

General anaesthetics
Ketamine HCl

Immunosuppressants
Azathioprine, mycophenolate mofetil, tacrolimus

Local anaesthetics
Oxybuprocaine HCl

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide

Muscle relaxants
Baclofen, tizanidine HCl

Nutritional agents and vitamins
Arginine HCl, calcium folinate, folic acid, glucose, isoleucine, pyridoxine HCl, sucrose, valine, zinc acetate, zinc sulfate

Paraffins and similar bases
Cholesterol, liquid paraffin

Prostaglandins
Misoprostol

Sex hormones
Ethinylestradiol

Supplementary drugs and other substances
Ammonia, macrogol 4000, melatonin, strychnine nitrate, thalidomide, ursodeoxycholic acid

Thyroid and antithyroid drugs
Iodine, levothyroxine sodium, potassium iodide, sodium perchlorate

Urological drugs
Sildenafil citrate

In total, 8 different compounded medicines were dispensed as multi-drugs, as follows: dibasic potassium phosphate and monobasic potassium phosphate; iodine and potassium iodide (Lugol's Solution, see below); levodopa and carbidopa; monobasic potassium phosphate and dibasic sodium phosphate; oxybuprocaine HCl and naphazoline; polymyxin B sulfate and neomycin; sodium chloride, sodium citrate, potassium chloride and glucose (WHO Oral Rehydration Salts - ORS - see below); and sulfadoxine and pyrimethamine.

Two compounded medicines were reported by the given titles which they are commonly known for, as follows:

- Lugol's Solution (5%): it was dispensed by 1 hospital in a total of 37 containers of 20 mL (Appendix 16).
- WHO ORS (27.9 g): it was dispensed by 1 hospital in a total of 30 packs of oral solids of 20 sachets each (to be dissolved in 1 L of water). The WHO ORS corresponds to a balanced glucose-electrolyte mixture, recommended by WHO/UNICEF, for the treatment of clinical dehydration throughout the world; and it has substantially contributed to the global reduction in mortality from diarrhoea. The standard solution (311 mOsm/L) was improved to a hypo-osmolar solution (245 mOsm/L), by reducing the glucose and sodium chloride concentrations, to avoid possible adverse effects of hypertonicity on net fluid absorption (WHO and UNICEF, 2006). The Swiss hospital dispensed the WHO ORS standard; both standard and hypo-osmolar solutions are shown in Appendix 16.

The majority of compounded medicines were reported by active substances and only 9% by the respective proprietary medicines as, for instance: Adalat (nifedipine), Prograf (tacrolimus) and Viagra (sildenafil citrate). Proprietary medicines were reported by a total of 8 hospitals and these were used in the preparation of both oral solid and oral liquid dosage forms.

5.4.2 **Oral compounded medicines**

In Switzerland, the most frequently dispensed oral compounded medicines were liquid dosage forms. A total of 33,328 packs/units (74.1%) of oral liquids were reported, whereas 11,556 packs (25.7%) of oral solids and 80 units (0.2%) of oromucosal preparations were reported by the participant hospitals (Figure 5.3). This is not in accordance with Brion *et al.* (2003), who concluded that capsules were the most frequently dispensed oral dosage forms for children in Switzerland but their findings were based on only 2 Swiss hospitals.

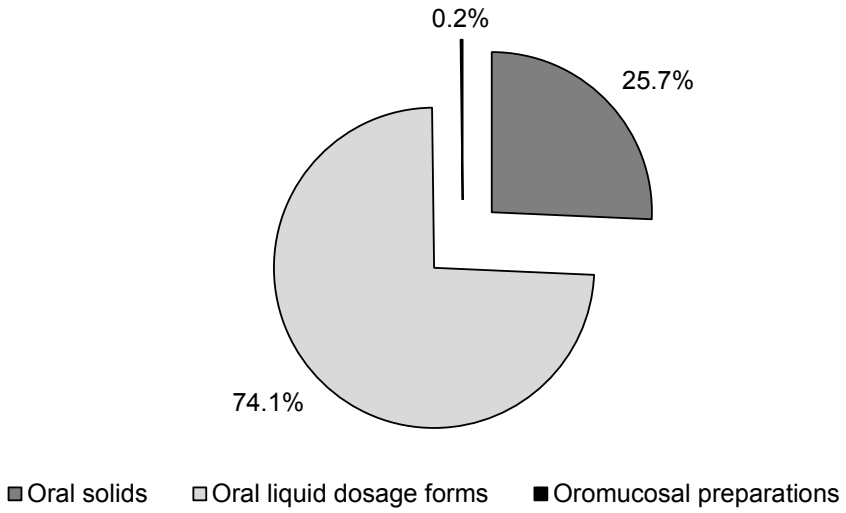


Figure 5.3 Number of packs/units of oral (and oromucosal) compounded medicines dispensed in Switzerland, per dosage forms.

The most frequently dispensed active substance was morphine (Figure 5.4). Morphine was dispensed as oral liquids (solutions), both as morphine and morphine HCl, in a total of 20,313 packs/units, which represented 42% of all active substances dispensed. It was reported by 6 hospitals, in 6 different strengths (0.01-4%), either in packs of single-dose units (2-10 mL) or individual multidose units (20-200 mL).

The next most frequently dispensed active substances were neomycin (6%), sodium citrate (5%) and omeprazole (4%), as shown in Figure 5.4. Neomycin was dispensed as oral solids (capsules) and oral liquids (solutions and syrups) by 2 hospitals only; it was reported as neomycin sulfate and neomycin in combination with polymyxin B sulfate.

Sodium citrate was dispensed as oral solids (capsules and sachets) and oral liquids (solutions) by a total of 6 hospitals; it was reported as single-drug as well as part of the WHO ORS (Appendix 16).

Omeprazole was dispensed as oral liquids (solutions and suspensions) and in the single strength of 2 mg/mL; it was reported by 4 hospitals as multidose units of 50 mL, 60 mL and 100 mL.

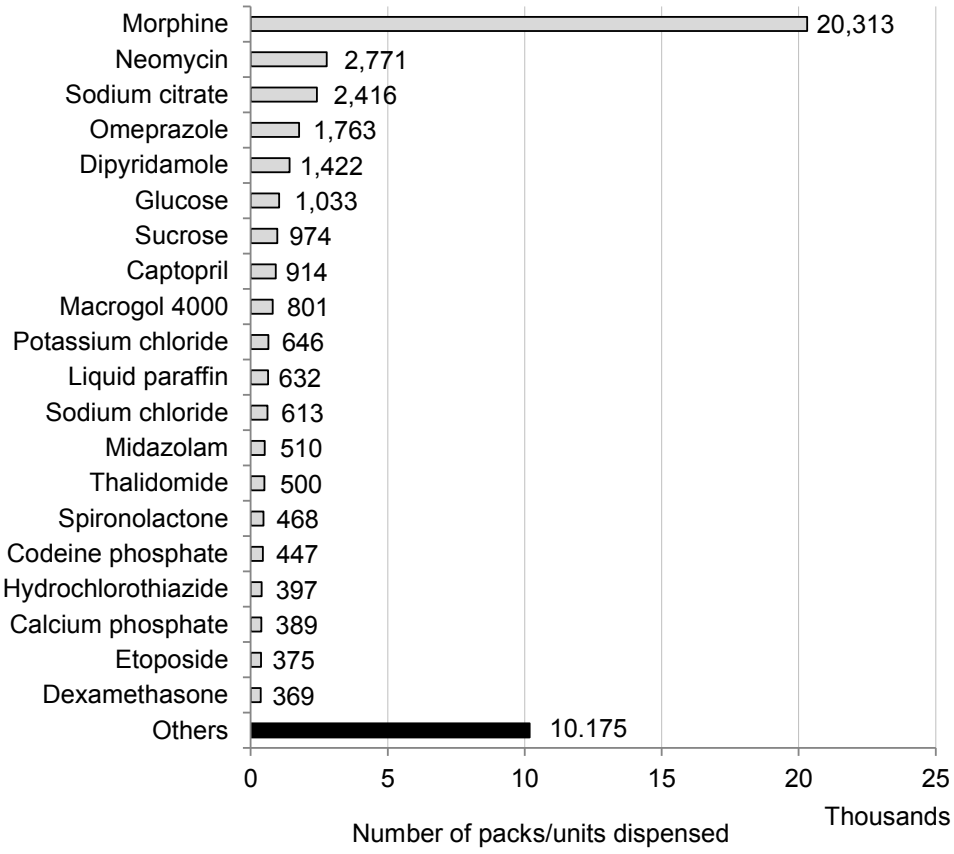


Figure 5.4 Overall top 20 active substances per number of packs/units dispensed.

The top 20 active substances included captopril, spironolactone and hydrochlorothiazide, which corresponded to the oral unlicensed medicines

included in the top 10 (unlicensed and off-label) dispensed in a Swiss paediatric hospital (Di Paolo *et al.*, 2006).

In Switzerland, oral compounded medicines were reported in a wide range of strengths, particularly with regards to oral solids. The active substances dispensed in the greatest range of strengths were:

- Captopril: 19 (0.01-7.5 mg) oral solids and 1 (1 mg/mL) oral liquid.
- Phenobarbital: 14 (0.05-30 mg) oral solids and 3 (1-5 mg/mL) liquids.
- Carvedilol: 13 (0.1-5 mg) oral solids.
- Propranolol HCl: 10 (1-8 mg) oral solids and 1 (2 mg/mL) oral liquid.
- Spironolactone: 8 (0.25-7.25 mg) oral solids and 3 (2-10 mg/mL) liquids.
- Hydrochlorothiazide: 9 (1-8 mg) oral solids and 1 (5 mg/mL) oral liquid.
- Propafenone HCl: 9 (5-70 mg) oral solids.
- Sildenafil citrate: 9 (0.5-20 mg) oral solids.

Oral solids were reported in a wider range of strengths that oral liquid dosage forms, which is expected considering that oral liquids allow dosing flexibility by variable volumes, which is not easily achieved with solid dosage forms (Section 2.1.3). The strength of compounded medicines dispensed to paediatric patients is based on the age and body weight (mg/kg) / surface area (mg/m^2) of patients (Section 1.1.5.1) and, therefore, variable strengths may be required in this population. The wide range of strengths encountered in Switzerland reinforces the importance of compounding in meeting the needs for particular strengths in the paediatric population (Section 1.1.4).

The overall top 10 therapeutic groups are displayed in Figure 5.5. The most frequent therapeutic group was analgesics, anti-inflammatory drugs and antipyretics, which corresponded to almost 50% of all therapeutic groups (mainly because of the large quantities reported of morphine). The next most frequent therapeutic groups were electrolytes (11%) and cardiovascular drugs (10.5%). A total of 9 hospital pharmacies reported active substances from the top 2 groups; whilst cardiovascular drugs were reported by all participant hospitals.

In 2005, the number of patients discharged from all hospitals (including through death) in Switzerland was highest for diseases of the

musculoskeletal system (2,145 patients / 100,000 population); injury and poisoning; and diseases of the circulatory system (Figure 5.6) (WHO Regional Office for Europe, 2008). Thus, it was to be expected then that "analgesics, anti-inflammatory drugs and antipyretics" and "cardiovascular drugs" were part of the top therapeutic groups in Switzerland (Figure 5.5).

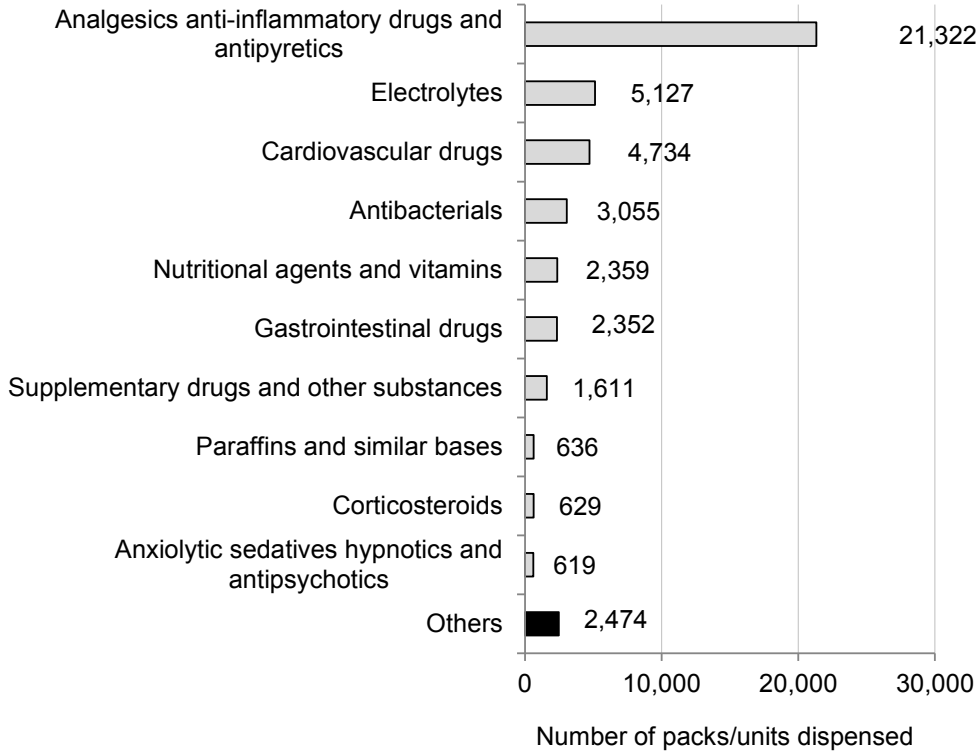


Figure 5.5 Overall top 10 therapeutic groups ranked by number of packs/units dispensed.

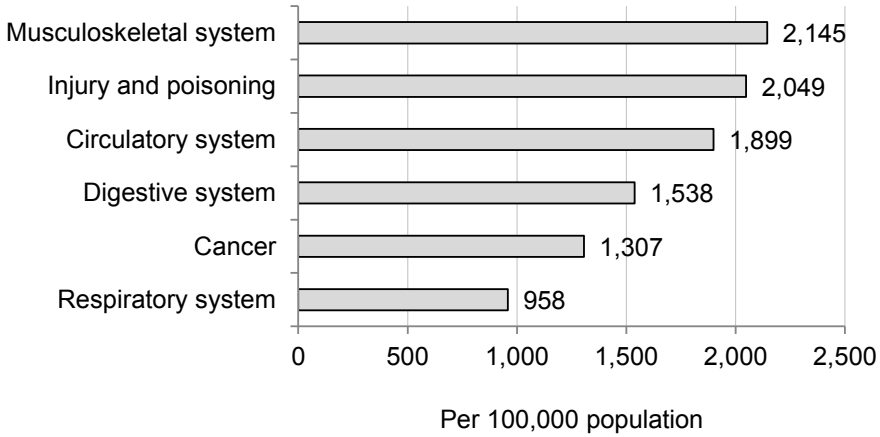


Figure 5.6 Number of patients per 100,000 population discharged from all hospitals (including through death) in Switzerland during 2005 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

5.4.2.1 **Oral solids**

Oral solid dosage forms corresponded to 25.7% of all compounded medicines (Figure 5.3) and were dispensed by all participant hospitals, with the exception of 1 hospital that reported oral liquids only (93%). The oral solids dispensed included capsules, oral powders and tablets.

Capsules accounted for 85% of oral solids (Figure 5.7) and were reported by all participant hospitals that dispensed oral solids. Considering that data in Switzerland referred to paediatric patients only, it is likely that the capsules reported were commonly opened before administration and their contents added to liquids or food. The top 3 active substances dispensed as capsules (and ranked by number of individual units) corresponded to the top 3 dispensed as oral solids, as follows: potassium citrate (39,200 units, 2 hospitals), captopril (37,916 units, 8 hospitals) and cystamine dihydrochloride (33,000 units, 1 hospital). Captopril (capsules) was also identified by Di Paolo *et al.* (2006) as a frequently dispensed oral compounded medicine in a Swiss paediatric hospital. One hospital stated that their capsules included mannitol (as a main excipient), which represents a good alternative for lactose intolerant patients. Capsules were dispensed in variable pack sizes, from 1 unit to 1,000 individual units of capsules. The most frequently dispensed pack sizes were 50 units (37.2%), followed by 100 units (14.8%), 60 units (13.3%) and 30 units (11.8%). Therefore, an estimate of 50 units of capsules, per pack dispensed, was adopted for the purposes of overall data comparison.

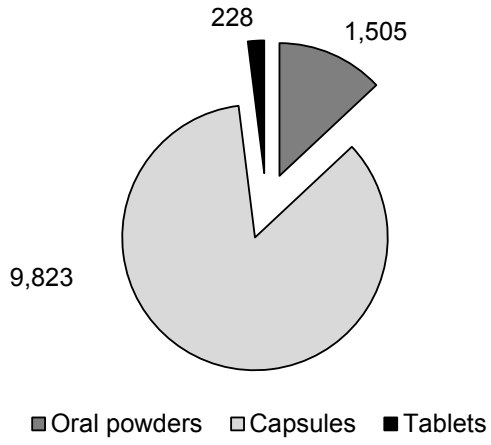


Figure 5.7 Oral solid dosage forms dispensed per number of packs.

Oral powders corresponded to 13% of oral solids (Figure 5.7) and were reported by 5 hospitals only. The top 3 *active substances* so dispensed (and ranked by number of individual units) were: calcium carbonate (996 units, 1 hospital); macrogol 4000 (801 units, 1 hospital); and the WHO ORS (Section 5.4.1).

Tablets comprised only 2% of all oral solids (Figure 5.7) and were reported by only 1 hospital. The preparation of tablets requires specialist tableting equipment and not all hospitals can afford such an investment (Section 2.1.3). A total of only 4 active substances were reported as tablets: isoniazid 100 mg (packs of 100); deferiprone 500 mg (packs of 500); arginine HCl 500 mg (packs of 100); and levamisole 50 mg (packs of 50).

The top 3 therapeutic groups (for oral solids only) were: cardiovascular drugs (98,888 units of capsules), electrolytes (92,477 units of capsules and oral powders) and supplementary drugs and other substances (938,261 units of capsules and oral powders). Cardiovascular drugs and electrolytes were in the overall top 3 therapeutic groups (Figure 5.5).

5.4.2.2 **Oral liquids**

Oral liquid dosage forms corresponded to 74.1% of all compounded medicines (Figure 5.3) and were dispensed by all participant hospitals, with the exception of 1 hospital that reported oral solids only (93%). The dosage forms dispensed[32] included solutions, suspensions, syrups and oral drops[33]. Oral liquids allow dosing flexibility and are easy to administer (in particular to paediatric patients) (Section 2.1.3) and, hence, it was expected that these were the most frequently dispensed dosage forms to paediatric patients in Switzerland.

The volumes reported ranged from 2 mL to 500 mL, which included both unidose and multidose containers. Unidose containers were reported by number of packs (e.g. 12x2.5 mL) and included volumes from 2 mL up to 10 mL. The most frequently dispensed pack size was 12 individual units, which

[32]There was evidence of a tincture (opium) dispensed by 1 hospital but it was classified as an oral solution and, therefore, it was not considered a tincture.
[33]Oral drops are solutions, emulsions or suspensions that are administered in small volumes such as drops by means of a suitable device (EDQM, 2007).

was adopted for the purposes of overall data comparison. The active substances reported as unidose were morphine HCl (0.1% and 1%) and caffeine citrate (10 mg/mL), which were dispensed as unidose solutions, in a total of 19,079 packs (228,689 units), by 2 hospitals. These 2 active substances were identified by Di Paolo *et al.* (2006) as part of the compounded medicines prepared as batches in a Swiss paediatric hospital. Multidose containers, on the other hand, were reported by number of individual containers and included volumes from 10 mL up to 500 mL. For volumes of 10 mL, oral liquids were considered multidose, with the exception of those reported by number of packs.

Solutions and suspensions corresponded to 92.9% (30,971 multidose containers / unidose packs) of all oral liquids and were reported by 14 hospitals. The top 3 active substances dispensed as solutions and suspensions were: morphine, sodium citrate and omeprazole (Section 5.4.2), which were all part of the top 5 overall active substances (Figure 5.4). One hospital pharmacy stated that their suspensions were prepared with the proprietary suspending vehicles Ora-Sweet and Ora-Plus.

Syrups corresponded to 7% (2,343 multidose containers; 15-250 mL) of all oral liquids and were reported by 8 hospitals. Nevertheless, it is likely that the classification of some oral liquids by the hospital pharmacies was not accurate and, therefore, part of the solutions/suspensions might have corresponded to syrups (and vice-versa) (Section 2.1.3). A total of 14 active substances were dispensed as syrups and the top 3 were as follows: neomycin in combination with polymyxin B sulfate (41.6%), potassium chloride (26.3%) and codeine / codeine phosphate (21.2%).

Oral drops were reported by only 1 hospital and only 1 compounded medicine was dispensed, namely: morphine solution 2% (50 mL), which corresponded to less than 0.1% (14 multidose containers) of all oral liquids. Likewise, the classification of some oral liquids by the hospital pharmacies may not have been accurate and, therefore, part of the solutions/suspensions might have corresponded to oral drops (and vice-versa) (Section 2.1.3).

5.4.2.3 **Oromucosal preparations**

In Switzerland, only 1 oromucosal preparation was dispensed, namely: chlorhexidine 0.05% solution (Appendix 12) by only 1 hospital (7%). A total of 80 multidose containers of 250 mL were reported, which corresponded to 0.2% of all compounded medicines reported (Figure 5.3).

5.5 **Summary**

- Switzerland was the only non-member of the EU included in the international survey but it is considered the non-member with the greatest relations with the EU.
- Compounded medicines in Switzerland correspond to magistral, officinal and own formulae, which may be prepared individually or in batches of small quantities. Batch preparation must comply with the respective GMP and the compounded medicines prepared in small quantities are restricted to the formulas included in the PhHelv.
- Data collection in Switzerland was undertaken by a Masters' student at Swissmedic and referred to oral compounded medicines dispensed to paediatric patients (only).
- A purposive sample of 33 hospitals was included in the research and a response rate of 45% was obtained. A total of 142 different active substances (including 3 NTI drugs) were reported corresponding to 31 different therapeutic groups. The top 3 therapeutic groups were cardiovascular drugs (n=29), electrolytes (n=14) and antibacterials (n=12).
- Oral solid dosage forms were reported by 93% of all participant hospitals and included capsules, oral powders and tablets. Capsules were dispensed in a sum of 9,823 packs and the top 3 active substances were: potassium citrate, captopril and cystamine dihydrochloride. Oral powders were dispensed in a total of 1,505 packs and the top 3 *active substances* were: calcium carbonate, macrogol 4000 and the WHO ORS. Tablets were dispensed in a total of 228 packs and only 4 active substances were reported, namely: isoniazid, deferiprone, arginine HCl and levamisole.
- Oral liquid dosage forms were reported by 93% of all participant hospitals and included solutions, suspensions, syrups and oral drops. Oral liquids were dispensed in a total sum of 33,328 multidose containers / unidose packs and the top 3 active substances were: morphine, sodium citrate and omeprazole. Solutions and suspensions were dispensed in a total of 30,971 (92.9%) multidose containers / unidose packs whereas syrups were dispensed in a total of 2,343 (7%) and oral drops in a total of 14 (<0.1%) multidose containers.
- Oral liquids (74.1%) were more frequently dispensed than oral solids (25.7%).
- Oromucosal preparations were dispensed by only 1 hospital (7%) and corresponded to chlorhexidine 0.05% solution, in a sum of 80 multidose containers (0.2%) of 250 mL.

6. **Compounding in Poland**

Poland is an Eastern European country that joined the EU in 2004 and its official language is Polish (*Europa*, 2009). Poland occupies an area of 312,700 Km^2, from the Baltic Sea in the North to Slovakia in the South, and is the 6^{th} most populated country in the EU, with a population of 38.2 million in 2007 (Figure 2.2) (*Europa*, 2008). Poland is administratively divided in 16 districts (*Informator turystyczny*, 2012).

In 2006, there were 792 hospitals in Poland (ratio of 2.08 hospitals per 100,000 population) and a total of 196,828 hospital beds (ratio of 516.17 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2006, there were 22,442 pharmacists in Poland (ratio of 58.85 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4), of which 9% were hospital pharmacists (Pawłowska[34], 2006a). According to the EAHP survey, the average number of pharmacists in Polish hospitals is 3.4, compared to the European average of 4.7. Moreover, Polish hospitals have an average of 3.8 qualified pharmacy technicians/assistants per hospital (European average is 6). Poland also has an average of 2.0 non-qualified pharmacy assistants per hospital (EAHP, 2005; Hartmann, 2010). In the opinion of Kozaczuk (2007), hospital pharmacies need to employ enough pharmacists/technicians for an adequate provision of services but pharmaceutical legislation in Poland lacks regulations on the ratio of pharmacists/technicians per number of beds/services.

The preparation of compounded medicines occurs in both hospital and community pharmacies throughout Poland. Sterile and non-sterile compounded medicines are prepared in the hospital setting but not all hospitals have an aseptic preparation area (Pawłowska, 2010). Hospital pharmacy is one of the pharmaceutical specialisations in Poland and specialised hospital pharmacists are expected to be familiar with formulation improvement and compounding procedures, particularly in relation to sterile

[34] Janina Pawłowska is the director of the department of hospital pharmacy affairs of the Polish pharmaceutical chamber (Section 6.2.1).

compounding (Kozaczuk, 2006). As pharmaceutical compounding allows pharmacists the adjustment of dosage forms and strengths to individual patient needs, it is considered an important pharmaceutical service carried out at Polish hospitals (Kozaczuk, 2006; 2007; Grześkowiak, 2010; Pawłowska, 2010). For instance, the adjustment of strengths of omeprazole for paediatric use is common practice in Poland and the preparation of capsules containing a customised number of enteric-coated pellets (Section 4.4.1) was recommended by Gajewska *et al.* (2007). However, hard (gelatin) capsules (Section 2.1.3) are not common in Poland and the most frequently dispensed (solid) compounded medicines are, instead, starch capsules or cachets (Section 6.4.2). In fact, Polish hospitals prepare large quantities of starch capsules by weighing each dose of the powder into individual capsules, which is an arduous and time-consuming manual process (Płaczek and Sznitowska, 2006). As a consequence, the preparation of hard gelatin capsules (in capsule machines) was recommend by Płaczek and Sznitowska (2006) as an alternative.

6.1 **Legislation**

In Poland, pharmacy services include the preparation of compounded medicines (Kozaczuk, 2007). Two types of compounded medicines may be distinguished: *Lekiem Aptecznym* and *Lekiem Recepturowym*, which correspond to the officinal and magistral formulae considered in the European legislation (Section 14.1). *Lekiem Aptecznym* is, therefore, a medicine prepared in a pharmacy, according to the Polish Pharmacopoeia or pharmacopoeias recognised in EU member states, and dispensed directly by the pharmacy (officinal formula). *Lekiem Recepturowym* is a medicine prepared in a pharmacy according to a doctor's prescription (magistral formula) (Ministerstwo Zdrowia, 2001; Janicki *et al.*, 2003). In practice, no distinction is made with regards to the type of compounded medicines prepared and dispensed by Polish pharmacies, but almost all compounded medicines correspond to magistral formulae (*Lekiem Recepturowym*).

The *Główny Inspektorat Farmaceutyczny* (main pharmaceutical inspectorate) for the Polish district of *Pomorskie* was visited by MC and, in an interview with the pharmaceutical inspector Weronika Żebrowska, the Polish legislation

for pharmaceutical compounding was discussed in detail (Główny Inspektorat Farmaceutyczny, 2008; 2010; Żebrowska, 2008). In Poland, the advance preparation of compounded medicines is not permitted and, therefore, batch preparation is only possible if several requests for the same compounded medicine are placed at the same time (Główny Inspektorat Farmaceutyczny, 2008). In addition, the preparation of compounded medicines for other pharmacies (third-party compounding) is not permitted and, as a result, compounded medicines have to be prepared and dispensed by the pharmacy receiving the order (EAHP, 2005; Główny Inspektorat Farmaceutyczny, 2008).

Polish legislation does not restrict the use of any active substances in pharmaceutical compounding, provided that these are included in the Polish Pharmacopoeia. In addition, Polish legislation does not specify any QA/QC requirements for pharmaceutical compounding, apart from acknowledging that it is the pharmacist's responsibility to assure the quality of the compounded medicines dispensed (Główny Inspektorat Farmaceutyczny, 2008).

With regards to record keeping, each request has to be given a reference code and 3 dates (date of prescription, preparation and dispensing) have to be recorded. Records have to be kept for a minimum of 5 years. Thus, it is not required to keep detailed documentation of the compounded medicines prepared, which makes it arduous and time-consuming to track down the medicines dispensed at a given time. The price of compounded medicines is established by law and depends on the dosage form and number of units dispensed (Ministerstwo Zdrowia, 2008). Therefore, the cost of compounded medicines should be the same throughout the country (Główny Inspektorat Farmaceutyczny, 2008).

6.2 **Professional organisations and information sources**

6.2.1 **Polish professional organisations**

In Poland, there is not currently a specific professional organisation for pharmaceutical compounding. Instead, there are organisations dedicated to pharmacy and pharmacists, including:

- *Naczelna Izba Aptekarska*: is the Polish pharmaceutical chamber, a self-governing professional body for pharmacists that represents their professional, social and economic interests. Membership is compulsory for all pharmacists who perform professional services (Naczelna Izba Aptekarska, 2012). This chamber comprises several national pharmaceutical departments, including the department of hospital pharmacy affairs that deals with the problems and challenges within hospital pharmacy in Poland (Pawłowska, 2006b).
- *Polskie Towarzystwo Farmaceutyczne* (PTFarm): is the Polish pharmaceutical society, an organisation established for more than 60 years that supports pharmacists and ensures the overall development of pharmacy in Poland. The PTFarm is responsible for several publications, including the Polish Pharmacopoeia (PTFarm, 2012).

6.2.2 **Polish information sources**

In Poland, there are 2 official pharmacopoeias in force, as follows:

- *Farmakopea Polska VIII* (PTFarm, 2008): is a translation of the PhEur and, hence, does not include monographs for compounded medicines.
- *Farmakopea Polska VI* (PTFarm, 2002): is the traditional Polish Pharmacopoeia, which has greater use among pharmacists than the *Farmakopea Polska VIII*. This pharmacopoeia includes a chapter on galenic preparations, with monographs containing the formula and method of preparation for selected topical and herbal preparations.

There is no official national formulary for pharmaceutical compounding. Instead, there are several textbooks which address the preparation of compounded medicines, including: *Receptariusz* (Stanisław *et al.*, 1992); *Ćwiczenia z Receptury* (Krówczyński and Jachowicz, 2000); *Zbiór Recept* (Janicki *et al.*, 2003); and *Receptura Apteczna* (Jachowicz, 2005).

6.3 **Methods**

Małgorzata Sznitowska, Vice-Rector for research and Director of the department of pharmaceutical technology at the Faculty of Pharmacy from the *Gdański Uniwersytet Medyczny* (Medical University of *Gdańsk*), was contacted as a stakeholder for collaboration. The Medical University of

Gdańsk is the largest medical academic institution in northern Poland and one of the 2 that specialise in hospital pharmacy (Kozaczuk, 2006; Medical University of Gdańsk, 2010). Małgorzata Sznitowska agreed to collaborate and was assisted by the researcher Monika Gajewska and the Masters' student Aleksandra Neubauer-Vasquez.

In April 2008, MC visited the Medical University of *Gdańsk* to discuss and initiate the research project, to gain a better understanding of the current compounding practices in Poland and to start data collection (Section 6.3.2).

6.3.1 **Purposive sample of hospitals**

The purposive sample of hospitals was established following consultation with Małgorzata Sznitowska and included 13 hospitals in northern and central Poland, as follows: *Bydgoszcz* (3 hospitals), *Gdańsk* (4 hospitals), *Poznań* (4 hospitals), *Warszawa* (1 hospitals) and *Wejherowo* (1 hospital) (Figure 6.1). These hospitals were likely to dispense the largest quantities of compounded medicines in northern and central Poland; 10 hospitals were classified as general hospitals and 3 as paediatric hospitals.

Figure 6.1 Map of Poland adapted from National Geographic Society (1998d); indicating the location of the purposive sample of hospitals pharmacies (●).

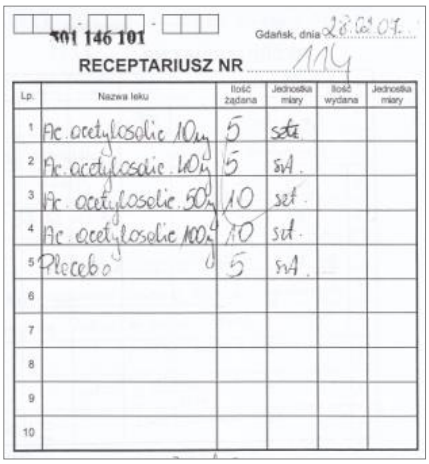
6.3.2 **Data collection**

Data collection in Poland was initiated during a 5-day visit to the Medical University of *Gdańsk* and included a visit to 2 hospitals and 1 community pharmacy. The fieldwork was organised by the stakeholder and was undertaken by MC, the Masters' student and other researchers.

It was acknowledged during fieldwork that the pharmacy staff did not speak English and, therefore, the visits were undertaken in Polish but were simultaneously translated by the Masters' student and/or the researchers. At this stage, it was evident that language was a strong limitation to clear and effective communication between MC and the Polish pharmacy staff (Section 2.1). Therefore, it was decided that the Masters' student would contact the purposive sample of hospitals in Polish, by telephone and email, instead of MC in English.

Another important finding during fieldwork was that Polish pharmacies kept manual records of the compounded medicines dispensed and, therefore, retrieving the required data was an arduous and time-consuming process. In fact, computing systems for drug information were very modest in Poland (EAHP, 2005). In addition, for those pharmacies that only recorded a reference code and 3 dates per compounding request (Section 6.1), retrieving the required data was even more arduous and time-consuming since it was necessary to track down and analyse each compounding request individually (Figure 6.2). Therefore, it was decided that the purposive sample of hospitals would be encouraged to contribute data in the most convenient format, instead of filling out a country-specific questionnaire (which was unlikely to elicit any responders), including the following information: active substance, strength, dosage form, pack size and number of times dispensed for the oral compounded medicines most frequently dispensed in 2007.

Because of the difficulties in retrieving the required data from manual records, the majority of hospital pharmacies were not willing to participate in the research. For this reason, the Masters' student visited 5 additional hospitals (total of 7 participant hospitals visited) with the purpose of collecting data on site by consulting the manual records and the corresponding compounding requests (Figure 6.3).



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RECEPTARIUSZ NR 114

Lp.	Nazwa leku	Ilość żądana	Jednostka miary	Ilość wydana	Jednostka miary
1	Ac. acetylosalic. 10mg	5	szt.		
2	Ac. acetylosalic. 40mg	5	szt.		
3	Ac. acetylosalic. 50mg	10	szt.		
4	Ac. acetylosalic. 100mg	10	szt.		
5	Placebo	5	szt.		
6					
7					
8					
9					
10					

Figure 6.2 (left) Compounding request for 5 different oral solid compounded medicines: aspirin 10-100 mg (n=4) and 1 placebo (n=1) (patient and pharmacy details omitted).

Figure 6.3 (right) Compounded medicines prepared in a Polish hospital pharmacy and the corresponding compounding requests and manual records.

6.4 **Results and discussion**

Of the 13 hospitals contacted, 12 hospital pharmacies responded to the request for collaboration (response rate of 92%) (Figure 6.4). All 12 hospitals participated in the research and contributed data regarding the oral compounded medicines most frequently dispensed by their pharmacies in 2007. In total, 10 hospitals provided complete datasets and 2 hospitals supplied only qualitative/semi-quantitative information because of the difficulties associated with data collection (Section 6.3.3).

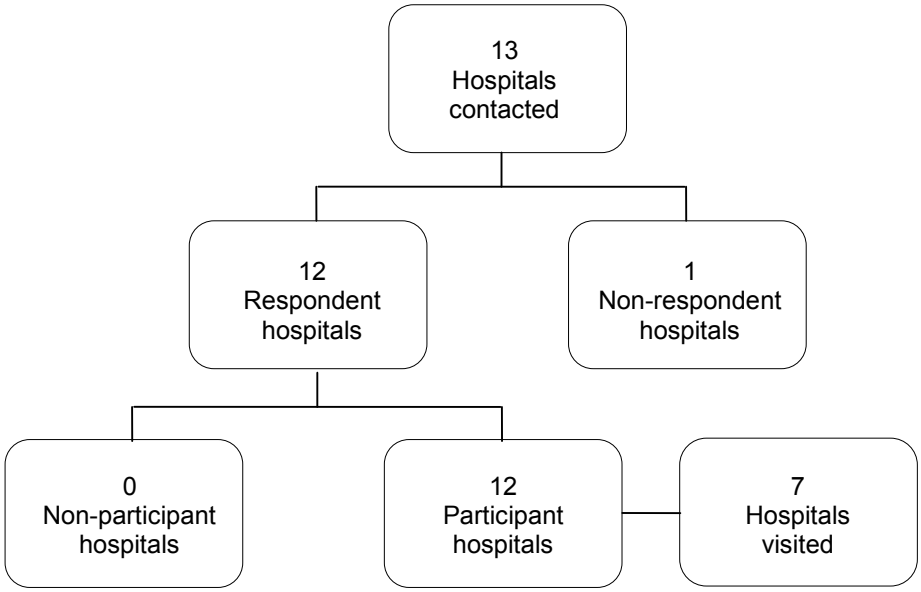


Figure 6.4 Purposive sample distributed by respondent, participant and visited hospitals.

A total of 7 participant hospitals were visited by MC and/or the Masters' student (Figure 6.4) and the respective datasets were collected during the visits. All other hospitals shared the required data directly with the Masters' student by telephone/email. The fact that 54% of the hospitals were visited was probably one of the major reasons for the high response rate achieved.

6.4.1 **Active substances**

A list of the active substances most frequently dispensed as oral compounded medicines is shown in Table 6.1. All active substances reported were included in *Martindale 35* (2007) and these were grouped according to the respective therapeutic classification, giving a total of 149 different active substances and 31 therapeutic groups. Cardiovascular drugs was the group with the greatest number of different active substances (n=28), followed by antibacterials (n=15) and analgesics, anti-inflammatory drugs and antipyretics / electrolytes / supplementary drugs and other substances (n=10).

Although these active substances were all reported as oral compounded medicines, the title of 2 therapeutic groups suggested non-oral (therapeutic) indications, namely: disinfectants and preservatives (Appendix 12) and supplementary drugs and other substances (Appendix 15). The active substances included in these groups are described in the respective appendixes.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 6 NTI drugs were dispensed as oral compounded medicines (underlined in Table 6.1). NTI drugs were reported by the majority (67%) of participant hospitals.

The active substances dispensed by most hospitals were: furazidin, phenobarbital and ursodeoxycholic acid (n=11), spironolactone (n=9) and midazolam (n=8).

Compounded medicines were also reported by the given titles which they are commonly known for in Poland as, for instance, *Sol. Sal. Erlenmayeri* and *Mixture Nervinae* (Section 6.4.3).

Table 6.1 Active substances most frequently dispensed as oral compounded medicines in Poland (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aminophenazone, aspirin, codeine phosphate, dipyrone, ethylmorphine HCl, ibuprofen, morphine, morphine HCl, paracetamol, sodium salicylate

Antibacterials
Azithromycin, ciprofloxacin HCl, ciprofloxacin lactate, clindamycin, colistin sulfate, co-trimoxazole, doxycycline, furazidin, gentamicin sulfate, isoniazid, neomycin, rifampicin, spiramycin, sulfadiazine, vancomycin

Antidementia drugs
Piracetam

Antidepressants
Doxepin HCl, fluoxetine HCl, mianserin HCl

Antiepileptics
Carbamazepine, clonazepam, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid, vigabatrin

Antifungals
Fluconazole, ketoconazole, nystatin, voriconazole

Antihistamines
Cetirizine HCl, hydroxyzine HCl

Antimalarials
Pyrimethamine

Antineoplastics
Cyclophosphamide, mercaptopurine, methotrexate, tioguanine

Antiparkinsonian drugs
Benserazide, levodopa, selegiline HCl

Antiprotozoals
Metronidazole

Antivirals
Aciclovir, inosine pranobex

Anxiolytic, sedatives, hypnotics and antipsychotics
Allobarbital, diazepam, midazolam, nitrazepam

Blood products, plasma expanders and haemostatics
Aminocaproic acid, tranexamic acid

Bronchodilators and anti-asthma drugs
Aminophylline, caffeine, theophylline

Cardiovascular drugs
Acebutolol, acenocoumarol, amiloride HCl, amiodarone, amlodipine besilate, atenolol, bisoprolol fumarate, captopril, carvedilol, colestyramine, diltiazem HCl, doxazosin mesilate, enalapril, flecainide acetate, furosemide, hydrochlorothiazide, losartan potassium, metildigoxin, metoprolol, nifedipine, nitrendipine, potassium canrenoate, propranolol HCl, ramipril, sotalol HCl, spironolactone, trimetazidine HCl, verapamil HCl

Chelators, antidotes and antagonists
Methylthioninium chloride, sodium polystyrene sulfonate

Corticosteroids
Fludrocortisone acetate, hydrocortisone, methylprednisolone, prednisone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Acetylcysteine, ephedrine HCl

Disinfectants and preservatives
Sodium benzoate

Electrolytes
Calcium chloride, calcium gluconate, calcium lactate, dibasic sodium phosphate, magnesium, monobasic sodium phosphate, potassium chloride, sodium bicarbonate, sodium chloride, sodium citrate

GI drugs
Calcium carbonate, cisapride, magnesium carbonate, metoclopramide, omeprazole, oxyphenonium bromide, ranitidine HCl, sulfasalazine

Hypothalamic and pituitary hormones
Desmopressin acetate

Immunosuppressants
Mycophenolate mofetil, tacrolimus

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide

Muscle relaxants
Baclofen, tolperisone HCl

Nutritional agents and vitamins
Arginine HCl, calcium folinate, carnitine, folic acid, ornithine aspartate, pyridoxine HCl, thiamine, vitamin A, vitamin D

Sex hormones
Megestrol acetate

Supplementary drugs and other substances
Ammonium bromide, citric acid, crataegus, drotaverine, pancreatin, potassium bromide, sodium bromide, thyme, ursodeoxycholic acid, valerian

Thyroid and antithyroid drugs
Levothyroxine sodium, potassium iodide

Urological drugs
Oxybutynin HCl, papaverine HCl, sildenafil citrate

The majority of compounded medicines were recorded at the hospital pharmacies according to the respective proprietary medicines. This finding suggests that proprietary medicines are frequently used in the preparation of compounded medicines, instead of raw materials in bulk (Section 1.1.2.2). In fact, it was acknowledged during fieldwork (Section 6.3.2) that, in Poland, it is not always easy to acess raw materials in bulk (and in small quantities). When compounded medicines were recorded by the respective active substances, these were frequently recorded in Latin, which facilitated data processing and analysis by MC.

6.4.2 **Oral solids**

The dosage forms reported included cachets (12 hospitals) and hard (gelatin) capsules (1 hospital), which correspond to 2 different categories of capsules (Section 2.1.3) (Figure 6.5). Cachets consist of a hard shell made of unleavened bread (usually from rice flour), divided in 2 cylindrical sections, which enclose a single dose of 1 or more active substances (EDQM, 2007) (Figure 6.6). Cachets are also known as starch capsules (Płaczek and Sznitowska, 2006). When moistened with water, cachets become soft, elastic and slippery (Rudnic and Schwartz, 2005). Therefore, before administration, cachets are usually immersed in water for a few seconds, placed on the tongue and swallowed with a draught of water (EDQM, 2007). Due to their large size (Figure 6.5), patients are likely to experience difficulties when swallowing cachets, particularly the paediatric population. For this reason, cachets are commonly opened just before administration and their contents

added to liquids or food (Figure 6.6) (Płaczek and Sznitowska, 2006; Gajewska *et al.*, 2007).

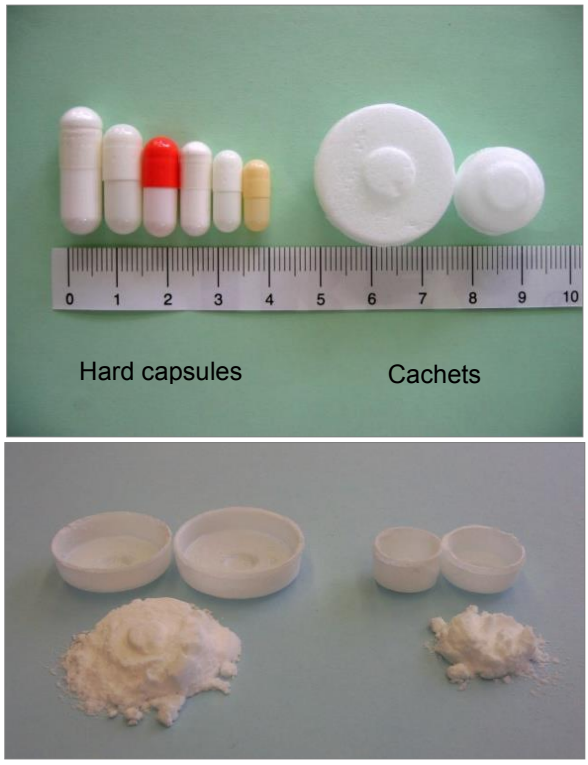


Figure 6.5 (above) Capsules: hard (gelatin) capsules and cachets (courtesy of Sznitowska and Gajewska, 2009).

Figure 6.6 (below) Cachets and corresponding contents (courtesy of Sznitowska and Gajewska, 2009).

Cachets are commonly prepared by weighing each dose of the powder into each unit, which is an arduous and time-consuming manual process that may be substituted by the preparation of hard (gelatin) capsules (in capsule machines) (Płaczek and Sznitowska, 2006). Therefore, cachets are often considered an obsolete dosage form that was formerly used in pharmacy but is very rarely used in practice today (RPS, 2002b; Winfield and Kennedy, 2004; Rudnic and Schwartz, 2005; Marriott *et al.*, 2010). However, according to Płaczek and Sznitowska (2006), cachets are prepared in large quantities in Poland, which was confirmed with the fact that out of the 213,021 units of oral solids dispensed by the participant hospitals, 191,060 units (89.7%) were cachets and only 21,961 units (10.3%) were hard (gelatin) capsules. This finding suggests that compounding practices in Poland are still very traditional, which is supported by the fact that some compounding

laboratories still store raw materials in amber recipients (Figure 6.7), instead of the suppliers' GMP-conditioned original containers, as observed during fieldwork.

Figure 6.7 Storage of raw materials in a Polish compounding laboratory.

The top 5 active substances dispensed as oral solids are listed in Table 6.2. Although cisapride was the most frequently dispensed active substance, its use in pharmaceutical compounding should be restricted because it is likely to cause cardiac arrhythmias. In fact, cisapride has already been withdrawn completely in the UK (*Martindale 35*, 2007). Furthermore, aminophenazone has also been considered unsuitable for use because of the risk of agranulocytosis, which may be sudden and unpredictable (*Martindale 35*, 2007). Aminophenazone (and papaverine) was frequently dispensed in combination with other active substances such as, for example: aminophenazone, sodium salicylate, caffeine, sodium benzoate, dipyrone and phenobarbital. This particular combination was named "neurological" cachets and was dispensed by 1 hospital.

Table 6.2 Top 5 active substances dispensed as oral solids.

Active substances	Number of strengths	Number of hospitals	Number of units
Cisapride	28	6	17,513
Calcium Carbonate	9	6	13,710
Aminophenazone (in combination)	2	4	12,950
Captopril	23	6	12,941
Papaverine (in combination)	6	4	11,513

Although the majority of oral solids (78%) comprised 1 active substance only, combinations of up to 6 different active substances (in the same unit) were also dispensed by the participant hospitals. These combinations are commonly known as polypharmacy[35] and their rational was, in most cases, to minimise the intake of several medicines. As a result, not all combinations were therapeutically coherent and, therefore, the safety and efficacy of the compounded medicines dispensed was likely to be affected. An example of such combinations is shown in Appendix 2.

In polypharmacy, attention should be paid to the compatibility and possible interactions between the different active substances so that the stability of the compounded medicine is consistent with the beyond-use date assigned (Allen, 2008). In addition, when active substances are combined in the same dosage form, they are administered at the same time, which raises pharmacokinetics issues as the ADME of the compounded medicine is likely to be affected. For these reasons, despite the convenience of polypharmacy (particularly in the hospital setting), the combination of different active substances should be supported by adequate literature. Nevertheless, in most cases, there is insufficient data to support multiple combinations and, therefore, the practice of polypharmacy should be generally avoided.

The top 5 active substances (Table 6.2) were dispensed by 4 to 6 participant hospitals and, in general, in several different strengths. However, the active substance dispensed in the greatest number of strengths was ursodeoxycholic acid: 29 strengths (0.1 mg to 250 mg). When used for dissolution of cholesterol-rich gallstones, the licensed dose of ursodeoxycholic acid (Appendix 15) is 6-12 mg/kg daily; for primary biliary cirrhosis, the licensed dose is 10-15 mg/kg daily (*Martindale 35*, 2007). Therefore, the low strengths of 0.1 mg and 0.6 mg, reported by only 1 hospital, were likely a mistake and only the strengths from 5 mg onwards were considered. Ursodeoxycholic acid is commercially available in Poland as solid dosage forms (capsules and tablets) only and in just 3 strengths (150 mg, 250 mg and 300 mg). Therefore, there is a need for alternative dosage

[35]Combination of several drugs in one dose; synonym: “shotgun” therapy (Worthen, 2004).

forms and strengths (Section 1.1.4), in particular for the paediatric population, which are made available by the preparation of compounded medicines. The next active substances dispensed in the greatest range of strengths were cisapride (28 strengths, 0.2-10 mg) and mercaptopurine (27 strengths, 6-59 mg). The usual dose of cisapride (where still licensed) is 5-10 mg (three to four times daily) and of mercaptopurine (as initial antineoplastic dose) is 2.5 mg/kg daily (*Martindale 35*, 2007), which are in accordance with the strengths reported (considering also the paediatric population).

The top therapeutic groups (oral solids only) were: cardiovascular drugs (30%), GI drugs (20.1%), multiple combinations of active substances from different groups (19.4%) and supplementary drugs and other substances (8.5%). Cardiovascular drugs and GI drugs represented over 50% of all oral solids dispensed, which is consistent with the fact that diseases of the circulatory system and digestive system are the major causes of discharge from all Polish hospitals, as shown in Figure 6.8.

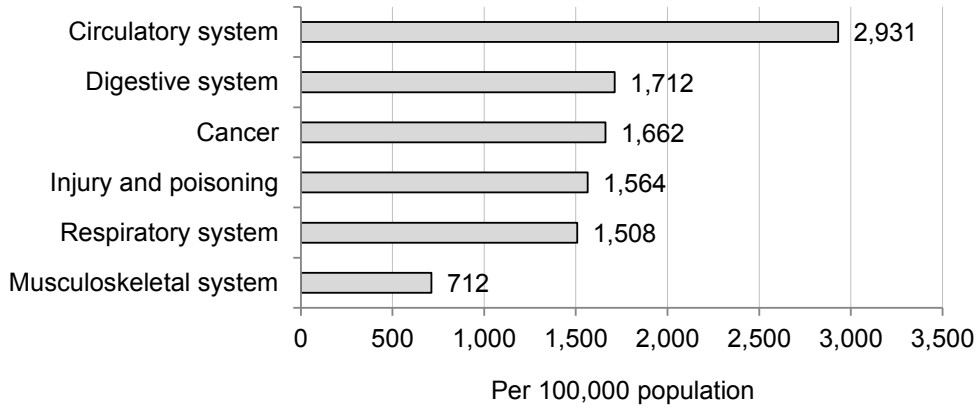


Figure 6.8 Number of patients per 100,000 population discharged from all hospitals (including through death) in Poland during 2004 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

6.4.3 **Oral liquids**

Oral liquid dosage forms were dispensed by 92% of all participant hospitals (only 1 hospital did not report oral liquids) and included solutions and suspensions (n=10), mixtures (n=5) and syrups (n=5). In total, 9 hospitals shared quantitative datasets with regards to the oral liquids dispensed, whereas 1 hospital disclosed only qualitative data and another hospital only

semi-quantitative data, which was processed and analysed accordingly (Section 2.4).

A total of 5,797 units of oral liquids were reported and, considering that volumes were not always clear, these were all assumed to be multidose. The majority of oral liquids were reported as solutions (71.5%) (Figure 6.9) but it is likely that the classification of some oral liquids was not accurate and, therefore, a proportion of the solutions may have corresponded to suspensions or mixtures/syrups (and vice-versa) (Section 2.1.3). Altogether, solutions and suspensions represented 81.3% of all oral liquids dispensed.

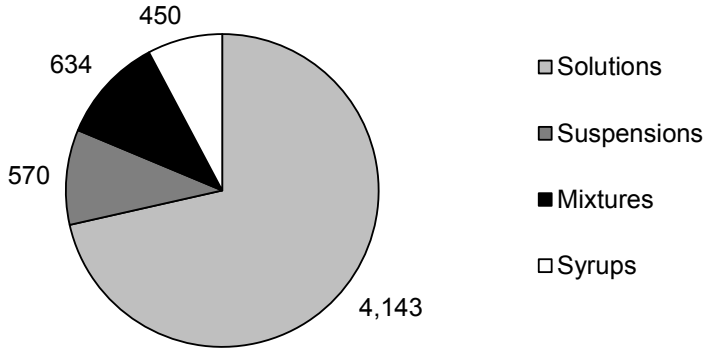


Figure 6.9 Oral liquid dosage forms dispensed per number of (multidose) units.

The most frequently dispensed oral liquids were *Sol. Sal. Erlenmayeri* and *Mixture Nervinae* (Appendix 16), which were dispensed by 3 hospitals and represented 41.1% of all oral liquids. These compounded medicines correspond to bromide oral liquids including ammonium, potassium and sodium bromide, in variable strengths; such preparations are described as triple bromides (Hollister, 1983). Bromides depress the CNS and have been used as sedatives, anti-epileptics and anticonvulsants. However, potassium and sodium bromide are considered toxic and have generally been replaced by more effective, less toxic drugs (*Martindale 35*, 2007) as, for instance, the benzodiazepines for sedative-hypnotic effects. Bromides have a long shelf life and, therefore, tend to accumulate with repeated doses. The most common manifestation of bromides toxicity is a confusional state with marked delirium (Hollister, 1983). In conclusion, the most frequently dispensed oral

liquids in Poland are potentially toxic and, therefore, the risk-benefit balance (Section 1.1.3) of these compounded medicines should be considered.

The next most frequently dispensed oral liquids included midazolam, which was reported as solutions, suspensions, mixtures and syrups, by a total of 8 hospitals. The most frequent strengths reported were 2 mg/mL and 2.5 mg/mL. *Sol. Sal. Erlenmayeri*, *Mixture Nervinae* and midazolam oral liquids represented almost 52% of all oral liquids dispensed in Poland.

Mixtures corresponded to 10.9% of all oral liquids (Figure 6.9) and were reported by 5 hospitals. The most frequently dispensed mixture was *Mixture Nervinae* (Appendix 16), which corresponded to almost 50% of all mixtures reported. Syrups, on the other hand, corresponded to 7.8% of all oral liquids (Figure 6.9) and were reported by 5 hospitals. In total, only 5 active substances were dispensed as syrups, as follows (in decreasing order): midazolam, phenobarbital, vancomycin, codeine and ephedrine.

The top 3 therapeutic groups (oral liquids only) were: supplementary drugs and other substances, which included the bromide oral liquids, followed by electrolytes and “anxiolytic, sedatives, hypnotics and antipsychotics”, which included the midazolam oral liquids. These 3 therapeutic groups represented over 70% of all oral liquids dispensed, which suggests that there is a need for licensed oral liquid dosage forms in Poland particularly from these 3 groups.

The multidose oral liquids may be quantitatively compared to the oral solids dispensed (in packs). Considering that cachets are comparable to oral powders, in relation to the method of preparation (hence no oral powders were reported in Poland), an estimation of 13 units of cachets were dispensed per pack (Section 2.1.3). As a result, the 191,060 individual units of cachets corresponded to approximately 14,697 packs (of 13 units each). In addition, considering that capsules were dispensed in packs of 50 units (Section 2.1.3), the 21,961 individual units of capsules corresponded approximately to 439 packs (of 50 units each). Therefore, when the 5,797 units of (multidose) oral liquids are compared to the estimation of 15,136 packs of oral solids, it is concluded that oral solids were dispensed in larger quantities than oral liquids.

6.4.4 **Oromucosal preparations**

In Poland, oromucosal preparations were not reported by any participant hospital.

6.5 **Summary**

- Compounded medicines in Poland may be identified in officinal and magistral formulae. Batch preparation (in advance) and third-party compounding are not permitted; QA/QC requirements are not specified by law; a reference code and 3 dates are the only requirements for record keeping.
- A professional organisation and a formulary for pharmaceutical compounding are not currently in existence. Compounding practices in Poland are still very traditional.
- A purposive sample of 13 hospitals was included in the research and a response rate of 92% was obtained. A total of 143 different active substances (including 6 NTI drugs) were reported corresponding to 31 different therapeutic groups. The top 3 therapeutic groups were cardiovascular drugs (n=28), antibacterials (n=15) and analgesics, anti-inflammatory drugs and antipyretics / electrolytes / supplementary drugs and other substances (n=10).
- Oral solid dosage forms were reported by all participant hospitals and included cachets and hard (gelatin) capsules only. A total of 213,021 individual units of oral solids were reported, with the majority (89.7%) being cachets, which were dispensed by all participant hospitals, whereas hard capsules (10.3%) were dispensed by only 1 hospital. The top 5 active substances dispensed as oral solids were: cisapride, calcium carbonate, aminophenazone (in combination), captopril and papaverine (in combination).
- Oral liquid dosage forms were reported by 92% of all participant hospitals and included solutions, suspensions, mixtures and syrups, in a total sum of 5,797 multidose (estimated) units. The most frequently dispensed oral liquids were: *Sol. Sal. Erlenmayeri* and *Mixture Nervinae*, which are potentially toxic, followed by oral liquids including midazolam.
- Mixtures were dispensed in a total sum of 634 units (10.9% of all oral liquids) and the most frequently dispensed was *Mixture Nervinae.* Syrups accounted for 7.8% of all oral liquids and only 5 active substances were dispensed: midazolam, phenobarbital, vancomycin, codeine and ephedrine.
- Oral solids were dispensed in larger quantities than oral liquids.

7. Compounding in the Netherlands

The Netherlands is one of the 6 founding member states of the EU and its official language is Dutch (*Europa*, 2009), although English is spoken by almost everyone (NBTC, 2010). The Netherlands, in Western Europe[36], occupies an area of 33,800 Km^2 between Belgium and Germany, and is the 8th most populated country in the EU, with a population of 16.3 million in 2007 (Figure 2.2) (*Europa*, 2008).

In 2007, there were 190 hospitals in the Netherlands (ratio of 1.16 hospitals per 100,000 population) and a total of 78,764 hospital beds (ratio of 480.8 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2007, there were 2,871 pharmacists in the Netherlands (ratio of 17.53 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4). According to the EAHP survey, there are on average 5.2 pharmacists per hospital, which is higher than the European average of 4.7. Moreover, Dutch hospitals have an average of 28.3 qualified pharmacy technicians/assistants per hospital, also higher than the European average of 6. Regarding non-qualified pharmacy assistants, the Netherlands has an average of 4.8 (EAHP, 2005; Hartmann, 2010).

The Netherlands has a long history of preparing compounded medicines, both individually and for stock, and this remains an important activity of Dutch hospital pharmacists (Simons-Sanders, 2005; Le Brun, 2007a). In the past, pharmacists used to prepare compounded medicines that were commercially available, however, current policy in most Dutch hospitals is that the compounded medicines prepared must not be commercially available (Simons-Sanders, 2005; Le Brun, 2007b). Actually, according to the Dutch GMP in Hospital Pharmacy (GMP-H, Section 7.1), the preparation of medicinal products in hospital pharmacy aims at enabling every accepted pharmacotherapy, if the prescribed medicine is not commercially available (Berg *et al.*, 1998). With the increasing quality standards in hospital pharmacy, pharmaceutical compounding is less profitable and Dutch hospital

[36]The Netherlands Antilles and Aruba (NBTC, 2010) were not considered in the research.

pharmacists have to choose whether to invest in meeting the standards or to outsource the compounded medicines dispensed (Le Brun, 2007a). Hence, the majority of Dutch hospitals (74%) prepare compounded medicines for other hospitals and community pharmacies (EAHP, 2005). The requirements for outsourcing compounded medicines are the following: only non-commercially available medicines may be outsourced; a formal agreement must be established between the preparation and dispensing pharmacies; the dispensing pharmacy must be GMP-H approved and a product dossier must be developed for every compounded medicine outsourced (Le Brun, 2007a; 2011).

Jong *et al.* (2001) conducted a 5-week prospective study on the use of off-label and unlicensed medicines prescribed at a Dutch academic children's hospital. According to their findings, 237 patients from 4 hospital units received a total of 2,139 prescriptions, out of which 760 (36%) were compounded medicines (of which 9% were prepared from proprietary medicines). Compounded medicines were prescribed to paediatric patients in all hospital units, with a particularly high incidence in the neonatal intensive care unit. The top 5 active substances prescribed as off-label and unlicensed medicines were cisapride, caffeine, tobramycin, spironolactone and furosemide (Jong *et al.*, 2001).

With regards to the community setting, Buurma *et al.* (2003) conducted a 2-week prospective study on the frequency, nature and determinants of prescriptions for compounded medicines in 79 Dutch community pharmacies. Compounded medicines corresponded to 3.4% of all prescriptions in the community setting, but with 2.3% actually prepared at the dispensing pharmacy. Although the majority of compounded medicines (66.3%) were prepared at the dispensing pharmacy, 28.4% were prepared by compounding companies and a minority by hospitals. Dermatological products were the most frequent dosage forms and therapeutic groups (Buurma *et al.*, 2003).

Apart from compounded medicines prepared by Dutch hospital and community pharmacies, there is evidence of compounded medicines being prepared by "compounding companies" in the Netherlands. According to Buurma *et al.* (2003), the considerable proportion of compounded medicines

from these companies is of concern since the legality of this practice is controversial. Compounding companies usually prepare and sell compounded medicines that are more broadly needed and, until now, have been able to avoid any formal medicine approval (Buurma *et al.*, 2003). Examples include potassium chloride 75 mg/mL oral liquid FNA (*Formularium der Nederlandse Apothekers*, Section 7.2.2) and *Hoestdrank* FNA (Appendix 16) (Fagron, 2012).

7.1 **Legislation**

In the Netherlands, it was acknowledged that the preparation of compounded medicines in hospital pharmacy required more than methods of preparation and QC and, in the 1970s, the GMP philosophy was gradually introduced (Berg *et al.*, 1998). In 1996, the first guide to GMP in hospital pharmacy (GMP-Z) was published by the Dutch association of hospital pharmacists (NVZA) and the Royal Dutch association for the advancement of pharmacy (KNMP) (Section 7.2.1), in cooperation with the Netherlands public health inspectorate and other experts (Le Brun, 2007b; Kirchdorfer, 2011). In 1998, the official English version of the GMP-Z was published, which is generally abbreviated to GMP-H (Berg *et al.*, 1998). The structure of GMP-H is similar to the industrial (European) GMP (Section 14.1) but comprises 4 additional chapters specifically applicable to hospital pharmacy, as follows: H1. Quality of design of the formulation and preparation method; H2. Extemporaneous compounding; H3. Aseptic dispensing, and H4. Dispensing of hazardous materials and products (Berg *et al.*, 1998; Simons-Sanders, 2005). Industrial GMP does not apply to pharmaceutical compounding and, therefore, the GMP-H (in particular the 4 additional chapters) enables Dutch hospital pharmacies to prepare compounded medicines in accordance with GMP (Berg *et al.*, 1998; Le Brun, 2011). The NVZA set up a steering committee to coordinate the implementation of GMP-H (Simons-Sanders, 2005), an expensive and time-consuming process but, at present, the majority of Dutch hospital pharmacies are GMP-H approved (Le Brun, 2011).

GMP-H has been the quality standard for manufacturing in Dutch hospital pharmacies (Simons-Sanders, 2005) and, as a result, the Netherlands is considered one of the European countries with the most rigorous GMP

regulations and QC requirements (EAHP, 2005). According to the latest EAHP survey, SOP (for compounding) are used in more than 90% of Dutch hospital pharmacies (EAHP, 2005).

The GMP-H distinguishes 2 types of compounded medicines, as follows:

- Standardised preparations, "performed in the pharmacy on a regular basis, as stock preparation or extemporaneous compounding, and for which sufficient guarantees are available to assure the quality of both formulation and method of preparation". Examples of standardised preparations are the FNA compounded medicines (Section 7.2.2). Standardised preparations may be prepared individually (extemporaneous compounding) or for stock (Berg *et al.*, 1998).
- Non-standardised preparations, "for which no well-investigated formulation and/or no well-investigated (and validated) preparation method are available". As stated in the GMP-H, the risks of limited "quality of design" data in non-standardised preparations should be weighed against the risk of not supplying the requested medicine to the patient. Non-standardised preparations may only be prepared individually (Berg *et al.*, 1998).

Documentation for both standardised and non-standardised preparations should be compiled in product files. The preparation of compounded medicines for stock must follow validated instructions, from the preparation to the respective QC, which should be included in the respective product files. Because of the facilitated QC of batches, stock preparation should always be preferable to individual preparation (Berg *et al.*, 1998; Simons-Sanders, 2005). It is expected that pharmaceutical compounding will increase in the Netherlands (Vree, 2007) and, in the near future, that stock preparation will be centralised in teaching hospitals and a few large regional hospitals, whereas all other hospitals will be restricted to individual preparations (Le Brun, 2007a).

7.2 **Professional organisations and information sources**

7.2.1 **Dutch professional organisations**

- *Koninklijke Nederlandse Maatschappij ter Bevordering der Pharmacie* (KNMP): is the Royal Dutch association for the advancement of pharmacy,

an organisation that supports hospital and community pharmacy in the Netherlands by offering a range of products and services, including the Dutch official formulary (FNA, Section 7.2.2) and the *Laboratorium der Nederlandse Apothekers* (LNA) - the laboratory of Dutch pharmacists. The LNA is focused on pharmaceutical compounding and supports the preparation and control of compounded medicines by the pharmacy members (KNMP, 2012a). Some of the items provided by LNA include 400 batch preparation records and 150 SOP for "general preparation operations" (LNA procedures) (Bouwman, 2007). The *Wetenschappelijk Instituut Nederlandse Apothekers* (WINAp) is the scientific institute for Dutch pharmacists, which is part of KNMP. Over 90% of all pharmacists in the Netherlands are members of KNMP (2012b).

- *Nederlandse Vereniging van Ziekenhuisapothekers* (NVZA): is the Dutch association of hospital pharmacists, a professional organisation that represents and supports pharmacists in the hospital setting. The NVZA and KNMP, in cooperation with the Netherlands public health inspectorate and other experts, are responsible for the development and implementation of the GMP-H (Section 7.1) (Hoeven, 2008; NVZA, 2012). The NVZA includes a Paediatrics Special Interest Group (SIG), which conducted a survey on paediatric hospitals and concluded that there were many different (non-standardised) compounded medicines in Dutch hospitals. According to Liem (2008), this situation is problematic especially when patients are discharged from hospitals and compounded medicines are then supplied by community pharmacies. The SIG, in cooperation with the WINAp, are developing monographs for standardised oral liquids including active substances frequently prescribed to paediatric patients (e.g. furosemide 2 mg/mL, enalapril 1 mg/mL and hydrochlorothiazide 0.5 mg/mL) (Liem, 2008).

7.2.2 **Dutch information sources**

- *Formularium der Nederlandse Apothekers* (FNA): is the Dutch official formulary for pharmaceutical compounding (Barbosa and Pinto, 2001), edited by the WINAp and commissioned by the KNMP. The FNA was first published in 1967 and is regularly updated: every 5 years (print version) and every month (web version). This formulary currently comprises 200 standardised monographs for compounded medicines and is divided in 11 chapters, from

dermatologicals to parenterals. For each monograph, more than 1 strength may be described as, for example: morphine HCl (oral liquid) 1, 5 and 20 mg/mL; and dithranol (cream) 0.05, 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1, 2 and 3% (WINAp, 2004; Bouwman, 2007), which supports the importance of pharmaceutical compounding in meeting the individual needs of patients for particular strengths (Section 1.1.4). The monographs included in the FNA do not have any corresponding proprietary medicines across the EU and are regularly revised and updated by the LNA (Postma, 2011). There is evidence of compounding companies preparing and selling FNA compounded medicines (e.g. potassium chloride 75 mg/mL oral liquid FNA; *Hoestdrank* FNA, Appendix 16) to Dutch hospital and community pharmacies (Fagron, 2012) but the legality of this activity is unclear (Section 7.1). There is cooperation between the Dutch formulary and the German formulary (NRF, Section 13.2.2) in relation to formulations, procedures and guidelines, which is gradually developing into harmonisation of both (Bouwman, 2007).

- *Recepteerkunde*: *Productzorg en Bereiding van Geneesmiddelen*: is a textbook by Bouwman-Boer *et al.* (2009), recommended in the GMP-H (Berg *et al.*, 1998), that includes practical information regarding the design and preparation of medicines in the pharmacy setting. According to Le Brun (2011), this textbook contains modern formulations, figures and pictures; an international edition is under discussion with the EAHP.

7.3 **Methods**

The research project in the Netherlands was set up in collaboration with Frits Boom (hospital pharmacist at the *Zaans Medisch Centrum*) who provided invaluable guidance at all stages of the research, from the development of the customised questionnaire to the data collection stage. The stakeholder also planned and scheduled visits to 4 hospital pharmacies, and other institutions, in the Netherlands (Section 7.3.3). The purposive sample of hospitals was completed by Yvonne Bouwman (pharmacist at LNA), who suggested a list of 13 additional hospitals likely to dispense the largest quantities of compounded medicines in the Netherlands (Section 7.3.2).

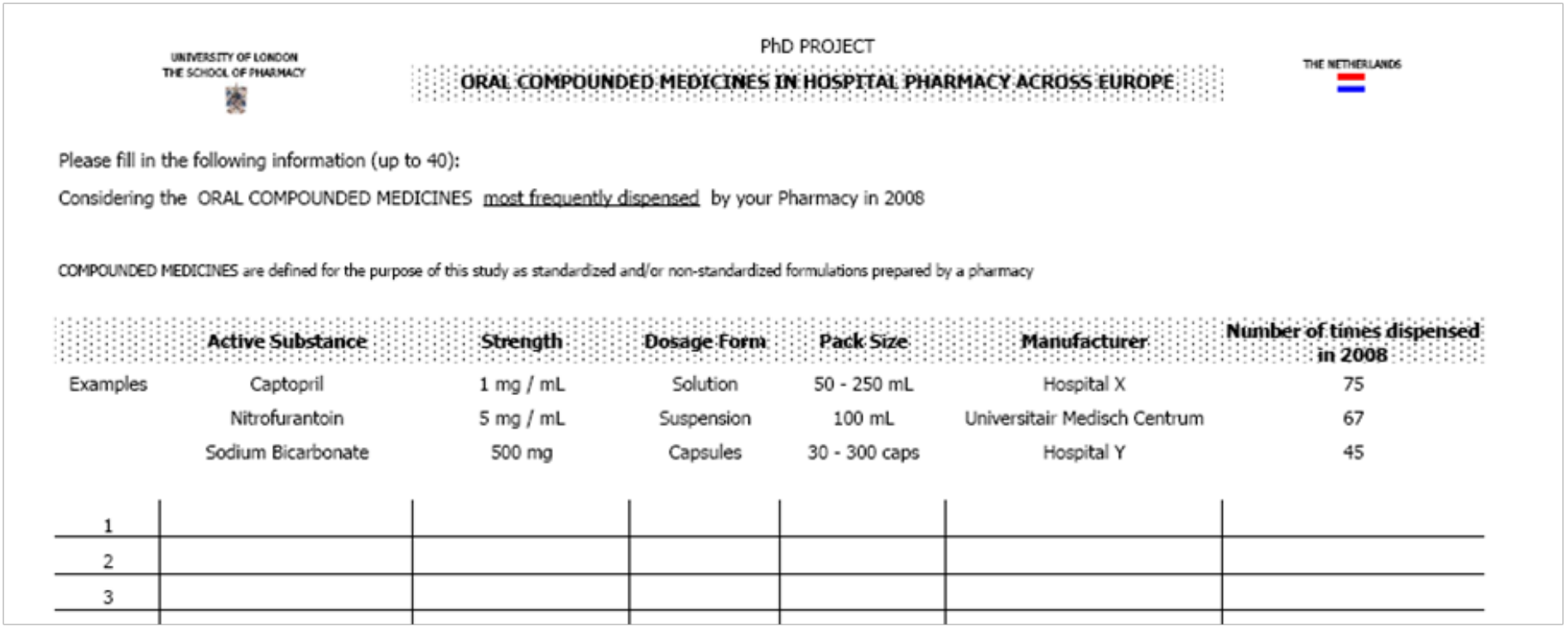
7.3.1 **Country-specific questionnaire**

The research instrument developed to collect information regarding oral compounded medicines most frequently dispensed in Dutch hospital pharmacies was a self-completion questionnaire (main heading in Figure 7.1), which was based on the template established for Portugal (Section 3.3.1) and adapted to the practice of pharmaceutical compounding in the Netherlands.

So that the Dutch questionnaire was not too extensive, the separate PDF introduction (Appendixes 8 / Portugal and 21 / UK) was substituted by a brief introduction in the body of the email and the final sheet with questions and comments (Appendixes 10 / Portugal and 22 / UK) was eliminated from the questionnaire. Considering the questions, although the overall total number of compounded medicines dispensed and the number of pharmacists / technicians would provide relevant information, these questions were considered non-essential for the aim of the research. With regards to comments, it was expected that pharmacists would add their comments directly in the data, or in the body of the email, where applicable, as seen in previous countries. As a result, the Dutch questionnaire comprised 1 table only, in order to simplify the request for information and to enhance the response rate.

The Dutch questionnaire was developed in English, following recommendations of the stakeholder who asserted that translating was unnecessary since the Dutch population was generally fluent in English. This was confirmed from other sources such as the Netherlands Board of Tourism & Conventions (NBTC, 2010). Data collection in the Netherlands was undertaken mainly in 2009 and, therefore, the questionnaire addressed information relating to 2008.

Compounded medicines were defined in the Dutch questionnaire as “standardised and/or non-standardised formulations prepared by a pharmacy”, which is in accordance with the concept of compounded medicines in the Netherlands (Section 7.1).



UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

ORAL COMPOUNDED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

THE NETHERLANDS

Please fill in the following information (up to 40):

Considering the ORAL COMPOUNDED MEDICINES most frequently dispensed by your Pharmacy in 2008

COMPOUNDED MEDICINES are defined for the purpose of this study as standardized and/or non-standardized formulations prepared by a pharmacy

	Active Substance	Strength	Dosage Form	Pack Size	Manufacturer	Number of times dispensed in 2008
Examples	Captopril	1 mg / mL	Solution	50 - 250 mL	Hospital X	75
	Nitrofurantoin	5 mg / mL	Suspension	100 mL	Universitair Medisch Centrum	67
	Sodium Bicarbonate	500 mg	Capsules	30 - 300 caps	Hospital Y	45
1						
2						
3						

Figure 7.1 Country-specific questionnaire (Netherlands).

An extra column “Manufacturer” was added to the questionnaire so that the compounded medicines prepared in other hospital/community pharmacies would be identified. To avoid duplication of data, it is important to identify the “manufacturer” of the compounded medicines dispensed and, if applicable, to exclude the repeated data entries from the hospital’s datasets.

7.3.2 **Purposive sample of hospitals**

A total of 17 hospitals were selected across the Netherlands, from the cities of: *Amersfoort*, Amsterdam (capital), *Arnhem*, *Dordrecht*, *Eindhoven*, *Groningen*, *Haarlem*, *Heerlen*, *Hengelo*, *Hertogenbosch*, *Nijmegen*, *Rotterdam*, *The Hague*, *Utrecht*, *Zaandam* and *Zwolle* (Figure 7.2). Each city corresponded to 1 hospital, with the exception of Amsterdam (2 hospitals). These hospitals were identified by the stakeholders as the ones in which the largest quantities of compounded medicines were likely dispensed in the Netherlands.

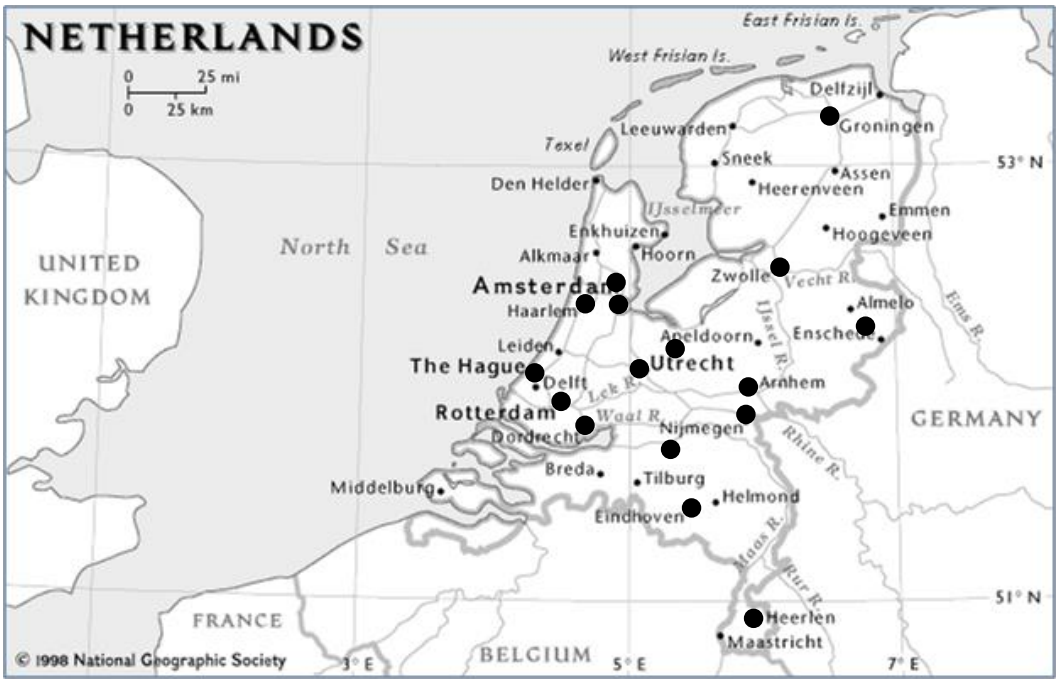


Figure 7.2 Map of the Netherlands adapted from National Geographic Society (1998e); indicating the location of the purposive sample of hospitals (●).

7.3.3 **Data collection**

Data collection in the Netherlands was initiated during 10 days of fieldwork planned and scheduled by Frits Boom. The purpose of this fieldwork was to allow a better understanding of the current compounding practices in the

Netherlands and to start data collection. Fieldwork was undertaken by MC in September 2008, and consisted in visits to selected hospital pharmacies and other institutions, as follows: 4 hospitals in *Zaandam*, *Haarlem*, *Groningen* and *Utrecht*; 2 community pharmacies in *Breda*; the LNA in *The Hague*; and the Health Care Inspectorate in *Hertogenbosch*. Data regarding oral compounded medicines most frequently dispensed in 2007 was collected by MC in 1 hospital; another hospital shared the required data during the visit; and the 2 other hospitals after the visit, by email.

The list of 13 additional hospitals suggested by Yvonne Bouwman was provided including the address of each hospital and the name of the key contact person in the respective pharmacy. The telephone number of each hospital was then searched online and all 13 hospitals were contacted by telephone by MC. However, only 3 hospital pharmacists were available by telephone and, after a brief explanation of the research project, they all accepted to contribute data by email. The majority of hospital pharmacists were not available by telephone (even after several calls, for some hospitals) and the email address of the key contact persons were provided by the hospital pharmacy staff.

The customised questionnaire was attached to a brief introductory email, as well as an electronic copy of the article published in the IJPC by Carvalho *et al.* (2008) and the power-point slides for an oral presentation by MC at the 1st Conference of the EuPFI (European Paediatric Formulation Initiative) (Carvalho, 2009). The IJPC article introduced the design and purpose of the research and the EuPFI presentation described preliminary findings. Non-respondents were sent periodical email reminders, up to a maximum of 5 emails per hospital pharmacy (excluding the EuPFI presentation to avoid an overload of information).

At the EDQM Expert Workshop on "Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients", in November 2009, Frits Boom offered to contact all non-respondents with the request to contribute data. This invaluable support resulted in a considerable increase in the response rate at the final stage of data collection.

7.4 **Results and discussion**

Of the 17 hospitals contacted, 13 hospital pharmacies responded to the request for collaboration and 4 were non-respondents, resulting in a response rate of 76%. Of the 13 respondents, 12 contributed data regarding the oral compounded medicines most frequently dispensed by their pharmacies and only 1 hospital was non-participant (Figure 7.3); this hospital dispensed oral compounded medicines, but data were not readily accessible and the staff at the pharmacy did not have the resources, at that time, to gather the required information. All participant hospitals shared complete datasets and no partial data were provided in the Netherlands.

A total of 4 participant hospitals were visited by MC (Figure 7.3) in September 2008 (Section 7.3.3) and, therefore, data was shared regarding 2007. Notwithstanding, 1 hospital did not provide the required information soon after the visit but, instead, in 2009 and data was shared regarding both 2007 and 2008. All other hospitals shared data in 2009 and the respective datasets related to 2008. As a result, the Dutch database included datasets regarding both 2007 (3 hospitals) and 2008 (9 hospitals).

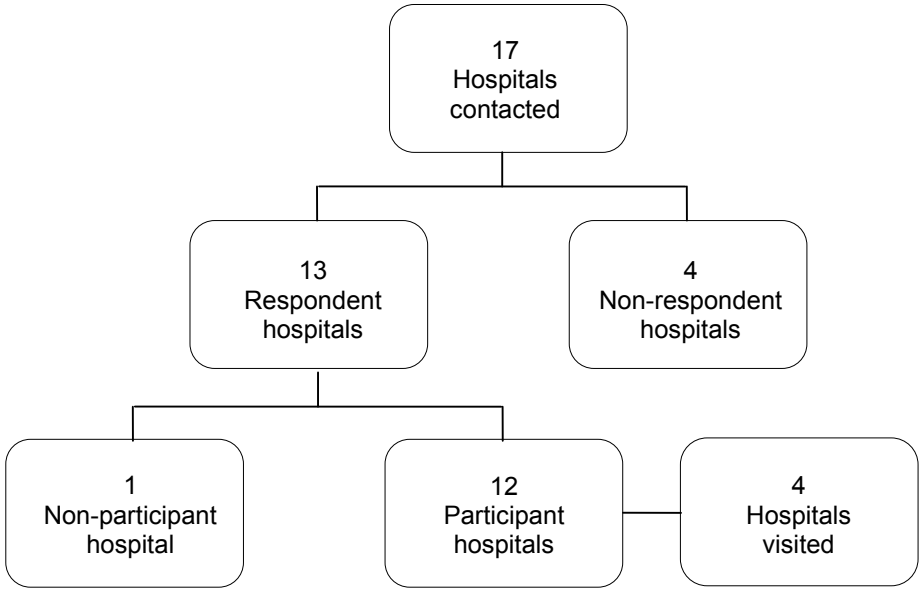


Figure 7.3 Purposive sample of hospitals in the Netherlands.

All participant hospitals provided datasets in electronic formats: 5 hospital pharmacies in the questionnaire provided and 7 hospital pharmacies in their

own formats, which (in general) were very complete, extensive and detailed. For instance, the strength and pack size of the compounded medicines dispensed were almost always stated. Compounded medicines that were included in the FNA were often reported. Active substances were commonly described in full, including the respective salts and hydration states. Dosage forms were usually described in detail, including the description of the final container. Moreover, some participant hospitals even distinguished standardised from non-standardised preparations (Section 7.1). According to the EAHP survey, between 2000 and 2005, computerisation for pharmaceutical compounding increased by more than 20% in the Netherlands (EAHP, 2005).

Although the questionnaire provided included the column "Manufacturer" (Section 7.3.1), so that the compounded medicines prepared in other hospital/community pharmacies would be identified, none of the participant hospitals stated that they had dispensed medicines prepared by others. Because the hospitals contacted were deemed to be the ones that dispensed the largest quantities of compounded medicines in the Netherlands, and also because the information provided was (in general) very complete and detailed, it is likely that all medicines dispensed were, in fact, prepared in the respective pharmacies.

Non-oral compounded medicines (i.e. vaginal, rectal and topical) were reported by 3 hospitals and the reconstitution of proprietary antibiotics (i.e. Floxapen 25 mg/mL, 100 mL) by another hospital, which were all excluded from the hospital's datasets (Section 2.4.1). After data processing, the Dutch database included a total of 1,208 data entries, corresponding to the datasets of 12 hospitals.

7.4.1 **Active substances**

A list of the active substances most frequently dispensed as oral compounded medicines in the Netherlands is shown in Table 7.1. Active substances were grouped according to the respective therapeutic classification (*Martindale 35*, 2007), giving a total of 226 different active substances and 38 therapeutic groups.

Table 7.1 Active substances most frequently dispensed as oral compounded medicines in the Netherlands (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aspirin, carbasalate calcium, codeine, codeine phosphate, diclofenac, etoricoxib, ibuprofen, methadone HCl, morphine, morphine HCl, naproxen, opium, paracetamol, propyphenazone, tramadol HCl

Anthelmintics
Diethylcarbamazine citrate

Antibacterials
Aztreonam, clindamycin, clioquinol, colistin sulfate, demeclocycline, ethambutol HCl, isoniazid, neomycin, neomycin sulfate, nitrofurantoin, norfloxacin, sulfadiazine, sulfamethoxazole, thioacetazone, tobramycin, trimethoprim, vancomycin

Antidepressants
Imipramine HCl, lithium carbonate

Antidiabetics
Tolbutamide

Antiepileptics
Clobazam, phenobarbital, phenytoin, phenytoin sodium, pregabalin, primidone, topiramate, vigabatrin

Antifungals
Amphotericin B, nystatin

Antigout drugs
Allopurinol, colchicine, probenecid

Antihistamines
Alimemazine tartrate, deptropine citrate, fexofenadine HCl, promethazine, tripelennamine citrate

Antimalarials
Chloroquine, primaquine, primaquine phosphate

Antimyasthenics
3,4-diaminopyridine, fampridine

Antineoplastics
Busulfan, cyclophosphamide, lomustine, mercaptopurine, methotrexate

Antiparkinsonian drugs
Amantadine, carbidopa, levodopa, trihexyphenidyl HCl

Antivirals
Valaciclovir HCl, valganciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Chloral hydrate, clozapine, diazepam, haloperidol, levomepromazine, lorazepam, midazolam, midazolam HCl, nitrazepam, oxazepam, pericyazine, perphenazine, quetiapine fumarate, temazepam, zuclopenthixol decanoate

Blood products, plasma expanders and haemostatics
Tranexamic acid

Bronchodilators and anti-asthma drugs
Caffeine, theophylline

Cardiovascular drugs
Acenocoumarol, adrenaline, amiloride HCl, amlodipine besilate, atenolol, atropine, atropine sulfate, bosentan, captopril, carvedilol, clonidine HCl, clopidogrel bisulfate, colestyramine, diazoxide, enalapril, enalapril maleate, furosemide, hydrochlorothiazide, isosorbide, labetalol HCl, mannitol, metoprolol tartrate, nifedipine, phenprocoumon, propranolol HCl, sotalol HCl, spironolactone, triamterene, warfarin sodium;

Chelators, antidotes and antagonists
Methionine, methylthioninium chloride, penicillamine, prussian blue, sodium polystyrene sulfonate, trientine dihydrochloride

Contrast media
Barium sulfate, meglumine amidotrizoate, meglumine ioxitalamate, sodium amidotrizoate, sodium ioxitalamate

Corticosteroids
Dexamethasone, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, prednisolone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Ammonium chloride, ephedrine HCl

Disinfectants and preservatives
Cetrimide, chlorhexidine HCl, povidone-iodine, sodium benzoate, sodium metabisulfite

Electrolytes
Calcium, calcium acetate, calcium gluconate, magnesium gluconate, magnesium sulfate, monobasic potassium phosphate, phosphate, potassium chloride, potassium citrate, potassium phosphate, sodium chloride, sodium citrate

GI drugs
Calcium carbonate, lactulose, liquorice, metoclopramide, ranitidine, ranitidine HCl, senna, sennosides, sodium sulfate, sulfasalazine

Hypothalamic and pituitary hormones
Desmopressin acetate

Immunosuppressants
Azathioprine, tacrolimus

Local anaesthetics
Cocaine HCl, lidocaine, lidocaine HCl

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide, carbachol

Muscle relaxants
Baclofen, dantrolene sodium

Nutritional agents and vitamins
Alpha tocopherol, arginine HCl, ascorbic acid, citrulline, colecalciferol, ferrous fumarate, folic acid, folinic acid, fructose, glucose, glucose monohydrate, lactose, nicotinamide, phytomenadione, pyridoxine HCl, riboflavin, sodium fluoride, sucrose, thiamine, tocopherol, vitamin A, vitamin D, vitamin E, vitamin K, zinc sulfate

Organic solvents
Dimethyl sulfoxide

Sex hormones
Oxandrolone, oxymetholone, prasterone

Stabilising and suspending agents
Cellulose, methylcellulose

Stimulants and anorectics
Amfetamine, dexamfetamine sulfate, methylphenidate HCl

Supplementary drugs and other substances
Cannabis, citric acid, glycerol, glycopyrronium bromide, hydrochloric acid, macrogols, melatonin, monosodium glutamate, pancreatin, sodium carbonate, sodium phenylbutyrate, tetrabenazine, trypsin, ursodeoxycholic acid

Thyroid and antithyroid drugs
Iodine, levothyroxine sodium, potassium iodide, potassium perchlorate, sodium perchlorate

Urological drugs
Sildenafil citrate

Cardiovascular drugs was the group with the greatest number of different active substances (n=29), followed by nutritional agents and vitamins (n=25) and antibacterials (n=17).

Although these active substances were all reported as oral compounded medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: disinfectants and preservatives (Appendix 12); organic solvents (Appendix 25); stabilising and suspending agents (Appendix 14); and supplementary drugs and other substances (Appendix 15). The active substances included in these groups are described in the respective appendixes.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 9 NTI drugs were dispensed as oral compounded medicines

(underlined in Table 7.1). NTI drugs were reported by the majority (83%) of participant hospitals.

The active substances dispensed by most hospitals were: furosemide and phenobarbital (n=11), hydrochlorothiazide (n=10) and spironolactone (n=9).

All active substances reported were included in *Martindale 35* (2007), with the exception of the following:

- Ammonia spirit aniseed: was reported by 2 hospitals as part of an anti-cough preparation, named *Hoestdrank* FNA or *Mixtura resolvens,* which is included in the Dutch official formulary (FNA, Section 7.2.2) and is shown in the given titles formulary (Appendix 16). Ammonia spirit aniseed (Appendix 26) is commercially available in the Netherlands for the preparation of compounded medicines.
- Heptobarbital: was reported by 2 hospitals as capsules of heptobarbital 200 mg and heptobarbital 60 mg combined with phenobarbital. Heptobarbital is described in the literature as a barbiturate (Louis *et al.*, 2009).

The majority of compounded medicines dispensed included 1 active substance only. Nevertheless, combinations of up to 3 active substances were also dispensed, in a total of 17 compounded medicines, as follows:

- 3 active substances: *Hoestdrank FNA* (mentioned above); mannitol, lactulose and sucrose.
- 2 active substances: ammonium chloride and liquorice (similar to *Hoestdrank FNA*); amphetamine and phenobarbital; atropine sulfate and diazepam; citric acid and glycerol; colistin sulfate and norfloxacin; Gastrografin (meglumine amidotrizoate and sodium amidotrizoate); heptobarbital and phenobarbital; methadone HCl and metoclopramide; Movicolon (macrogols and electrolytes); sodium ioxitalamate and meglumine ioxitalamate; sodium phosphate and potassium phosphate; spironolactone and hydrochlorothiazide; tobramycin and colistin sulfate; triamterene and hydrochlorothiazide; tripelennamine citrate and codeine.

Apart from compounded medicines including active substances, 3 hospitals also reported compounded medicines including placebo, namely tablets and capsules, in a total of 130,652 units.

In addition, 8 proprietary medicines were reported as part of the oral compounded medicines dispensed, both as solid and liquid dosage forms and by 7 hospitals, as follows: Capoten (captopril), Cyklokapron (tranexamic acid), Gastrografin (meglumine amidotrizoate and sodium amidotrizoate), Movicolon (macrogols and electrolytes), Mysoline (primidone), Prunasine (senna), Resonium (sodium polystyrene sulfonate) and Telebrix (sodium ioxitalamate).

7.4.2 **Oral solids**

Oral solid dosage forms were reported by 92% of all participant hospitals and included capsules (n=11), oral powders (n=8), powders for oral liquids (n=3) and tablets (n=2). In total, 3,281,601 individual units of oral solids were reported but the majority (79.8%) corresponded to tablets (Figure 7.4).

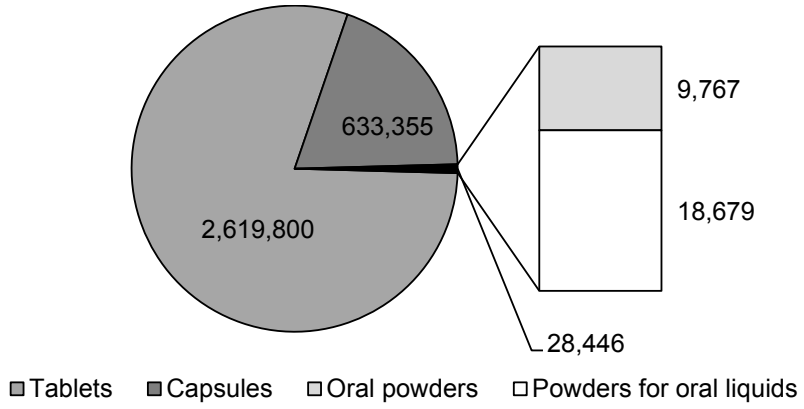


Figure 7.4 Oral solid dosage forms dispensed per number of units.

Tablets were dispensed in a total of 2,619,800 units (Figure 7.4) but only by 2 participant hospitals, which supplied other hospital pharmacies. The preparation of tablets requires specific tableting equipment and not all hospitals can afford such an investment (Section 2.1.3). Therefore, it is not unexpected that not all hospitals reported this dosage form. The top 5 active substances (and respective strengths) dispensed as tablets were: oxazepam (5-50 mg), furosemide (20-40 mg), haloperidol (0.5-5 mg), ferrous fumarate (200 mg) and dexamethasone (0.5-20 mg) (Table 7.2). These 5 active substances represented 57% of all tablets and were dispensed in packs of 50 units. Despite the fact that tablets are commonly prepared in large scale (because of the characteristics of the tableting equipment) and, therefore, it

would be expected that active substances were prepared in limited strengths, the majority of active substances were reported by Dutch hospitals in a wide range of strengths.

Capsules corresponded to 19.3% of all oral solids (Figure 7.4) and were reported by all participant hospitals. The top 5 active substances (and respective strengths) dispensed as capsules were: captopril (0.5-6.25 mg, 7 strengths), dexamethasone (1-40 mg, 6 strengths), spironolactone (0.1-20 mg, 11 strengths), atropine sulfate (0.5 mg) and hydrocortisone (0.25-5 mg, 6 strengths) (Table 7.3).

Dexamethasone was the only active substances common to both top 5 active substances dispensed as tablets and as capsules, and was reported by a total of 7 hospitals. The overall top 5 active substances dispensed as oral solids (and respective number of hospitals) were, in decreasing order: oxazepam (n=1), captopril (n=6), furosemide (n=5), haloperidol (n=1) and ferrous fumarate (n=1) (Tables 7.2 and 7.3).

Table 7.2 Top 5 active substances dispensed as tablets.

Active substances	Number of units
Oxazepam	600,000
Furosemide	300,000
Haloperidol	220,000
Ferrous fumarate	215,000
Dexamethasone	160,000

Table 7.3 Top 5 active substances dispensed as capsules.

Active substances	Number of units
Captopril	387,260
Dexamethasone	41,222
Spironolactone	21,280
Atropine sulfate	19,000
Hydrocortisone	15,571

Furosemide (Table 7.2) and spironolactone (Table 7.3) were also part of the active substances dispensed by most hospitals (Section 7.4.1). Furthermore, these 2 active substances were also included in the top 5 active substances prescribed as off-label and unlicensed medicines at a Dutch children's hospital (Jong *et al.*, 2001). The other active substances identified by Jong *et al.* (2001) were cisapride, caffeine and tobramycin but, since unlicensed medicines corresponded to only 36% of the prescriptions analysed and only 1 hospital was included in their research, it was expected that only a few results would be directly comparable.

Powders for oral liquids and oral powders represented only 0.9% of all oral solids (Figure 7.4). Powders for oral liquids (0.6%) were dispensed by 3 hospitals, for a total of 10 active substances. Tobramycin (640 mg) and colistin sulfate (800 mg), in combination, were the most frequently dispensed active substances. Oral powders (0.3%) were dispensed by 8 hospitals, with a total of 26 active substances. Sodium polystyrene sulfonate (15 g) and magnesium sulfate (15-30 g) were the most frequently dispensed active substances. The top therapeutic groups (oral solids only) were: “anxiolytic, sedatives, hypnotics and antipsychotics” and “cardiovascular drugs”, which represented 58% of all oral solids dispensed (Figure 7.5). The active substances most frequently dispensed from these groups were oxazepam and haloperidol (anxiolytic, sedatives, hypnotics and antipsychotics), captopril and furosemide (cardiovascular drugs), as displayed in Tables 7.2 and 7.3.

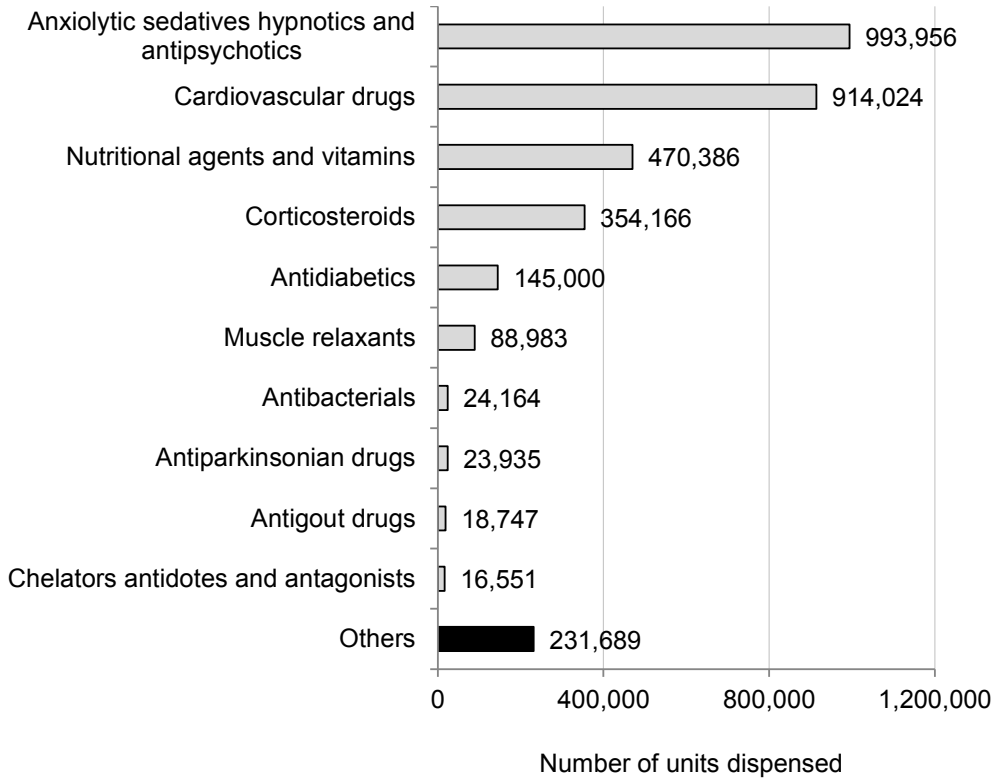


Figure 7.5 Top 10 therapeutic groups (oral solids) ranked by number of units dispensed.

7.4.3 **Oral liquids**

Oral liquid dosage forms were reported by all participant hospitals and included both multidose and unidose containers (Figure 7.6), as follows:

- Multidose: solutions and suspensions (n=12), oral drops (n=8) and syrups (n=3).
- Unidose: oral syringes (n=5).

Only 1 hospital distinguished the oral liquids dispensed as (unidose) oral syringes[37] but it was assumed that quantities <10 mL corresponded to unidose whereas quantities ≥10 mL corresponded to multidose containers (Section 2.1.3). As a result, it was concluded that 5 hospitals dispensed unidose oral liquids in the Netherlands, as displayed in Figure 7.6.

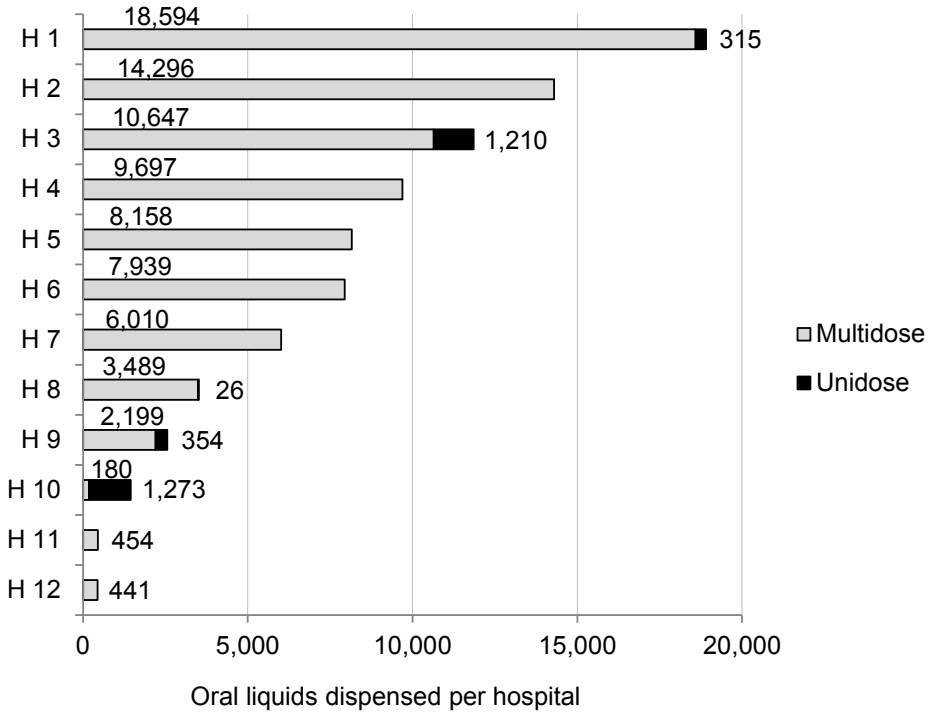


Figure 7.6 Number of units of oral liquids (unidose and multidose) dispensed per hospital.

Eight active substances were dispensed as unidose (n=3,178 units), in limited strengths and in volumes of 0.5 mL to 8 mL. The top 5 compounded medicines dispensed as unidose oral liquids are displayed in Table 7.4.

[37]An oral syringe is used for accurate measurement and controlled administration of an oral liquid medicine. Oral syringes should be clearly labelled “Oral” or “Enteral” and should not be compatible with IV or other parenteral devices, to avoid inadvertent IV administration of oral liquid medicines (Paediatric Formulary Committee, 2008).

Table 7.4 Top 5 compounded medicines dispensed as unidose oral liquids.

Active substances	Strengths	Volumes	Number of units
Mercaptopurine	10 mg/mL	1.4-6 mL	2,020
Azathioprine	10 mg/mL	2.5-8 mL	369
Phytomenadione	10 mg/mL	5 mL	315
Amphotericin B	100 mg/mL	0.5 and 1 mL	269
Methotrexate	5-7.2 mg/mL	2-5 mL	108

Multidose oral liquids were dispensed in larger quantities than unidose oral liquids (82,104 multidose units vs 3,178 unidose units) and were reported by all hospitals with 180 to 18,594 units per hospital (Figure 7.6). Multidose oral liquids were reported as solutions, suspensions and oral liquids (92%), oral drops (6%) and syrups (2%) (Figure 7.7).

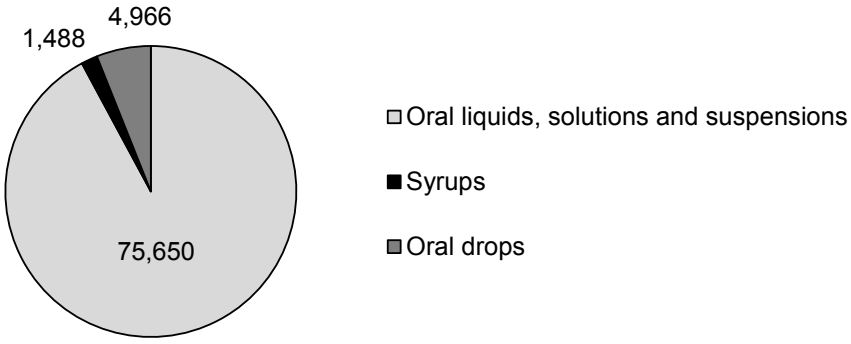


Figure 7.7 Multidose oral liquid dosage forms dispensed per number of units.

Solutions, suspensions and oral liquids (in general) were reported by all participant hospitals, in a total sum of 75,650 units (from 10 mL to 2,000 mL). The majority were reported as oral liquids (75%), followed by solutions (17%) and suspensions (8%) but it is likely that the classification of some oral liquids was not accurate and, therefore, part of the solutions/suspensions may have corresponded to other liquid dosage forms (and vice-versa) (Section 2.1.3). The top 5 active substances were: sodium ioxitalamate and meglumine ioxitalamate (3 hospitals); this is contrast media commonly given in combination by mouth for imaging the GI tract (*Martindale 35*, 2007); potassium chloride (7 hospitals), magnesium sulfate (5 hospitals) and mercaptopurine (3 hospitals). These active substances represented 59% of all solutions, suspensions and oral liquids dispensed.

Oral drops corresponded to 6% of all oral liquids (Figure 7.7) and were reported by 8 hospitals. In total, 13 active substances were reported as oral drops and the top 5 (in decreasing order) corresponded to: temazepam, adrenaline, vitamin K, potassium iodide and iodine. Potassium iodide and iodine were almost always dispensed as *Sterke Waterige Jooddruppels*, an oral solution equivalent to the Lugol's Solution 5% (Appendix 16). These oral drops are included in the FNA (Section 7.2.2), at the section *Vervallen*, which comprises compounded medicines that are no longer commonly used in the Netherlands (WINAp, 2004).

Syrups comprised only 2% of all oral liquids (Figure 7.7) and were reported by just 3 hospitals. The most frequently dispensed syrup was named “cough syrup” (300 mL) and was reported by only 1 hospital. The other syrups included a total of 5 different active substances and were dispensed in containers of 10 mL to 300 mL.

The top therapeutic groups (oral liquids only) were: contrast media and electrolytes, which represented 57% of all oral liquids dispensed (Figure 7.8). The active substances most frequently dispensed from these groups were sodium ioxitalamate and meglumine ioxitalamate (contrast media); potassium chloride and magnesium sulfate (electrolytes), which corresponded to the most frequently dispensed active substances as solutions, suspensions and oral liquids (above).

The multidose oral liquids may be quantitatively compared to the oral solids dispensed (in packs). Since almost all tablets were dispensed in packs of 50 units (Section 7.4.2), the 2,619,800 units of tablets corresponded to 52,396 packs of tablets (of 50 units each). In addition, considering that capsules were dispensed in packs of 50 units (estimated; Section 2.1.3), the 633,355 individual units of capsules corresponded approximately to 12,667 packs of oral capsules (of 50 units each). As a result, a total of approximately 65,063 packs of oral solids were dispensed in the Netherlands. Therefore, when the 82,104 units of multidose oral liquids are compared to the estimation of 65,063 packs of oral solids, it is concluded that oral liquids were dispensed in larger quantities than oral solids, though similar within an order of magnitude.

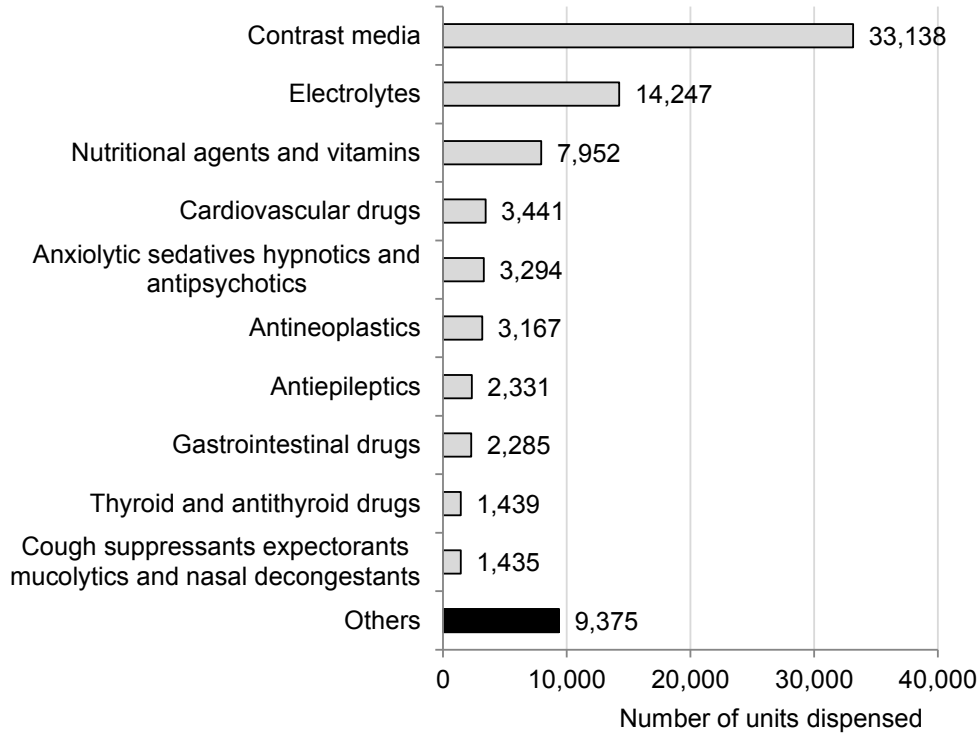


Figure 7.8 Top 10 therapeutic groups (oral liquids) ranked by number of units dispensed.

When further comparing oral solids and oral liquids, there were 3 therapeutic groups common to the top 5 groups for oral solids and oral liquids. This finding suggests that the respective active substances are dispensed both as solid and liquid dosage forms. The common therapeutic groups were: “nutritional agents and vitamins”, “cardiovascular drugs” and “anxiolytic, sedatives, hypnotics and antipsychotics“, which is consistent with the fact that diseases of the circulatory system and digestive system corresponded to the major causes of discharge from all Dutch hospitals, as shown in Figure 7.9.

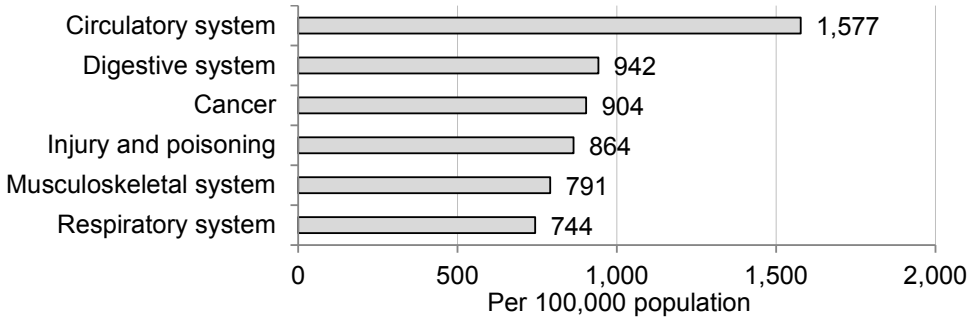


Figure 7.9 Number of patients per 100,000 population discharged from all hospitals (including through death) in the Netherlands during 2006 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

7.4.4 **Oromucosal preparations**

In the Netherlands, oromucosal preparations were reported by 4 hospitals (33% of all participant hospitals) and, in total, 8 different compounded medicines were dispensed, in a sum of 1,838 multidose containers, namely: amphotericin B 2% paste (5 g); cetrimide 0.1% mouthwash (300 mL); chlorhexidine HCl 2% ointment; colistin sulfate 1 mg/mL mouthwash (100 mL); povidone-iodine 1% mouthwash (100 mL); sodium fluoride 1% mouthwash and gel (100 mL); and tacrolimus 1mg/g paste (30 g).

7.5 **Summary**

- Compounded medicines in the Netherlands may be distinguished in standardised preparations (individual or for stock) and non-standardised preparations (individual only).
- GMP-H is the quality standard for pharmaceutical compounding in Dutch hospital pharmacies. The LNA (WINAp/KNMP) is a Dutch laboratory focused on pharmaceutical compounding and the FNA is the official national compounding formulary.
- A purposive sample of 17 hospitals was included in the research and a response rate of 76% was obtained. A total of 227 different active substances (including 9 NTI drugs) were reported corresponding to 38 different therapeutic groups. The top 3 therapeutic groups were cardiovascular drugs (n=29), nutritional agents and vitamins (n=25) and antibacterials (n=17). Placebo was dispensed in a total sum of 130,652 units of capsules and tablets (n=3).
- Oral solid dosage forms were reported by 92% of all participant hospitals and included tablets, capsules, powders for oral liquids and oral powders. Tablets were dispensed in a total sum of 2,619,800 units (79.8% of all oral solids) and the top 5 active substances were: oxazepam, furosemide, haloperidol, ferrous fumarate and dexamethasone. Capsules were dispensed in a total of 633,355 units (19.3% of all oral solids) and the top 5 active substances were: captopril, dexamethasone, spironolactone, atropine sulfate and hydrocortisone. Powders for oral liquids and oral powders represented only 0.9% of all oral solids.
- Oral liquid dosage forms were reported by all participant hospitals and included solutions and suspensions, oral drops and syrups (multidose) and oral syringes (unidose). Multidose oral liquids were dispensed in larger quantities than unidose oral liquids (82,104 multidose units vs 3,178 unidose units). Solutions and suspensions (and oral liquids in general) were dispensed in a total sum of 75,650 multidose containers (92% of all multidose oral liquids) and the top 5 active substances were: sodium ioxitalamate and meglumine ioxitalamate, potassium chloride, magnesium sulfate and mercaptopurine. Oral drops were dispensed in a total of 4,966 containers (6% of all multidose oral liquids) and the top 5 active substances were: temazepam, adrenaline, vitamin K, potassium iodide and iodine. Syrups accounted for only 2% of all multidose oral liquids dispensed. Unidose oral liquids were dispensed in a total of 3,178 unidose units and the top 5 active substances were: mercaptopurine, azathioprine, phytomenadione, amphotericin B and methotrexate.
- Oral liquids were dispensed in larger quantities than oral solids, though similar within an order of magnitude.
- Oromucosal preparations were reported by 33% of hospitals and included 7 different active substances (amphotericin B, cetrimide, chlorhexidine HCl, colistin sulfate, povidone-iodine, sodium fluoride and tacrolimus), in a total of just 1,838 multidose containers.

8. **Compounding in Denmark**

Denmark is a Scandinavian country, bordered by the North Sea and Germany, that joined the EU in 1973 and its official language is Danish (*Europa*, 2009; Ministry of Foreign Affairs of Denmark, 2010). Denmark is small, with a surface area of 43,100 km^2, that consists of the peninsula of *Jylland* and some 400 named islands, the largest being *Fyn* and *Sjælland* (*Europa*, 2008; 2009). Denmark is divided into 5 regions: Capital Region of Denmark, Zealand Region, Region of Southern Denmark, Central Denmark Region and North Denmark Region (Danish Regions, 2008). The hospital sector is the responsibility of the 5 regions and each region must provide free treatment to the residents of the region (Ministry of Health and Prevention, 2008). Denmark is the 17th most populated country in the EU, with a population of 5.4 million in 2007 (Figure 2.2) (*Europa*, 2008). The most populated cities are Copenhagen (capital), followed by *Árhus*, *Odense* and *Álborg* (Ministry of Foreign Affairs of Denmark, 2010).

In 2005, there were 59 hospitals in Denmark (ratio of 1.09 hospitals per 100,000 population) and, in 2007, there were a total of 19,086 hospital beds (ratio of 349.48 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2006, there were 3,723 pharmacists in Denmark (ratio of 68.51 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4), and about 4% worked in hospital pharmacy (EAHP and HOPE, 2002). According to the EAHP survey, the average number of pharmacists in Danish hospitals is 10.3, which is more than twice the European average of 4.7 pharmacists per European hospital. In addition, Danish hospitals have an average of 28.2 qualified pharmacy technicians/assistants per hospital (36% increase in relation to the year 2000), which is much higher than the European average of 6. Denmark also has an average of 3.8 non-qualified pharmacy assistants per hospital (EAHP, 2005; Hartmann, 2010).

In Denmark, compounded medicines are prepared both in community and hospital pharmacies. Danish hospital pharmacies also manufacture licensed

medicines, previously authorised by the Danish Medicines Agency (DMA, Section 8.2.1). These licensed medicines are not supplied by the pharmaceutical industry and have a Marketing Authorisation that belongs to a company named Amgros. Amgros I/S is owned by the 5 Danish regions and is the holder of the Marketing Authorisation for all medicines manufactured by the Danish public hospital pharmacies (AMGROS, no date). Amgros is responsible for handling all aspects of medicines supply to public hospitals by hospital pharmacies, including the manufacture and purchase of medicines. As the holder of the Marketing Authorisation, Amgros is also responsible for ensuring that the manufacture of medicines in hospital pharmacies is performed in accordance with GMP standards (Kart and Teilmann, 2008). According to the EAHP survey, Denmark is one of the European countries with the most rigorous GMP regulations and QC requirements (EAHP, 2005). All Danish hospital pharmacies that participated in the EAHP survey used written SOP and tested finished batches. Between 2000 and 2005, hospital pharmacies increased the testing of raw materials, packaging materials and finished batches by 17% (EAHP, 2005).

In Denmark, the preparation of compounded medicines and the manufacture of licensed medicines are centralised and only selected hospitals and community pharmacies perform these activities. According to Bent Hansen, head of Amgros' Executive Committee, the medicines prepared in hospital pharmacies must be "coordinated and optimised on a national scale" (Kart and Teilmann, 2008). Hence, the majority of Danish hospitals (60%) prepare compounded medicines for other hospitals and community pharmacies (EAHP, 2005). With regards to the community setting, pharmaceutical compounding is performed in very few pharmacies. In 2007, it was reported that compounding was centralised in 3 community pharmacies only (Herborg *et al.*, 2007).

Amgros and the Danish hospital pharmacies are computerised and access an intranet service to share information and databases on medicines (Kart and Teilmann, 2008). All hospital pharmacies included in the EAHP survey used computer systems for drug information and, between 2000 and 2005,

computerisation for pharmaceutical compounding increased by more than 20% (EAHP, 2005).

The Odense University Hospital is the regional hospital for southern Denmark (1 of the 5 Danish regions) and one of Denmark's largest public hospitals. The hospital pharmacy, *Sygehusapotek Fyn,* is responsible for distributing the medicines throughout the hospital, including compounded medicines and the few manufactured licensed medicines. According to Lisbeth Muurholm (hospital pharmacy manager), the production department is the largest in the pharmacy with 52 employees distributed in 4 sectors: cytotoxic preparation, extemporaneous preparation, licensed medicines manufacture and technical assistance. The department of quality (QA/QC) has 17 employees who perform chemical and microbiological analyses and oversee the overall quality of medicines from the department of production (Muurholm, 2008).

8.1 **Legislation**

The Ministry of the Interior and Health was established in February 2010 and is responsible for the pharmacy sector in Denmark (Ministry of the Interior and Health, 2010). Under this Ministry, the DMA regulates medicinal products and pharmacies (DMA, 2010a). Relevant Danish legislation comprises 3 main acts: Danish Medicines Act, Danish Pharmacy Act and Danish Health Act.

The Danish Medicines Act establishes the definition of medicinal products and states that a medicinal product may only be marketed or dispensed in Denmark when a Marketing Authorisation has been granted. Nevertheless, there are exceptions that do not need a Marketing Authorisation; compounded medicines are one of these exceptions and are defined in the Danish Medicines Act as "medicinal products prepared in a pharmacy for an individual patient or animal in accordance with a prescription from a doctor or a veterinarian (the magistral formula)" (Ministry of the Interior and Health, 2005).

The Danish Pharmacy Act states the tasks that a pharmacy is responsible for carrying out, which includes pharmaceutical compounding. This Act states that pharmacists may only prepare and dispense compounded medicines

which are different to commercially available medicines (Ministry of the Interior and Health, 2008).

According to Danish legislation, pharmacies may only prepare batches of compounded medicines (in advance) upon previous authorisation by the DMA. The community pharmacies authorised to prepare batches of compounded medicines are: *Glostrup Apotek, Skanderborg Apotek, Lemvig Apotek, Hillerød Frederiksborg Apotek* and *Løgstør Apotek*. In Denmark, community pharmacies are allowed to prepare and dispense compounded medicines to other community pharmacies and also to hospital pharmacies. On the other hand, hospital pharmacies are only allowed to prepare and dispense compounded medicines to other hospitals. Exceptionally, hospital pharmacies may prepare and dispense compounded medicines to community pharmacies provided that several conditions are met, including the fact that no Danish community pharmacy is able to prepare the compounded medicines required for the continuation of a patient's treatment (DMA, 1996).

Danish legislation establishes in detail the cost of any compounded medicine prepared. This mainly depends on the dosage form, raw materials and the quantity prepared (DMA, 2010b).

8.2 **Professional organisations and information sources**

8.2.1 **Danish professional organisations**

- Danish Medicines Agency (DMA): is the regulatory agency in Denmark that aims to ensure the availability of effective and safe medicinal products, medical devices and new therapies; and to promote the proper use of such health care products (DMA, 2010a). The authorisation for hospital pharmacies to manufacture licensed medicines is issued by the DMA.
- Amgros I/S: is a company that belongs to the 5 Danish regions that is responsible for the manufacture of licensed medicines in public hospitals and own the respective Marketing Authorisations.
- Association of Danish Pharmacies: is the employer and professional organisation of the Danish community pharmacies. A total of 252 proprietary pharmacists belong to this organisation (Apotek, 2008) but, as mentioned

above, only a few prepare compounded medicines at their pharmacies (Section 8).

8.2.2 **Danish information sources**

Denmark has not published an official formulary for pharmaceutical compounding. The references used include the PhEur and the following information sources (EAHP and HOPE, 2002):

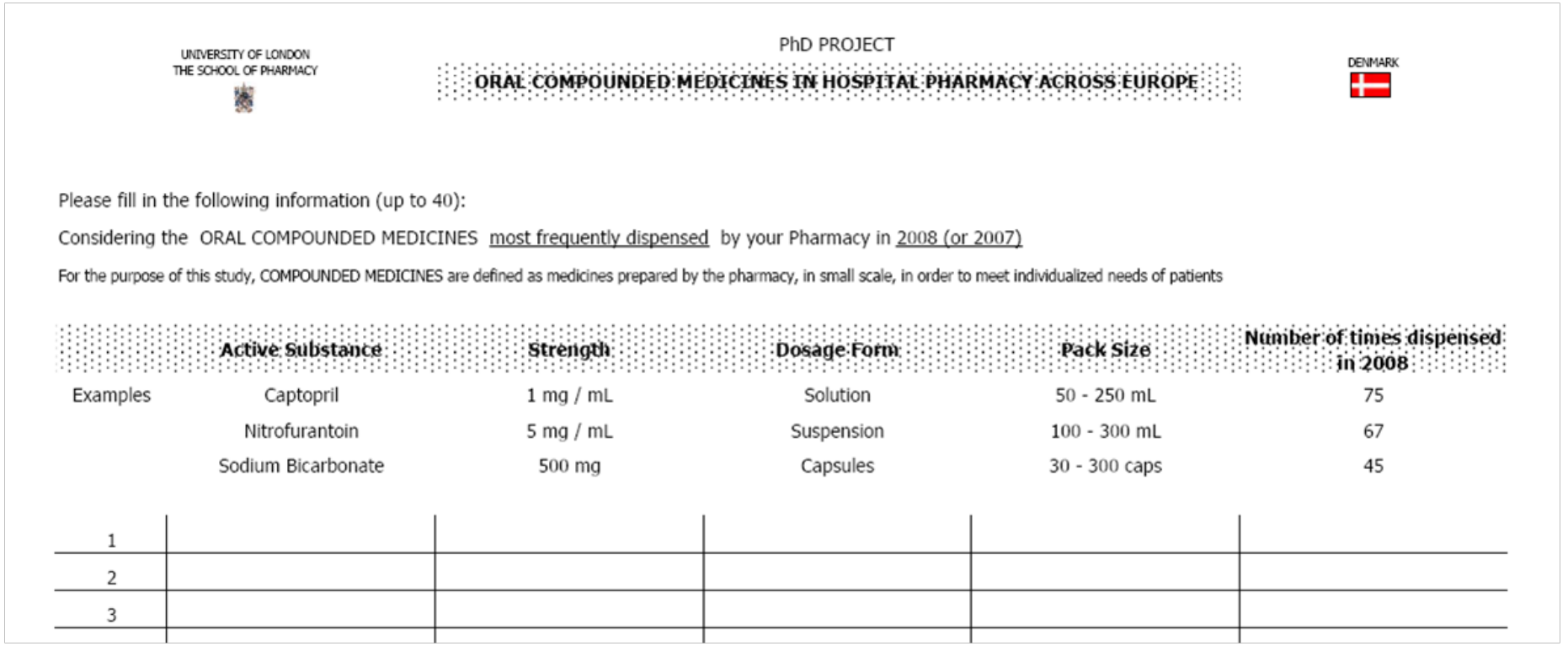
- *Danske Lægemiddelstandarder* (DLS): are the Danish drug standards, published by the DMA (2012), which include a chapter on the quality of compounded medicines (*Magistrelle Lægemidlers Kvalitet*) based on the PhEur and industrial (European) GMP (Section 14.1) (Handlos, 2007).

8.3 **Methods**

Denmark was included in the research following the interest of Daniel Bar-Shalom (University of Copenhagen, Faculty of Pharmaceutical Sciences) in collaborating to the Europe-wide project, presented at the 1st Conference of the EuPFI (Carvalho, 2009). The stakeholder provided invaluable guidance in the identification of the purposive sample and development of the customised questionnaire. Stakeholders from hospital pharmacy also contributed to the identification of the purposive sample, namely: Trine Schnor (*Region Hovedstadens Apotek*) and Line Poulsen (*Sygehusapoteket*). Because pharmaceutical compounding is centralised in a few hospital and community pharmacies, which prepare compounded medicines not only for their own patients but also for other pharmacies across the country, stakeholders suggested a purposive sample comprising both hospital and community pharmacies (Section 8.3.2).

8.3.1 **Country-specific questionnaire**

The research instrument developed to collect information regarding oral compounded medicines most frequently dispensed in Danish hospital and community pharmacies was a self-completion questionnaire (main heading in Figure 8.1), which was based on the template established for Portugal (Section 3.3.1) and adapted to the practice of pharmaceutical compounding in Denmark.



UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

ORAL COMPOUNDED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

DENMARK

Please fill in the following information (up to 40):

Considering the ORAL COMPOUNDED MEDICINES most frequently dispensed by your Pharmacy in 2008 (or 2007)

For the purpose of this study, COMPOUNDED MEDICINES are defined as medicines prepared by the pharmacy, in small scale, in order to meet individualized needs of patients

	Active Substance	Strength	Dosage Form	Pack Size	Number of times dispensed in 2008
Examples	Captopril	1 mg / mL	Solution	50 - 250 mL	75
	Nitrofurantoin	5 mg / mL	Suspension	100 - 300 mL	67
	Sodium Bicarbonate	500 mg	Capsules	30 - 300 caps	45
1					
2					
3					

Figure 8.1 Country-specific questionnaire (Denmark).

This customised questionnaire comprised 1 table only (to simplify the request for information and enhance response rates) and was developed in English, following recommendations of a stakeholder who asserted that translating was unnecessary since the Danish population was generally fluent in English. Data collection in Denmark was undertaken in 2009 and, therefore, the questionnaire addressed information relating to 2008 (or 2007), depending on the latest available data.

Compounded medicines were defined in the Danish questionnaire as "medicines prepared by the pharmacy, in small scale, in order to meet individualised needs of patients", which is in accordance with the official definition stated in the Danish Medicines Act (Section 8.1). The definition adopted, in comparison to the official definition, excluded the reference to veterinary since only human compounded medicines were being studied. Moreover, "in small scale" was added to the definition to ensure that "licensed" compounded medicines were excluded. Finally, "individual patient" was substituted for "in order to meet individualised needs of patients" for a better understanding of the concept of the medicines being studied.

8.3.2 **Purposive sample of pharmacies**

A total of 5 hospitals and 2 community pharmacies were selected across Denmark, from the cities of: *Ålborg*, *Århus, Hillerød, Holbæk* and *Odense*; *Glostrup* and *Skanderborg*, respectively (Figure 8.2), covering the 5 Danish regions and including the most populated cities. These pharmacies were identified by the stakeholders as the ones in which the largest quantities of compounded medicines were likely to be dispensed. The 2 community pharmacies selected were part of the list of pharmacies authorised by the DMA to prepare and dispense batches of compounded medicines (in advance) (DMA, 1996). According to the stakeholders, out of the 5 community pharmacies identified in Danish legislation (Section 8.1), only the 2 pharmacies identified prepared and dispensed compounded medicines in Denmark. The 2 community pharmacies were known to prepare both sterile and non-sterile compounded medicines for Danish hospitals and, therefore, research on pharmaceutical compounding in Denmark must acknowledge the compounded medicines prepared in these 2 pharmacies. According to

Handlos (2009), such a complete research has been tried in the past but it was unsuccessful because of the low response rate, in particular from the community setting.

Figure 8.2 Map of Denmark adapted from National Geographic Society (1998f); indicating the location of the purposive sample of hospitals and community pharmacies (●).

8.3.3 **Data collection**

The purposive sample was provided by the stakeholders including the name and email address of the key contact person in each hospital and community pharmacy. All 7 pharmacies were initially contacted by MC by email with the request to share data regarding the oral compounded medicines most frequently dispensed in 2008 (or 2007). The customised questionnaire was attached to a brief introductory email, together with an electronic copy of the IJPC article (Carvalho *et al.*, 2008). Non-respondents were sent periodical email reminders and, ultimately, these were contacted by telephone by MC. Persistent non-respondents were sent up to 8 email reminders and received up to 4 telephone calls.

It was considered that a visit to 1 community pharmacy and 2 hospital pharmacies was the necessary fieldwork for a better understanding of the practice of pharmaceutical compounding in Denmark.

At this stage, non-respondents were contacted again but with the purpose of scheduling a visit to the pharmacy / compounding laboratory. Because only 2 non-respondents accepted a visit to the pharmacy, one of the participant hospitals, which had already provided the required data, was contacted again with the request for a visit. Fieldwork was then undertaken in June 2009 and a total of 3 pharmacies were visited by MC: 1 community pharmacy and 2 hospital pharmacies (Figure 8.3).

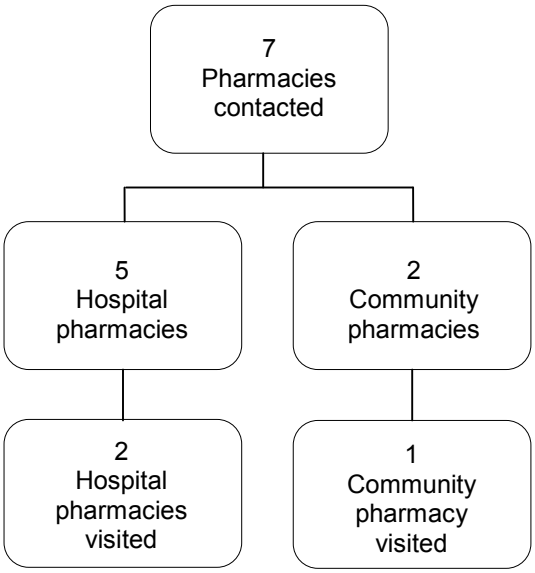


Figure 8.3 Purposive sample and pharmacies visited in Denmark.

8.4 **Results and discussion**

All 7 hospital and community pharmacies responded to the request for collaboration (100% response rate) and provided complete datasets for 2008. All pharmacies provided datasets in electronic formats by email, including the pharmacies visited by MC, with the exception of 1 pharmacy that sent the required data by post. A total of 5 pharmacies shared data in the questionnaire provided (Section 8.3.1) and 2 pharmacies in their own formats.

The fact that all pharmacists contacted were fluent in English and were willing to contribute data is likely to have contributed to the 100% response rate achieved. Also, the electronic copy of the IJPC article (Carvalho *et al.*, 2008), attached to the brief introductory email, might have encouraged pharmacists to participate in the ongoing Europe-wide research. Danish

hospital pharmacies are computerised (Kart and Teilmann, 2008) and it is likely that the pharmacies contacted kept electronic records of the compounded medicines dispensed, which will have contributed to the ease of retrieving the requested information.

One participant hospital stated that the compounded medicines dispensed were prepared either at their pharmacy or bought from other hospital/community pharmacies across the country. The hospital's dataset was provided including the name of the "manufacturer", in the column "Number of times dispensed in 2008" (Section 8.3.1), per compounded medicine dispensed. The "manufacturer" corresponded to the respective pharmacy and a total of 5 additional hospital/community pharmacies. This additional information was very important since 1 hospital and 2 community pharmacies were already included in the research and, therefore, the corresponding data was repeated. As a result, compounded medicines dispensed by this hospital that had already been reported by other participant pharmacies were excluded from the hospital's dataset. This finding indicates that pharmaceutical compounding is centralised in Denmark (Section 8) and reinforces the importance of having included the 2 community pharmacies in the research, since these are the "manufacturers" of some of the compounded medicines dispensed in Danish hospital pharmacies (Section 8.3.2).

Non-oral compounded medicines, rectal and topical dosage forms, were reported by 2 pharmacies and were all excluded from the pharmacies' datasets (Section 2.4.1).

8.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral compounded medicines in Denmark is shown in Table 8.1. Active substances were grouped according to the respective therapeutic classification (*Martindale 35*, 2007), giving a total of 87 different active substances and 24 therapeutic groups. Nutritional agents and vitamins was the group with the greatest number of different active substances (n=11), followed by electrolytes (n=10) and antibacterials (n=9).

Table 8.1 Active substances most frequently dispensed as oral compounded medicines in Denmark (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Capsaicin, codeine, indometacin, methadone HCl, morphine, opium

Antibacterials
Dapsone, ethambutol HCl, isoniazid, nitrofurantoin, pyrazinamide, sulfadiazine, sulfamethizole, sulfamethoxazole, trimethoprim

Antiepileptics
Clobazam, phenobarbital, phenytoin, topiramate

Antigout drugs
Allopurinol, colchicine

Antimalarials
Quinine HCl

Antineoplastics
Tegafur

Antiparkinsonian drugs
Amantadine, biperiden

Anxiolytic, sedatives, hypnotics and antipsychotics
Chloral hydrate, clozapine, levomepromazine, midazolam, nitrazepam, pentobarbital

Blood products, plasma expanders and haemostatics
Tranexamic acid

Bronchodilators and anti-asthma drugs
Caffeine, caffeine citrate

Cardiovascular drugs
Amlodipine besilate, atropine, captopril, carvedilol, metoprolol, nifedipine, propranolol HCl, spironolactone

Chelators, antidotes and antagonists
Methionine, naloxone HCl

Corticosteroids
Cortisone acetate, dexamethasone, fludrocortisone acetate, hydrocortisone, prednisolone

Disinfectants and preservatives
Chlorhexidine

Electrolytes
Dibasic sodium phosphate, dibasic potassium phosphate, magnesium chloride, magnesium sulfate, potassium chloride, potassium citrate, potassium phosphate, sodium bicarbonate, sodium chloride, sodium citrate

GI drugs
Bismuth salicylate, calcium carbonate

Local anaesthetics
Lidocaine

Muscle relaxants
Dantrolene sodium

Nutritional agents and vitamins
Alpha tocoferil acetate, carnitine, ergocalciferol, folic acid, glucose, lactose, levocarnitine, pyridoxine HCl, riboflavin, sucrose, zinc sulfate

Prostaglandins
Misoprostol

Stimulants and anorectics
Amfetamine sulfate, dexamfetamine sulfate

Supplementary drugs and other substances
Citric acid, disulfiram, glycerol, melatonin, potassium bromide

Thyroid and antithyroid drugs
Potassium iodide, potassium perchlorate, propylthiouracil, sodium iodide

Urological drugs
Sildenafil citrate

Although these active substances were all reported as oral compounded medicines, the title of 2 therapeutic groups suggested non-oral (therapeutic) indications, namely: disinfectants and preservatives (Appendix 12) and supplementary drugs and other substances (Appendix 15). The active

substances included in these groups are described in the respective appendixes.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 3 NTI drugs were dispensed as oral compounded medicines (underlined in Table 8.1).

The active substances dispensed by most pharmacies were: glucose and morphine (n=5), captopril and spironolactone (n=4).

All active substances reported were included in *Martindale 35* (2007), with the exception of uracil (Appendix 26), which was dispensed in combination with tegafur, by 1 pharmacy, as capsules prepared from the proprietary medicine Uftoral. Tegafur with uracil is indicated in the management of metastatic colorectal cancer (Joint Formulary Committee, 2008).

The majority of compounded medicines included just 1 active substance and only the following combinations of active substances were reported: isoniazid and pyridoxine HCl; trimethoprim and sulfamethizole; trimethoprim and sulfamethoxazole; combination of phosphates; and combination of vitamins.

Only a few compounded medicines were reported by the proprietary medicines used in their preparation, namely: Co-trimoxazole (tablets), Uftoral (capsules) and Viagra (oral liquid), which were dispensed by 2 pharmacies.

8.4.2 **Oral compounded medicines**

In Denmark, the most frequently dispensed oral compounded medicines were solid dosage forms. A total of 48,195 packs (62%) of oral solids were reported, whereas only 26,870 multidose units (34%) of oral liquids and 3,000 multidose units (4%) of oromucosal preparations were reported by the Danish pharmacies (Figure 8.4). This fact is not in accordance with Brion *et al.* (2003), who concluded that oral liquids were the most frequently dispensed oral dosage forms in Denmark but their findings resulted from only 1 Danish hospital.

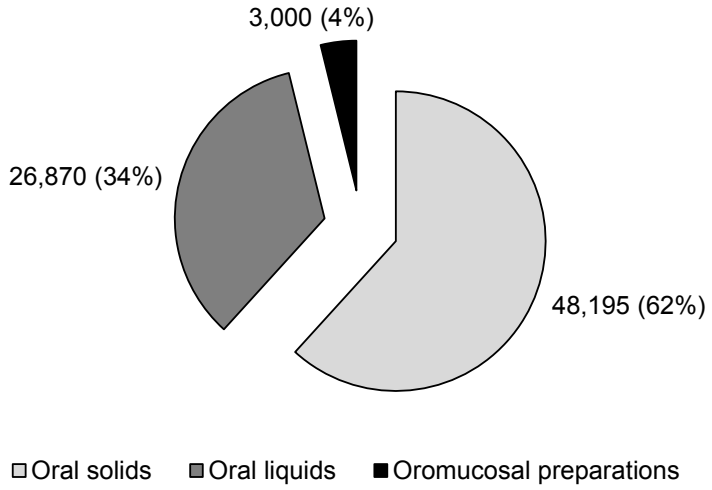


Figure 8.4 Number of packs/units of oral (and oromucosal) compounded medicines dispensed in Denmark, per dosage forms.

The majority of compounded medicines were dispensed in the 2 community pharmacies (54,885 packs/units) and only 30% (23,180 units) were dispensed in the 5 hospital pharmacies. In conclusion, community pharmacies dispensed a considerably larger quantity of compounded medicines when compared to the hospital setting, which reinforces the importance of having included the 2 community pharmacies in the research.

A total of 75,065 packs/units of oral solid and oral liquid compounded medicines were dispensed and the most frequent active substances were:

- Glucose (16%): a monosaccharide commonly used in the treatment of carbohydrate and fluid depletion, and also in the treatment of hypoglycaemia; the doses vary in accordance with the individual patient needs (*Martindale 35*, 2007) and, therefore, it is not unexpected that this was the most frequently dispensed active substance in Denmark. Glucose was dispensed as oral powders and oral liquids.
- Hydrocortisone (11%) and melatonin (10%), both dispensed as tablets.

The top 20 active substances are shown in Figure 8.5. and the top 5 corresponded to 51% of all active substances dispensed, which indicates the repetitive nature of pharmaceutical compounding in Denmark. In addition, the majority of active substances were dispensed in a limited number of strengths, which suggests that, to a certain extent, compounded medicines

are standardised in this country. The active substances dispensed in the greatest range of strengths were: glucose, 2 strengths (oral powders) and 4 strengths (oral liquids); sodium chloride, 1 strength (tablets) and 5 strengths (oral liquids); isoniazid, 1 strength (tablets) and 3 strengths (oral liquids); propranolol HCl, 4 strengths oral liquids (1-4 mg/mL) and sildenafil citrate, 4 strengths oral liquids (1-3 mg/mL). Oral liquids were associated with a greater range of strengths that oral solid dosage forms.

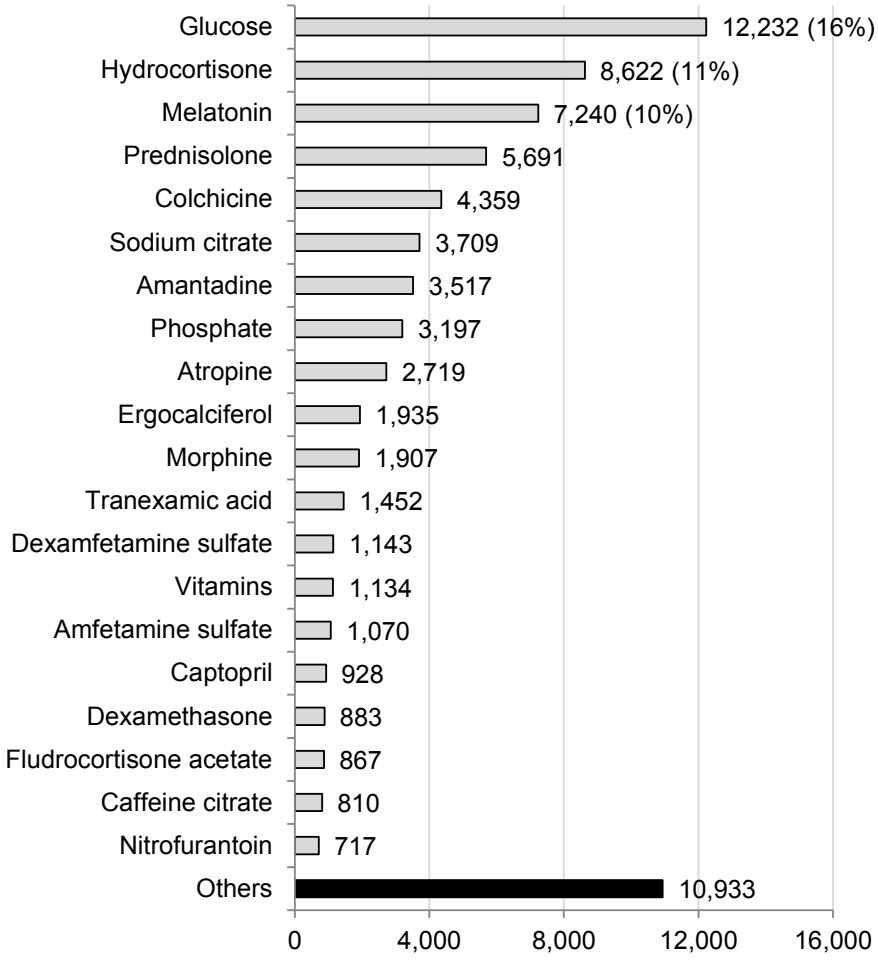


Figure 8.5 Overall top 20 active substances per number of packs/units dispensed.

Glucose and hydrocortisone are included in “nutritional agents and vitamins” and “corticosteroids”, respectively, which correspond to the top therapeutic groups and represent almost 50% of all therapeutic groups dispensed (Figure 8.6). All Danish pharmacies dispensed oral compounded medicines corresponding to “nutritional agents and vitamins” and “electrolytes”.

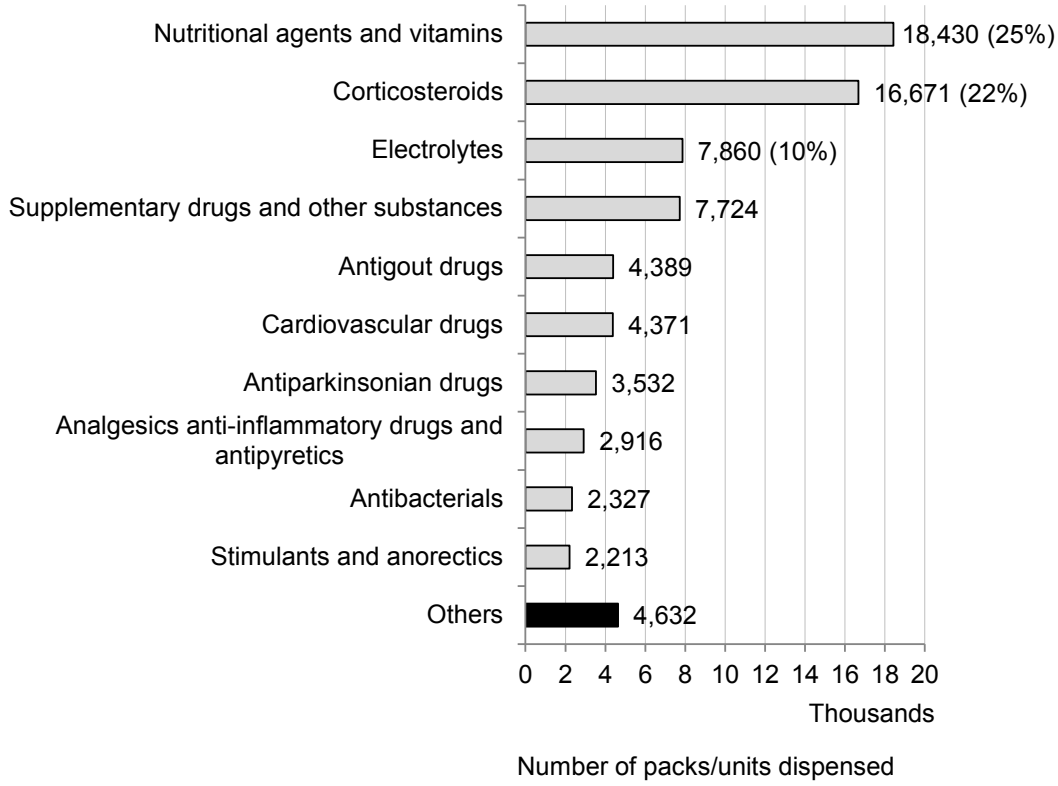


Figure 8.6 Overall top 10 therapeutic groups per number of packs/units dispensed.

In 2005, the number of patients discharged from all hospitals (including through death) in Denmark was highest for diseases of the circulatory system (2,559 patients / 100,000 population) (Figure 8.7) (WHO Regional Office for Europe, 2008). It was to be expected then that cardiovascular drugs were part of the top 10 therapeutic groups in Denmark (Figure 8.6).

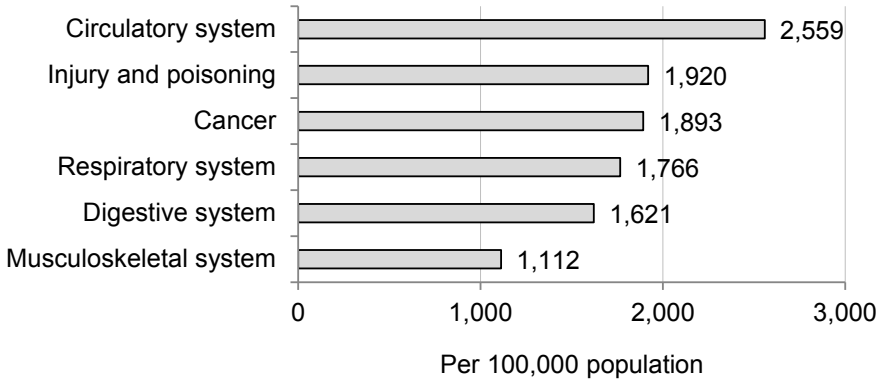


Figure 8.7 Number of patients per 100,000 population discharged from all hospitals (including through death) in Denmark during 2005 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

8.4.2.1 **Oral solids**

Oral solid dosage forms corresponded to 62% of all compounded medicines (Figure 8.4) but were dispensed by only 3 pharmacies (43%). The oral solids dispensed included, in decreasing order, tablets, oral powders and capsules (Figure 8.8).

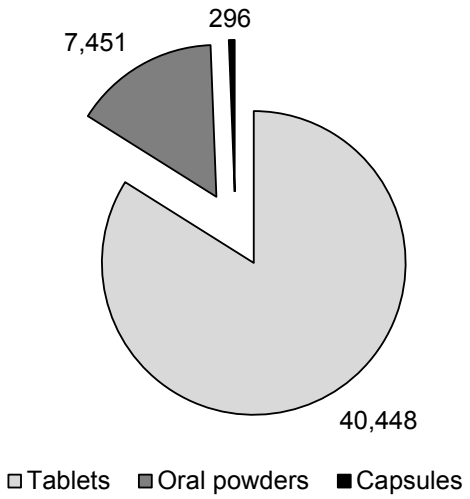


Figure 8.8 Oral solid dosage forms dispensed per number of packs.

Tablets corresponded to 84% of all oral solids (Figure 8.8) and were reported by 2 pharmacies. The preparation of tablets requires specific tableting equipment and not all pharmacies can afford such an investment (Section 2.1.3). The top 5 active substances (and respective strengths) dispensed as tablets were: hydrocortisone (1 mg and 5 mg), melatonin (3 mg), prednisolone (50 mg) and colchicine (500 µg), which were all part of the overall top 5 active substances (Figure 8.5), and amantadine (50 mg and 100 mg). Tablets are commonly prepared in large scale because of the characteristics of the tableting equipment and, therefore, it is not unexpected that active substances were prepared in only 1 or 2 different strengths. Tablets were dispensed as packs of 100 units (89%), 50 units (10.7%) and 10 units (0.3%).

Oral powders corresponded to 15% of all oral solids (Figure 8.8) and were also reported by only 2 pharmacies. The only 3 active substances (and respective strengths) dispensed as oral powders were: glucose (75 g and 82.5 g), which was the overall most frequently dispensed active substance

(Figure 8.5), lactose (200 g) and methionine (2.5 g). Oral powders were dispensed as sachets and envelopes (Section 2.1.3).

Capsules corresponded to just 1% of all oral solids (Figure 8.8) and were reported by only 1 pharmacy. The only 2 active substances dispensed as capsules were: misoprostol (25 µg) and tegafur with uracil (500 mg).

The top 3 therapeutic groups (oral solids only) were: corticosteroids (16,238 packs of tablets), nutritional agents and vitamins (8,907 packs of oral powders and tablets) and supplementary drugs and other substances (7,240 packs of tablets). “Nutritional agents and vitamins” and “corticosteroids” were also in the overall top 3 therapeutic groups (Figure 8.6).

8.4.2.2 **Oral liquids**

Oral liquid dosage forms corresponded to 34% of all compounded medicines (Figure 8.4) and were dispensed by all pharmacies. The oral liquids dispensed included solutions, suspensions, mixtures and oral drops. The majority of oral liquids were reported as solutions (76%) but it is likely that the classification of some oral liquids was not accurate and, therefore, part of the solutions might have corresponded to other liquid dosage forms (and vice-versa) (Section 2.1.3); as, for instance, to syrups, which were not specified by any Danish pharmacy. Suspensions (10.4%) were the next most frequently dispensed dosage form, followed by oral drops (10.1%) and mixtures (0.2%). Again, it is likely that some interchange might have occurred in categorisation, in particular with regards to the suspensions/mixtures. Finally, a total of 3.3% were generally classified as oral liquids or were not classified with regards to the specific dosage form.

The volumes reported ranged from 10 mL to 1,000 mL but the majority of oral liquids were in volumes of 100 mL and 500 mL. Oral syringes were not reported in Denmark and it was assumed that all oral liquids were multidose.

Solutions and suspensions were specifically reported by 5 pharmacies, in a total of 23,217 multidose containers, which corresponded to 86.4% of all oral liquids reported. The active substances most frequently dispensed as solutions/suspensions were glucose, which was the overall most frequently

dispensed active substance (Figure 8.5), sodium citrate, tranexamic acid, phosphate and captopril.

Mixtures represented only 0.2% of all oral liquids and were reported by only 1 pharmacy, in a total of 59 multidose units. The only 2 active substances (and respective strengths) dispensed as mixtures were: potassium chloride (75 mg/mL) and nitrazepam (0.5 mg/mL).

Oral drops corresponded to 10.1% of all oral liquids and were reported by only 1 pharmacy, in a total of 2,721 multidose units. The only 2 active substances (and the respective volumes) reported as oral drops were: ergocalciferol (10 mL) and morphine (30 mL).

The top 3 therapeutic groups (oral liquids only) were: nutritional agents and vitamins (9,523 units), electrolytes (5,993 units) and analgesics, anti-inflammatory drugs and antipyretics (2,916 units). “Nutritional agents and vitamins” and “electrolytes” were in the overall top 3 therapeutic groups (Figure 8.6).

8.4.2.3 **Oromucosal preparations**

In Denmark, oromucosal preparations were reported by 1 pharmacy and, in total, only 2 different compounded medicines were reported, as follows:

- Chlorhexidine mouthwash 0.12% (300 mL): chlorhexidine is an antiseptic and disinfectant that is formulated as a mouthwash for mouth infections, including candidiasis, and to reduce dental plaque accumulation (*Martindale 35*, 2007).
- Lidocaine gel 20% (100 mL): lidocaine may be used in local anaesthesia, and gels are commonly used for anaesthesia of the urinary tract in concentrations of 1-2%. Lidocaine ointments are used for anaesthesia of skin and mucous membranes in a maximum of 20 g daily of lidocaine ointment 5% (*Martindale 35*, 2007). The pharmacy dispensed lidocaine gel 20%, a much higher concentration than what is described in the literature.

A total sum of 3,000 multidose units of oromucosal preparations were dispensed but the majority corresponded to the chlorhexidine mouthwash.

8.5 **Summary**

- In Denmark, pharmaceutical compounding is centralised in a few community and hospital pharmacies. Hospital pharmacies also manufacture licensed medicines, which are not supplied by the pharmaceutical industry. Amgros is the company responsible for the manufacture of licensed medicines in public hospitals and own the respective marketing authorisations.
- A purposive sample of 7 hospital and community pharmacies was included in the research and a response rate of 100% was obtained. A total of 87 different active substances (including 3 NTI drugs) were reported corresponding to 24 different therapeutic groups. The top 3 therapeutic groups were nutritional agents and vitamins (n=11), electrolytes (n=10) and antibacterials (n=9).
- Oral solid dosage forms were reported by 43% of pharmacies and included tablets, oral powders and capsules. Tablets were dispensed in a total sum of 40,448 packs (84% of all oral solids) and the top 5 active substances were: hydrocortisone, melatonin, prednisolone, colchicine and amantadine. Oral powders were dispensed in a total sum of 7,451 packs (15% of all oral solids) and the only active substances dispensed were glucose, lactose and methionine. Capsules were dispensed in a total sum of 296 packs (1% of all oral solids) and the only active substances dispensed were misoprostol and tegafur with uracil.
- Oral liquid dosage forms were reported by all participant pharmacies and included solutions and suspensions, mixtures and oral drops (multidose). Solutions and suspensions were dispensed in a total sum of 23,217 units (86.4% of all oral liquids) and the top 5 active substances were: glucose, sodium citrate, tranexamic acid, phosphate and captopril. Mixtures and oral drops were dispensed in a total sum of 59 (0.2%) and 2,721 (10.1%) units, respectively. The only active substances dispensed were: potassium chloride and nitrazepam (mixtures); ergocalciferol and morphine (oral drops).
- Oral solids were dispensed in larger quantities than oral liquids.
- Oromucosal preparations were reported by only 1 pharmacy, in a total of 3,000 multidose units, as follows: chlorhexidine mouthwash 0.12% and lidocaine gel 20%.

9. **Compounding in Slovenia**

Slovenia is a Mediterranean country, located between Croatia and Italy, that became independent from Yugoslavia in 1991 and joined the EU in 2004. Slovenian is the country's official language (*Europa*, 2009). Slovenia is one of the smallest EU countries, occupying an area of 20,100 Km^2, and is also one of the least populated EU countries, with a population of 2.0 million in 2007 (Figure 2.2) (*Europa*, 2008).

In 2007, there were 29 hospitals in Slovenia (ratio of 1.44 hospitals per 100,000 population) and a total of 9,414 hospital beds (ratio of 466.18 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2006, there were 944 pharmacists in Slovenia (ratio of 47 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4). According to the EAHP survey, the average number of pharmacists in Slovenian hospitals is 2.7, which is lower than the European average of 4.7 pharmacists per European hospital. In fact, there has been a decrease in the number of hospital pharmacists in Slovenian hospitals which, according to Tajda Miharija Gala[38], is affecting the efficiency and influence of pharmacists in hospitals (Gala, 2004). Slovenian hospitals have an average of 4.9 qualified pharmacy technicians/assistants per hospital, which is also lower than the European average of 6, and an average of 0.9 non-qualified pharmacy assistants per hospital (EAHP, 2005; Hartmann, 2010).

In Slovenia, all hospital pharmacies may prepare and dispense (sterile and non-sterile) compounded medicines and no specific licences are required for the practice of compounding (EAHP, 2005). It is assumed that all Slovenian hospitals have some sort of compounding capability (Čufar, 2009) but, according to Morgan (2009), community pharmacies have the most important role in compounding throughout the country.

The largest hospital in Slovenia is the Ljubljana University Medical Centre, which employs more than 100 staff members at the pharmacy, including 29

[38]Tajda Miharija Gala is the president of the section of hospital pharmacists of the Slovenian Pharmaceutical Society (Section 9.2.1) (Gala, 2011).

with pharmacy degrees (Štefančič, 2007; Gala, 2009). This hospital pharmacy is equipped with several compounding units for the preparation of sterile and non-sterile compounded medicines (Gala, 2009). The second largest hospital is the University Medical Centre Maribor, which employs 28 staff members in the pharmacy, including 7 pharmacy graduates and 10 pharmacy technicians. This hospital prepares compounded medicines, both sterile and non sterile, either individually or in small batches (Koder, 2011). According to Silvo Koder (head of hospital pharmacy), QC is performed on raw materials and final products (Koder, 2011).

In 2003, a Department of Quality established by the Ministry of Health conducted a national survey in which all Slovenian hospitals were asked to complete a questionnaire. The “preparation and administration of drugs” was 1 of the 10 major topics addressed and, despite the fact that only 50% of all Slovenian hospitals returned the complete questionnaire, it was concluded that there was a need for “improved drug preparation in validated working environments” (Gala, 2006).

9.1 **Legislation**

In Slovenia, compounded medicines may be either magistral preparations or galenic preparations, which are defined in the Slovenian Medicines Act (Ministrstvo za Zdravje, 2006), as follows:

Magistral preparations for human use are medicines prepared in a pharmacy according to a prescription and intended for a specified patient.

Galenic preparations for human use are medicines prepared in a (pharmacy) galenic laboratory according to the pharmacopoeia in force and intended for being dispensed at the pharmacy. These medicines may be prepared for individual patients or in batches, provided that the pharmacy has a certified (galenic) laboratory (Section 9.3.1).

A proposal for a new Slovenian Medicines Act is being prepared, which will be compliant with the European Resolution CM/ResAP(2011)1 (Section 14.1) that came into force in January 2011 (Gala, 2011).

9.2 **Professional organisations and information sources**

9.2.1 **Slovenian professional organisations**

In Slovenia, there are 2 main professional organisations, namely: the Slovenian Chamber of Pharmacy and the Slovenian Pharmaceutical Society.

The Slovenian Chamber of Pharmacy is an independent organisation, comprising all community and hospital pharmacies in Slovenia, which was established in 1992 to protect professional honour. By law, every Slovenian pharmacy must be a member of this chamber (Lekarniška zbornica Slovenije, 2010). The Slovenian Chamber of Pharmacy and the Slovenian Pharmaceutical Society (Slovensko Farmacevtsko Društvo, 2010) perform various activities together in support of the professional and economical interests of its members (Gala, 2004). The Slovenian Chamber of Pharmacy is also responsible for planning and monitoring the specialisations for pharmacists, and "formulation of drugs" is one of the 5 specialisation programmes available (Čufar, 2007).

Both professional organisations have a section specifically dedicated to hospital pharmacy. The hospital pharmacy section in the Slovenian Pharmaceutical Society has proposed that all hospital pharmacies would perform the following compounding activities by 2011: "preparation of cytotoxics, radiopharmaceuticals, TPN and all sterile medicines for high-risk wards" (Štefančič, 2007).

9.2.2 **Slovenian information sources**

The Slovenian Medicines Act (article 20, number 1) establishes that medicinal products must be manufactured in accordance with the PhEur and the Slovenian national supplement to the PhEur (Ministrstvo za Zdravje, 2006), named *Formularium Slovenicum* (FS) and issued by the *Javna Agencija Republike Slovenije za Zdravila in Medicinske Pripomočke* (JAZMP) (Glover, 2011). The FS has been published since 1998 and is now in its 3rd edition (FS 3.0), which is available online by subscription and includes selected contents of the PhEur 7.0 (and respective supplements 7.1 and 7.2.), as well as specific national content (JAZMP, 2011a). The FS enables the implementation of the PhEur in Slovenia, taking into consideration

national requirements (Cvelbar *et al.*, 2003). In Chapter VI, national monographs include monographs for pharmaceutical preparations, for instance: Simple Syrup and Zinc Ointment, in a total of 14 different compounded medicines (JAZMP, 2011b).

The *Kodeks Galenskih Izdelkov* (codex of galenic products), published in 2009, includes a total of 103 monographs for both adult and paediatric compounded medicines (Obreza and Gašperlin, 2009). This codex is not legally binding and formulae have not been validated, which is considered a major deficiency by the working party of the codex (Glover, 2012).

9.3 **Methods**

The research project was initiated in 2007 with the help of Spela Godec (SG)[39] who, in the initial stages, put MC in contact with Slovenian stakeholders and, in a later stage, provided invaluable support with translations (Section 9.3.3). The research project in Slovenia was then set up considering the expertise and advice of Slovenian pharmacists from academia, hospital pharmacy and the Slovenian Chamber of Pharmacy (Section 9.2.1).

Tomi Laptoš (University Medical Centre Ljubljana) and Jure Bračun (*Splošna Bolnišnica Celje*), both pharmacists at Slovenian hospitals, contributed with important information regarding the concept of compounded medicines in Slovenia, and the respective compounding legislation. Jure Bračun also contacted selected Slovenian hospitals on behalf of MC (Section 9.3.3).

Andreja Čufar (president of the Slovenian Chamber of Pharmacy) and Brigita Najdenov (*Splošna Bolnišnica Jesenice*) provided the complete list of Slovenian hospitals, including the classification of each hospital and the contact details for each hospital pharmacy. Although the Ministry of Health stated 26 hospitals in the official website (Ministry of Health, 2010), a total of 29 hospitals were described in the literature and identified by the stakeholders, as follows: university hospitals (2); general hospitals (10); specialist hospitals (14); and 3 extra hospitals for diagnostic/surgical

[39]SG was, at that time, an Erasmus student from the University of Ljubljana, Faculty of Pharmacy, at the CPPR (UCL School of Pharmacy, University of London).

procedures. With reference to the specialist hospitals, these were further divided in: gynecological (2), oncology (1), orthopedic (1), psychiatric (5), pulmonary (3) and rehabilitation (2) (Najdenov, 2009; Čižman, 2011).

It was decided that no fieldwork would be undertaken in Slovenia (budgetary constraints) and, hence, all research was undertaken by MC at distance, which lengthened the timelines for the project in this country; data collection was initiated in 2009.

9.3.1 **Country-specific questionnaire**

The research instrument developed to collect information regarding oral compounded medicines most frequently dispensed in Slovenian hospital pharmacies was a self-completion questionnaire, based on the template established for Portugal (Section 3.3.1) and adapted to the practice of pharmaceutical compounding in Slovenia.

This customised questionnaire comprised 1 table only and was developed in English to ease the direct communication with MC (avoiding the need for translators). Data collection in Slovenia was initiated in the year 2009 and, therefore, the questionnaire addressed information relating to 2008 (or 2007), depending on the latest available data. Compounded medicines were defined in the questionnaire as “medicines prepared by the pharmacy, in small scale, in order to meet individualised needs of patients”. The official terminology (Section 9.1) was not adopted since, according to Slovenian stakeholders, a brief explanation would be preferable to the request for magistral and galenic preparations. In Slovenia, magistral preparations commonly comprise for individual compounded medicines whereas galenic preparations commonly comprise for compounded medicines prepared in batches. Since batch preparation (of galenic preparations) is only allowed in pharmacies with a certified (galenic) laboratory, the official terminology could be confusing and, therefore, a brief and general definition of compounded medicines was adopted instead.

In a later stage, the customised questionnaire and introductory email were translated into Slovenian by SG (Section 9.3.3) and, because the majority of translated emails were sent in January 2010, the translated questionnaire

addressed data from 2008 (and also 2009). The main heading of the translated Slovenian questionnaire is shown in Figure 9.1.

9.3.2 **Purposive sample of hospitals**

According to Čufar (2009), there were 3 specific hospitals that prepared the majority of compounded medicines in Slovenia but, in general, all Slovenian hospitals undertook some sort of compounding. A purposive sample constituted by 3 hospitals was considered too limited, and it was likely that more hospitals would also frequently dispense compounded medicines in Slovenia. For these reasons, instead of a purposive sample, all 29 hospitals in Slovenia (Section 9.3) were contacted and invited to participate in the study.

9.3.3 **Data collection**

The complete list of Slovenian hospitals was provided by 2 stakeholders including the contact details for each hospital pharmacy (Section 9.3). All 29 hospitals were contacted by MC by email (in English) with the request to share data regarding the oral compounded medicines most frequently dispensed in 2008 (or the latest available year). A brief introductory email was then sent to each hospital pharmacy, with the questionnaire attached as well as an electronic copy of the IJPC article (Carvalho *et al.*, 2008). After 1 month, only 4 hospitals had replied to the request for collaboration.

Because there was a possibility that some of the email addresses provided by the stakeholders were no longer in use, alternative email addresses were searched in the hospital's websites (Ministry of Health, 2010). Email reminders were then sent periodically to all non-respondents, to a maximum of 5 email reminders per hospital. Jure Bračun (Section 9.3) also contacted selected non-respondents on behalf of MC.

After a long period of time, only a few more hospital pharmacies had replied to the request for collaboration. It was suggested that the staff at the hospitals did not use email regularly. For this reason, all non-respondents were contacted by telephone by MC. It was very difficult to communicate with the receptionists at the hospitals, for language reasons, and also with the staff at the pharmacies.

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

OV BOLNIŠNIČNIH LEKARNAH PRIPRAVLJENA ZDRAVILA V EVROPI

SLOVENIJA

Prosim, izpolnite naslednje podatke (do 40 vnosov):

Gre za MAGISTRALNE PRIPRAVKE OZ. V BOLNIŠNIČNI LEKARNI pripravljena zdravila v letu 2008 (lahko tudi 2009).

Gre za zdravila, ki so bila v manjših serijah pripravljena v lekarni za zagotovitev individualnih potreb bolnikov.

	Zdravilna Učinkovina	Jakost	Farmacevtska Oblika	Velikost Pakiranja	Število izdaj v letu 2008
Primeri	*Captopril*	1 mg / mL	*Solution*	50 - 250 mL	75
	Nitrofurantoin	5 mg / mL	*Suspension*	100 - 300 mL	67
	Sodium Bicarbonate	500 mg	*Capsules*	30 - 300 caps	45
1					
2					
3					

Figure 9.1 Country-specific questionnaire (Slovenia).

In a last attempt to increase the number of participant hospitals, the questionnaire and introductory email were translated to Slovenian by SG and these were sent to all non-respondents.

9.4 **Results and discussion**

Out of the 29 hospitals contacted, 17 hospital pharmacies responded to the request for collaboration and 12 were non-respondents, resulting in a response rate of 59%. Furthermore, out of the 17 respondents, 9 contributed data regarding the oral compounded medicines most frequently dispensed by their pharmacies and 8 hospitals were non-participants (Figure 9.2).

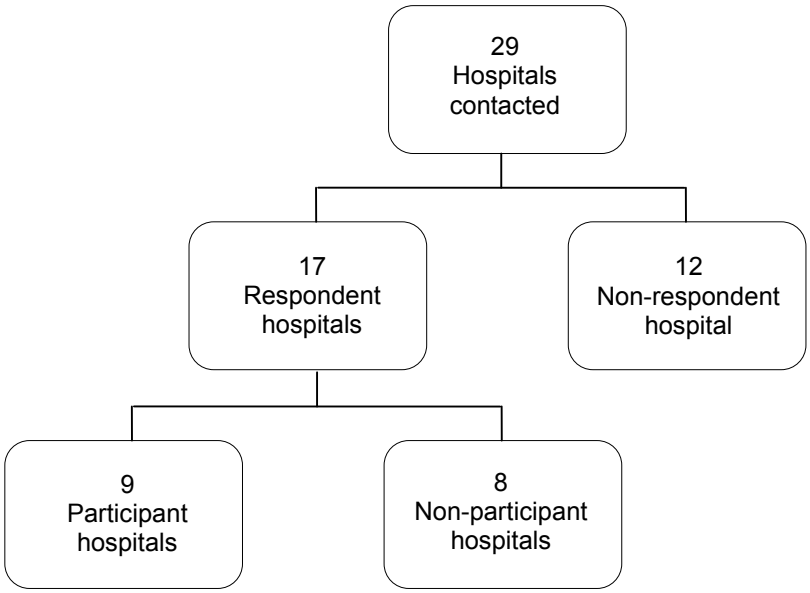


Figure 9.2 Purposive sample distributed by respondent and participant hospitals.

With reference to the coding frame in Table 2.2, the reasons given by hospital pharmacies for not participating in the research may be summarised as follows: 4 hospitals did not dispense oral compounded medicines; 2 hospitals dispensed oral compounded medicines but data was not readily accessible; 1 hospital dispensed very few oral compounded medicines; and 1 hospital did not provide any reason for not collaborating. Because all hospitals in Slovenia were included in the research, it was expected that those hospitals that dispensed few (or none) compounded medicines would be least likely to participate. In addition, the English language was a barrier to effective communication between MC and the staff at the hospitals, which might have discouraged participation. If a purposive sample of hospitals had

been contacted (instead of all hospitals in Slovenia), and if a Slovenian collaborator had been appointed to contact these hospitals, the response rate would likely had been higher. Nevertheless, the response rate achieved was still higher than the 50% achieved in the national survey conducted by the Department of Quality (Section 9). In total, 8 hospitals provided complete datasets and only 1 hospital supplied qualitative information. All 8 hospitals provided datasets in electronic formats and also in the questionnaire provided (Section 9.3.1). All hospitals provided data regarding 2008, with the exception of 1 hospital that provided data regarding 2009.

The participant hospitals were located across the country, in the cities of *Celje, Golnik, Izola, Jesenice,* Ljubljana (capital)*, Maribor, Novo Mesto, Ptuj* and *Sežana* (Figure 9.3), which included the largest Slovenian cities, namely: Ljubljana (capital) and *Maribor* (*Slovenia-Tourist-Guide*, no date).

Figure 9.3 Map of Slovenia adapted from National Geographic Society (2003); indicating the location of the participant hospitals (●).

9.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral compounded medicines in Slovenia is shown in Table 9.1. Active substances were grouped according to their therapeutic classification (*Martindale 35*, 2007), giving a total of 68 different active substances and 19 therapeutic

groups. Antibacterials was the therapeutic group with the greatest number of different active substances (n=11), followed by cardiovascular drugs (n=10) and electrolytes (n=7).

The title of all therapeutic groups suggest the respective oral indications, with the exception of supplementary drugs and other substances; the active substances included in this group were described in Appendix 15.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 3 NTI drugs were dispensed as oral compounded medicines (underlined in Table 9.1).

Table 9.1 Active substances most frequently dispensed as oral compounded medicines in Slovenia (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Indometacin, morphine, naproxen

Antibacterials
Amoxicillin, clavulanic acid, cloxacillin, isoniazid, nitrofurantoin, phenoxymethylpenicillin, pyrazinamide, rifampicin, roxithromycin, spiramycin, trimethoprim

Antiepileptics
Oxcarbazepine, phenobarbital, topiramate

Antimalarials
Pyrimethamine

Antineoplastics
Idarubicin HCl, lomustine, mercaptopurine, procarbazine HCl, tioguanine, trofosfamide

Antiprotozoals
Metronidazole

Antivirals
Oseltamivir phosphate, valganciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Chloral hydrate, midazolam, nitrazepam

Bronchodilators and anti-asthma drugs
Caffeine, theophylline

Cardiovascular drugs
Amiodarone, bisoprolol fumarate, captopril, clonidine, enalapril, furosemide, metoprolol, propafenone HCl, propranolol HCl, spironolactone

Electrolytes
Dibasic sodium phosphate, magnesium sulfate, monobasic sodium phosphate, potassium chloride, sodium bicarbonate, sodium chloride, sodium citrate

GI drugs
Calcium carbonate, pantoprazole, ranitidine, sodium sulfate

Immunosuppressants
Azathioprine, tacrolimus

Local anaesthetics
Benzocaine

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide

Nutritional agents and vitamins
Glucose, lactose, riboflavin, tocoferil acetate, tocopherol, zinc

Supplementary drugs and other substances
Amylase, citric acid, macrogols

Thyroid and antithyroid drugs
Levothyroxine sodium

Urological drugs
Sildenafil citrate

The active substances dispensed by most hospitals were: sodium bicarbonate (n=7), midazolam (n=6), ranitidine and theophylline (n=5).

All active substances reported were included in *Martindale 35* (2007), with exception of lipase and protease (Appendix 26) that were dispensed by only 1 hospital as oral powders (in combination with amylase). The source of these 3 pancreatic enzymes was a proprietary medicine (Panaze). Lipase, protease and amylase are constituents of pancreatin, or pancreas powder, a substance prepared from pancreases of mammals that is given orally in conditions of pancreatic exocrine deficiency (*Martindale 35*, 2007) (Appendix 15).

The majority of compounded medicines dispensed included 1 active substance only. In fact, only a few combinations of active substances were reported, as follows:

- Amoxicillin and clavulanic acid: a common antibacterial combination that is commercially available as, for example, in Co-amoxiclav (Joint Formulary Committee, 2008).
- Rifampicin and isoniazid: a common antituberculosis combination that is also commercially available as, for example, in Rifinah 150 (Joint Formulary Committee, 2008).
- Lipase, protease and amylase (mentioned above).
- Multiple combinations of electrolytes; electrolytes, glucose and macrogols; and also electrolytes, sodium sulfate and macrogols.

The majority of compounded medicines were reported by the respective active substances and only 2 compounded medicines were reported by the proprietary medicines used in their preparation: Imuran (azathioprine) and Panaze (lipase, protease and amylase), which were dispensed by 2 hospitals. It is likely that more compounded medicines were prepared from the respective proprietary medicines, in particular the commercially available combinations mentioned above.

9.4.2 **Oral solids**

Oral solid dosage forms were reported by all participant hospitals and included capsules (n=7), oral powders (n=6) and powders for oral liquids

(n=1). In total, 8 hospitals shared quantitative datasets, whereas 1 hospital disclosed only qualitative data with regards to the capsules dispensed, which was processed and analysed accordingly (Section 2.4).

The quantities of oral solids were provided as the number of individual units and/or the number of packs dispensed, which are shown separately below (Figure 9.4). A total of 2 hospitals provided the number of units (only) whereas 6 hospitals provided the number of packs; pack sizes were commonly reported as an interval (e.g. 30-50 units of capsules) and, therefore, the corresponding number of units could not be accurately estimated. In total, 40,838 units and 1,717 packs of oral solids were reported.

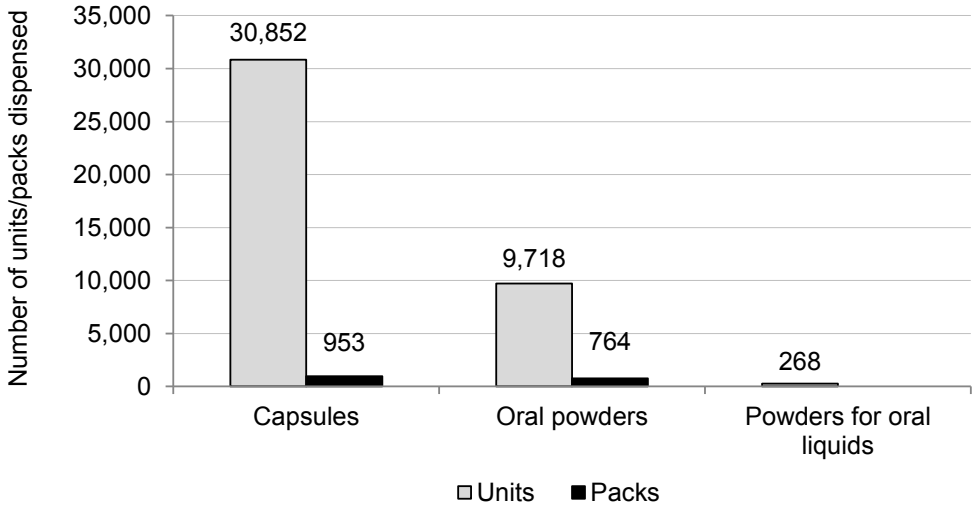


Figure 9.4 Oral solid dosage forms dispensed by number of units/packs.

The top 10 active substances dispensed as oral solids by number of packs and by number of units are listed in Figures 9.5 and 9.6, respectively. A total of 3 active substances were common to both rankings, namely: sodium bicarbonate, furosemide and ranitidine. Sodium bicarbonate was the most frequently dispensed active substance in both rankings and represented 33% and 32%, respectively, of all active substances dispensed as oral solids. Sodium bicarbonate is an alkalinising agent commonly indicated in the correction of metabolic acidosis, management of hyperkalaemia, alkalinisation of the urine and as an antacid. The treatment of acidotic states depends on the patient's acid-base balance and electrolyte status and, therefore, it requires customised doses of bicarbonate (*Martindale 35*, 2007).

Sodium bicarbonate was dispensed as capsules by 7 hospitals (500-2,000 mg, 5 strengths); one hospital reported capsules of 500 g but it was likely a mistake since the usual doses for the alkalinisation of the urine, for instance, correspond to a maximum of 10 g per day (in divided doses) and such a large amount of powder would not fit in an oral gelatin capsule (for human use).

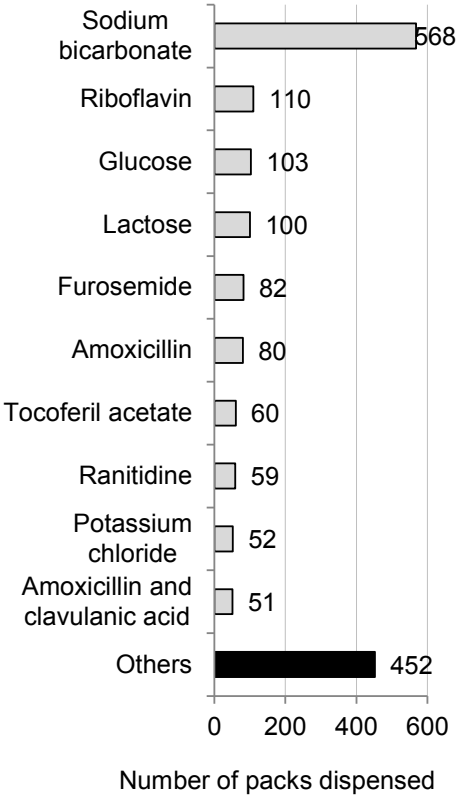


Figure 9.5 Top 10 active substances dispensed as oral solids by number of packs.

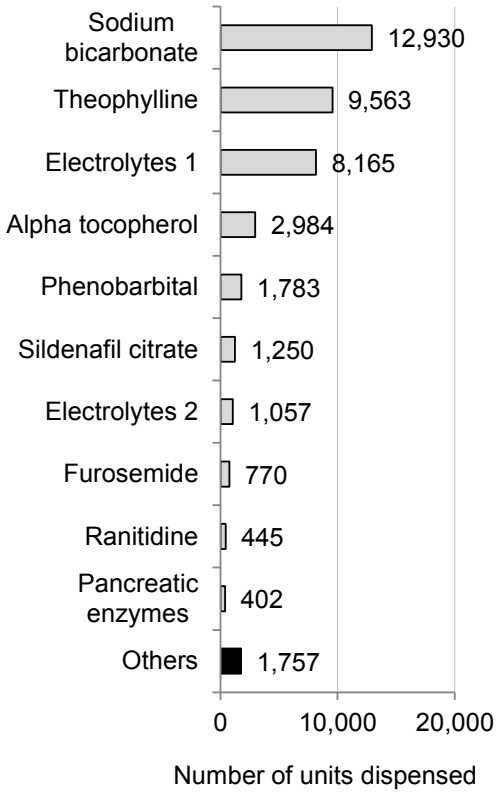


Figure 9.6 Top 10 *active substances* dispensed as oral solids by number of units.

Electrolytes 1 (Figure 9.6) stands for the combination of potassium chloride, sodium bicarbonate and sodium chloride, which corresponded to the majority (84%) of all oral powders dispensed (by number of units). This combination was named “laxative salts” and was reported by 2 hospitals. Electrolytes 2 (Figure 9.6) represents the same combination of potassium chloride, sodium bicarbonate and sodium chloride, with the addition of sodium sulfate and macrogols. This combination was reported both as oral powders and powders for oral liquids, by a total of 2 hospitals. It was named “laxative salts” and also “Golytely”, which corresponds to a proprietary medicine for bowel

evacuation constituted by macrogols and electrolytes (*Martindale 35*, 2007). Golytely is supplied in powdered form for oral administration as a solution, following reconstitution (Braintree Laboratories, 2001) and its composition is equivalent to the compounded medicines reported (Appendix 2). Therefore, the oral powders reported as Golytely were likely powders for oral liquids.

Capsules were the most frequently dispensed dosage form, both by number of units (75.5%) and by number of packs (55.5%) (Figure 9.4), and were reported by 78% of hospitals, for a total of 34 different active substances. The top 5 active substances (and respective strengths) were: sodium bicarbonate (800-2,000 mg), lactose, glucose, potassium chloride (3,000 mg) and caffeine (4-100 mg) (by number of packs); sodium bicarbonate (500 mg), theophylline (3-10 mg), alpha tocopherol (5 mg and 10 mg), phenobarbital (3-10 mg) and sildenafil citrate (0.3-4 mg) (by number of units). These active substances were all included in the top 10 listed in Figures 9.5 and 9.6, with the exception of caffeine.

Oral powders represented 23.8% and 44.5% of all oral solids dispensed by number of units and by number of packs, respectively. Oral powders were reported by 67% of hospitals, in a total of 29 different active substances. The top 5 active substances (by number of packs) and respective strengths were: riboflavin (25-200 mg), sodium bicarbonate (1,000 mg), furosemide (3-5 mg), amoxicillin (25-200 mg) and tocoferil acetate (5-200 mg), which were all included in the overall top 10 active substances dispensed as oral solids (Figure 9.5).

Powders for oral liquids represented only 0.7% of all oral solids (by number of units) (Figure 9.4) and were reported by only 1 hospital. However, as identified above, it is likely that the oral powders reported as Golytely, in fact, corresponded to powders for oral liquids.

The top 5 therapeutic groups, ranked by number of packs and by number of units of the corresponding oral solids, included the following 3 groups in common: electrolytes; nutritional agents and vitamins; and cardiovascular drugs. These 3 groups represented 67% and 63% of all oral solids dispensed by number of packs and by number of units, respectively.

9.4.3 **Oral liquids**

Oral liquid dosage forms were reported by 89% of the participant hospitals and included solutions (n=7), suspensions (n=3) and syrups (n=1). The majority of oral liquids were reported as solutions (79%) (Figure 9.7) but it is likely that the classification of some oral liquids was not accurate and, therefore, part of the solutions might have corresponded to suspensions or syrups (and vice-versa) (Section 2.1.3). Altogether, solutions and suspensions represented 99% of all oral liquids dispensed. The volumes reported ranged from 20 mL to 3,000 mL and, therefore, it was assumed that all 3,279 units of oral liquids dispensed were multidose.

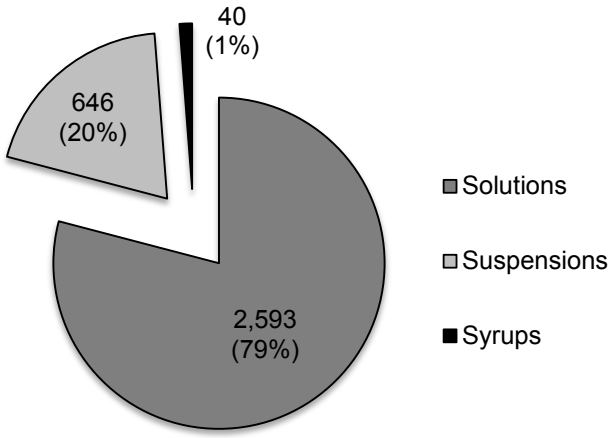


Figure 9.7 Oral liquid dosage forms dispensed by number of units.

A total of 32 different active substances were dispensed as oral liquids and the top 10 active substances are shown in Figure 9.8.

Golytely (Appendix 2) was one of the most frequently dispensed oral liquids (Figure 9.8) and was reported as a solution (1,000 mL) by 2 hospitals. Chloral hydrate (40 mg/mL and 50 mg/mL) and midazolam (1.5-2 mg/mL, 4 strengths), both “anxiolytic, sedatives, hypnotics and antipsychotics”, were reported by 78% of hospitals and represented 43% of all oral liquids (Figure 9.8). Phenobarbital was the only active substance common to the top 10 dispensed as oral solids (Figure 9.6), which suggests that active substances are preferably dispensed either as solid or liquid dosage forms.

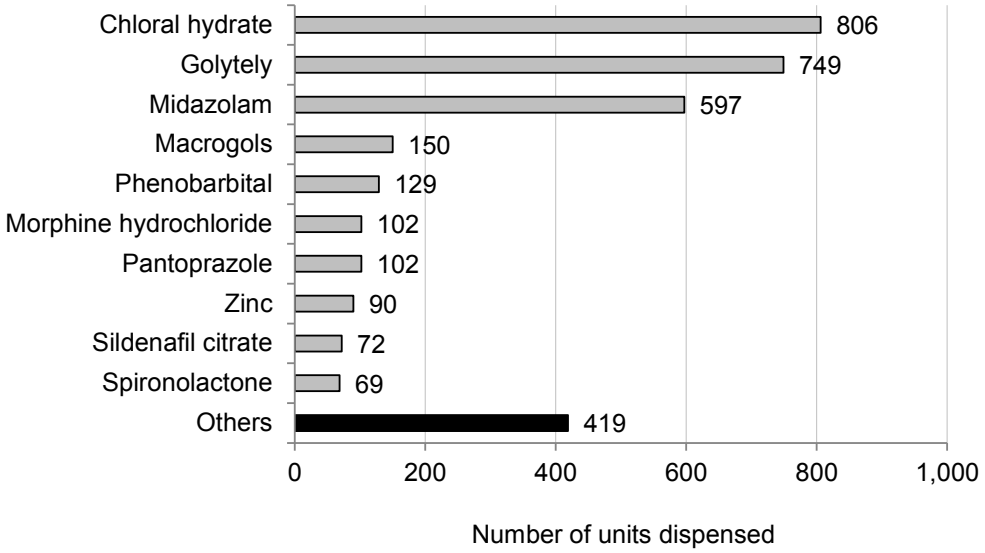


Figure 9.8 Top 10 *active substances* dispensed as oral liquids, ranked by number of units.

Syrups corresponded to just 1% of all oral liquids (Figure 9.7) and were reported by only 1 hospital. The only 2 active substances (and respective volumes) dispensed as syrups were: levothyroxine sodium (40 mL) and valganciclovir HCl (82 mL).

The top 3 therapeutic groups (oral liquids only) were: anxiolytic, sedatives, hypnotics and antipsychotics (chloral hydrate, midazolam and nitrazepam), which represented 43% of all oral liquids; followed by the combined electrolytes and gastrointestinal drugs (Golytely) and cardiovascular drugs (7 active substances).

The multidose oral liquids may be quantitatively compared to the oral solids dispensed (in packs). Estimating that capsules were dispensed in packs of 50 units (Section 2.1.3), the 30,852 individual units of capsules corresponded approximately to 617 packs of capsules (of 50 units each). In addition, considering that oral powders were dispensed in packs of 13 units (Section 2.1.3), the 9,718 individual units of oral powders corresponded approximately to 748 packs of oral powders (of 13 units each). As a result, a total of approximately 3,082 packs of oral solids were dispensed in Slovenia. Therefore, when the 3,279 units of multidose oral liquids are compared to the estimation of 3,082 packs of oral solids, it is concluded that oral liquids and oral solids were dispensed in approximately equal quantities. One hospital commented that they were substituting capsules for solutions/suspensions

and that is why they were currently preparing more oral liquids than oral solids. If other hospitals adopt this practice, oral liquids will become the most frequently dispensed dosage form in Slovenia.

9.4.4 **Oromucosal preparations**

In Slovenia, oromucosal preparations were not reported by any participant hospital.

9.5 **Summary**

- Compounded medicines in Slovenia may be categorised into magistral preparations and galenic preparations. Batch preparation (of galenic preparations) is only allowed in pharmacies with a certified (galenic) laboratory.
- *Formularium Slovenicum* is the Slovenian national supplement to the PhEur, which enables the implementation of the PhEur in Slovenia, taking into consideration national requirements, and includes monographs for compounded medicines.
- All 29 hospitals in Slovenia were included in the research and a response rate of 59% was obtained. A total of 68 different active substances (including 3 NTI drugs) were reported corresponding to 19 different therapeutic groups. The top 3 therapeutic groups were antibacterials (n=11), cardiovascular drugs (n=10) and electrolytes (n=7).
- Oral solid dosage forms were reported by all participant hospitals and included capsules, oral powders and powders for oral liquids. Capsules were dispensed in a total sum of 30,852 units (75.5% of all oral solids) and 953 packs (55.5%). The top 5 active substances were: sodium bicarbonate, lactose, glucose, potassium chloride and caffeine (by number of packs); sodium bicarbonate, theophylline, alpha tocopherol, phenobarbital and sildenafil citrate (by number of units). Oral powders were dispensed in a total sum of 9,718 units (23.8% of all oral solids) and 764 packs (44.5%). The top active substances dispensed were: riboflavin, sodium bicarbonate, furosemide, amoxicillin and tocoferil acetate (by number of packs); potassium chloride, sodium bicarbonate and sodium chloride (in combination) (by number of units). Powders for oral liquids were dispensed in a total of 268 units (0.7% of all oral solids).
- Oral liquid dosage forms were reported by 89% of all participant hospitals and included solutions, suspensions and syrups, dispensed in a total sum of 3,279 units. The top active substances dispensed were: chloral hydrate, Golytely (potassium chloride, sodium bicarbonate, sodium chloride, sodium sulfate and macrogols) and midazolam. Solutions and suspensions represented 99% of all oral liquids whereas syrups represented 1%. The only active substances dispensed as syrups were levothyroxine sodium and valganciclovir HCl.
- Oral liquids were dispensed in comparable quantities to oral solids.

10. **Compounding in Finland**

Finland is a Northern country, bordered by the Baltic Sea in the South and Sweden in the West, that joined the EU in 1995. Its official languages are Finnish and Swedish (*Europa*, 2009). Although the 6th largest European country, with a surface area of 304,500 Km^2, it is the 19th most populated (Figure 2.2), with a population of 5.3 million in 2007 (*Europa*, 2008).

In 2007, there were 341 hospitals in Finland (ratio of 6.45 hospitals per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3), including 21 central hospitals - 5 of which university hospitals (Pharmine, 2010). In Finland, there is regional organisation of hospitals into districts, with each district having a central hospital supervised by a university hospital. University hospitals are the largest hospitals, and central hospitals are the most central, large hospitals in a particular district. Specialised medical care is provided in the 5 university hospitals, which are associated with a faculty of medicine and are located in the largest cities: *Helsinki*, *Tampere*, *Turku*, *Oulu* and *Kuopio* (Ovaskainen *et al.*, 2005; Atkinson and Hirvonen, 2010).

In 2007, there were a total of 36,095 hospital beds (ratio of 682.49 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3), which was slightly lower than in 2006 (ratio of 696.11 hospital beds per 100,000 population) (Pharmine, 2010). The number of hospital beds has decreased faster in Finland (and in the Northern countries) than in the rest of the EU (Koskinen *et al.*, 2006). Nevertheless, the ratio of hospital beds in Finland is still fairly high when considering all the countries included in the research (Appendix 3).

In 2007, there were 5,655 pharmacists in Finland (ratio of 107.11 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2011) (Appendix 4) but there were only 545 hospital pharmacists (470 Bachelors and 75 Masters of Science) (Atkinson and Hirvonen, 2010).

The preparation of compounded medicines occurs in community and hospital pharmacies throughout Finland. All community pharmacies are required to have a laboratory for pharmaceutical compounding and a total of 0.5% of all

medicines dispensed in the community setting are compounded medicines (Bell *et al.*, 2007).

In Finnish hospital pharmacies, pharmaceutical compounding is one of the major activities (Ovaskainen *et al.*, 2005) and is an essential function of hospital pharmacists (Koskinen and Kela, 2009). Compounded medicines are prepared and dispensed only when an alternative proprietary medicine is not available. These medicines are normally prepared on an individual basis and are usually distributed within the hospital in which the preparation takes place (Torniainen, 2007). A large number of compounded medicines are prepared in Finland, particularly oral powders for paediatric patients (Eronen *et al.*, 2005; Koskinen and Kela, 2009); intensive care and dermatology are two other areas that frequently require compounded medicines (Torniainen, 2007). Both sterile and non-sterile compounded medicines are prepared in Finnish hospitals, but the university hospitals supply the largest variety of medicines, including a wide range of sterile products (Eronen *et al.*, 2005; Puumalainen, 2009). Larger hospitals have validated procedures in place and several hospital pharmacies have invested in facilities to meet GMP standards (Eronen *et al.*, 2005; Koskinen and Kela, 2009). According to the EAHP survey, SOP are used in more than 80% of Finnish hospital pharmacies (EAHP, 2005). In Finland, hospitals pharmacists are aware of the importance of preparing compounded medicines in accordance with standards of quality and, in February 2007, 50 hospital pharmacists (approximately) attended a course in *Helsinki* on the topic “Preparation of medicinal products in hospital pharmacies - GMP in focus” (Torniainen, 2007).

Inka Puumalainen (2009), president of the Finnish Hospital Pharmacists’ Association (Section 10.2), when asked about the future role of hospital pharmacy in the area of pharmaceutical compounding answered that “… medicines will be more patient-tailored and administration will vary. Hospital pharmacists will require specialised skills to produce these medicines.”

10.1 **Legislation**

The National Agency for Medicines (NAM) is the entity responsible for monitoring the overall medicinal field in Finland, including the regulation of pharmacies and pharmaceutical products (Bell *et al.*, 2007; NAM, no date). The NAM, working on behalf of the Ministry of Social Affairs and Health, supervises the activities of hospital pharmacists and has the authority to suspend permission for a pharmacy to operate, if activities do not comply with the laws and regulations in effect (Eronen *et al.*, 2005; Bell *et al.*, 2007).

In Finland, compounded medicines (*Ex tempore - Lääkevalmiste*) are defined as medicinal products prepared on request, or in accordance with a prescription, for the immediate use by patients (NAM, 2006a). Pharmacies' own medicinal (compounded) products (*Omat Lääkevalmisteet*) are also allowed in Finland, provided that the NAM is notified (Barbosa and Pinto, 2001; NAM, 2006a; 2006b).

In accordance with the Finnish Medicines Act (NAM, 2006b), "preparation other than industrial manufacture" may occur in community pharmacies (or in subsidiary pharmacies belonging to these) and also in hospital pharmacies. Pharmacies are allowed to dispense compounded medicines prepared in other pharmacies (contract manufacture), provided that the NAM is notified. A prerequisite for the preparation of compounded medicines is that "the personnel are sufficiently familiar with the preparation of medicinal products and that there are appropriate production facilities and equipment for such preparation" (NAM, 2006b). According to this legislation, the manufacture of medicinal products must comply with GMP. However, uncertainty exists regarding the interpretation of GMP in pharmaceutical compounding (Torniainen, 2007) and criteria may vary within Finnish hospital pharmacies.

10.2 **Professional organisations and information sources**

10.2.1 **Finnish professional organisations**

In Finland, a specific professional organisation for pharmaceutical compounding is not currently in existence. There are however several organisations dedicated to pharmacy and pharmacists, including:

- Finnish Pharmacists' Association: is a trade and professional body for individuals in the field of pharmacy (Farmasialiitto, 2012).
- Association of Finnish Pharmacies (AFP): is a professional organisation of proprietary pharmacists (AFP, 2008). AFP is the editor organisation of the Finnish national formulary (Section 10.2.2).
- Finnish Hospital Pharmacists' Association (Satefa): is both the trade union and professional association for hospital pharmacists; it was originally part of the Finnish Pharmacists' Association but it is now a separate entity (Leskinen, 2005).

10.2.2 **Finnish information sources**

- *Dispensatorium Fennicum*: is the Finnish national formulary, edited by the AFP (Section 10.2.1) (Suomen Apteekkariliitto, 2004), which corresponds to the official reference for pharmaceutical compounding in Finland. It was first published in 1971 and the 3rd edition (1993) includes 108 monographs for the compounded medicines suggested in an enquiry to Finnish pharmacies (Barbosa and Pinto, 2001).
- International informational sources, such as the IJPC and the "Trissel's stability of compounded formulations" (Section 14.2.2), are also commonly used in Finnish hospital pharmacies (Helin-Tanninen, 2010).

10.3 **Methods**

The research project was initiated in 2007, by consulting Finnish stakeholders in pharmacy and pharmaceutical compounding, but that data collection was not initiated until 2009 due to difficulties in identifying the purposive sample of hospitals.

Experts from academia, hospital pharmacy and the NAM - Anne Juppo (University of Helsinki, Faculty of Pharmacy); Hanna Tolonen (Hospital District of Helsinki and Uusimaa) and Kristine Salminen (NAM, Enforcement & Inspection) - contributed with their expertise and advice towards the development of the Finnish questionnaire (Section 10.3.1) and identification of the purposive sample of hospitals (Section 10.3.2). It was decided that no fieldwork would be undertaken in Finland (budgetary constraints) and, hence,

all research was undertaken by MC at distance, which contributed to the length of the project in this country.

10.3.1 **Country-specific questionnaire**

The research instrument developed to collect information about oral compounded medicines most frequently dispensed in Finnish hospital pharmacies was a self-completion questionnaire (main heading in Figure 10.1), which was based on the template established for Portugal (Section 3.3.1) and adapted to the practice of pharmaceutical compounding in Finland. This customised questionnaire comprised 1 table only and was developed in English, as recommended by the stakeholders (Section 10.3), who asserted that translating was unnecessary since the Finnish population is generally fluent in English. Data collection in Finland was undertaken in the year 2009 and, therefore, the questionnaire addressed information relating to 2008. Compounded medicines were defined as "extemporaneous formulations prepared by a pharmacy" because, according to the Finnish legislation, these correspond to *Ex tempore - Lääkevalmiste* and their preparation may occur in community pharmacies (or in subsidiary pharmacies belonging to these) and also in hospital pharmacies (Section 10.1). Although compounded medicines are mainly dispensed in the hospital where the preparation takes place (Torniainen, 2007), an extra column was added to the questionnaire, namely "Manufacturer", so that the compounded medicines prepared in other hospital/community pharmacies would be identified (Section 7.3.1).

10.3.2 **Purposive sample of hospitals**

A total of 8 hospitals were selected across Finland, including the 5 university hospitals and 3 central hospitals, from the following cities: Helsinki (capital), *Tampere*, *Turku*, *Kuopio*, *Oulu*, *Jyvaskyla*, *Kotka* and *Lahti* (Figure 10.2). University hospital pharmacies prepare the largest variety of compounded medicines (Puumalainen, 2009) and were identified by the stakeholders as the ones in which the largest quantities of compounded medicines were likely dispensed in Finland; for these reasons, all Finnish university hospitals were included in the research.

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

ORAL COMPOUNDED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

FINLAND

Please fill in the following information (up to 40):

Considering the ORAL COMPOUNDED MEDICINES most frequently dispensed by your Pharmacy in 2008

COMPOUNDED MEDICINES are defined for the purpose of this study as extemporaneous formulations prepared by a pharmacy

	Active Substance	Strength	Dosage Form	Pack Size	Manufacturer	Number of times dispensed in 2008
Examples	Captopril	1 mg / mL	Solution	50 - 250 mL	Tampere University Hospital	75
	Nitrofurantoin	5 mg / mL	Suspension	100 mL	Hospital X	67
	Sodium Bicarbonate	500 mg	Capsules	30 - 300 caps	Hospital Y	45
1						
2						
3						

Figure 10.1 Country-specific questionnaire (Finland).

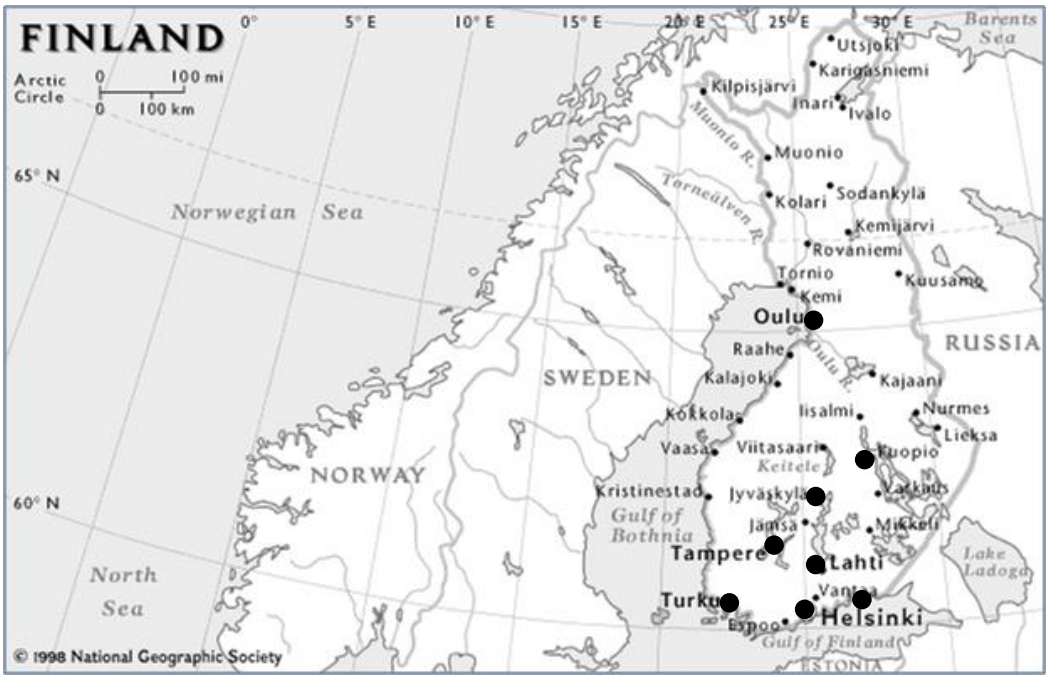


Figure 10.2 Map of Finland adapted from National Geographic Society (1998g); indicating the location of the purposive sample of hospitals (●).

It was concluded that it would be important to include non-university hospitals in the purposive sample so that data did not reflect the compounding practices of university hospitals only. As a result, the purposive sample included 3 additional central hospitals, which were also identified by the stakeholders as the ones in which the largest quantities of compounded medicines were likely dispensed in Finland.

10.3.3 **Data collection**

The purposive sample was provided by the Finnish stakeholders (Section 10.3) including the name and email address of the key contact person in each hospital pharmacy. All 8 hospital pharmacies were initially contacted by MC by email with the request to share data regarding the oral compounded medicines most frequently dispensed in 2008 (or the latest available year). The customised questionnaire was attached to a brief introductory email, together with an electronic copy of the IJPC article (Carvalho *et al.*, 2008) and the EuPFI presentation (Carvalho, 2009). Non-respondents were sent periodical email reminders, up to a maximum of 3 emails per hospital pharmacy (excluding the IJPC article and the EuPFI presentation to avoid an overload of information), after which non-respondents were contacted by

telephone. Persistent non-respondents, after being contacted by telephone and accepted to participate, were sent up to 4 additional email reminders. Data were collected by the hospital pharmacy's staff and none of the Finnish hospitals were visited by MC.

10.4 **Results and discussion**

In total, 7 hospitals responded to the request for collaboration (88% response rate) and 1 hospital was non-respondent. All respondents contributed data regarding the oral compounded medicines most frequently dispensed in 2008 (0 non-participant hospitals) (Figure 10.3).

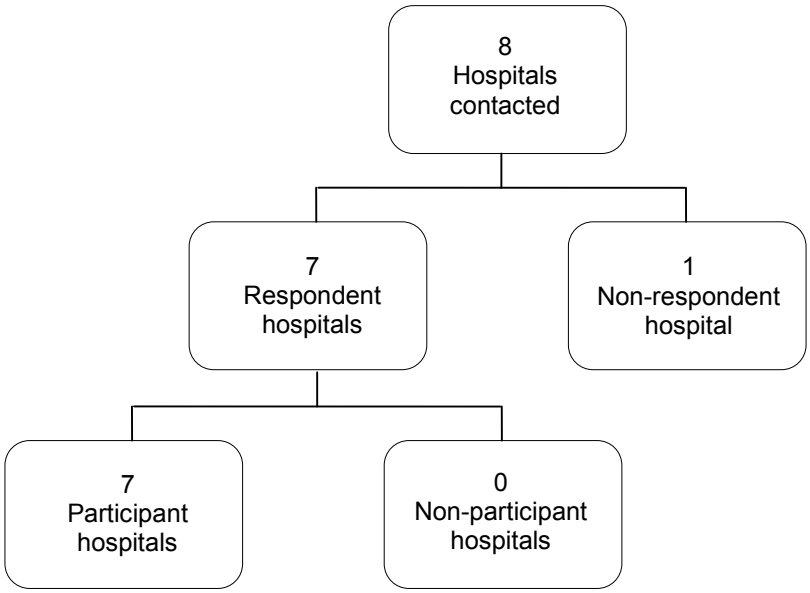


Figure 10.3 Purposive sample distributed by respondent and participant hospitals.

A total of 6 hospitals provided complete datasets, whereas 1 hospital provided quantitative information for oral liquids but only semi-quantitative information for oral solids (Section 10.4.2). All Finnish hospitals sent the required data (in electronic formats) by email and the majority (57%) following the first email; only 4 hospitals were sent email reminders and only 1 hospital was contacted by telephone. The fact that all contacted pharmacists were fluent in English and were willing to contribute data, was deemed to be one of the major reasons for the high response rate obtained. All Finnish hospital pharmacies are computerised and information technology plays an important role in pharmaceutical compounding (Eronen *et al.*, 2005). Therefore, it is likely that all participant hospitals had electronic records of the

compounded medicines dispensed, which certainly contributed to the ease of retrieving the required information. In total, 5 (71%) hospitals supplied data in the questionnaire provided and 2 (29%) hospitals in their own formats. Although the Finnish questionnaire included the column “Manufacturer” (Figure 10.1), so that the compounded medicines prepared in other hospital/community pharmacies would be identified, none of the participant hospitals indicated that they had dispensed medicines prepared by others (contract manufacturing, Section 10.1). It was thus considered that all compounded medicines dispensed in the participant hospitals were prepared in the respective pharmacies. All participant hospitals provided datasets including oral compounded medicines only (non-orals were excluded). After data processing, the Finnish database included a total of 186 data entries, corresponding to the datasets of 7 hospitals.

10.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral compounded medicines in Finland is shown in Table 10.1. All active substances reported were included in *Martindale 35* (2007) and these were grouped according to the respective therapeutic classification, giving a total of 85 different active substances and 25 therapeutic groups. Cardiovascular drugs was the group with the greatest number of different active substances (n=19), followed by nutritional agents and vitamins (n=10) and antiepileptics (n=8).

Although these active substances were all reported as oral compounded medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: dermatological drugs and sunscreens (Appendix 11); disinfectants and preservatives (Appendix 12); stabilising and suspending agents (Appendix 14); and supplementary drugs and other substances (Appendix 15). The active substances included in these groups were described in the respective appendixes.

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 4 NTI drugs were dispensed as oral compounded medicines (underlined in Table 10.1).

Table 10.1 Active substances most frequently dispensed as oral compounded medicines in Finland (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aspirin, ethylmorphine HCl, indometacin, methadone HCl, morphine, morphine HCl

Antibacterials
Isoniazid

Antidiabetics
Glibenclamide

Antiepileptics
Clobazam, clonazepam, oxcarbazepine, phenobarbital, phenytoin, sodium valproate, topiramate, vigabatrin

Antifungals
Miconazole

Antihistamines
Hydroxyzine HCl

Antineoplastics
Flutamide, mercaptopurine, methotrexate, tioguanine

Antiprotozoals
Metronidazole

Anxiolytic, sedatives, hypnotics and antipsychotics
Midazolam, nitrazepam

Cardiovascular drugs
Amiodarone, captopril, carvedilol, defibrotide, diazoxide, dipyridamole, enalapril, flecainide acetate, furosemide, hydrochlorothiazide, mannitol, metoprolol, nifedipine, nimodipine, phenoxybenzamine HCl, propranolol HCl, sotalol HCl, spironolactone, warfarin sodium

Chelators, antidotes and antagonists
Sodium polystyrene sulfonate

Contrast media
Barium sulfate

Corticosteroids
Dexamethasone, hydrocortisone, prednisolone

Dermatological drugs and sunscreens
Urea

Disinfectants and preservatives
Sodium benzoate, sodium hypochlorite

Electrolytes
Dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, sodium citrate

GI drugs
Aluminium hydroxide, calcium carbonate, magnesium hydroxide, simeticone

Hypothalamic and pituitary hormones
Desmopressin

Local anaesthetics
Cocaine, lidocaine

Muscle relaxants
Baclofen

Nutritional agents and vitamins
Ascorbic acid, ergocalciferol, glucose, lactose, phytomenadione, pyridoxine HCl, selenium, sodium fluoride, tocopherol, vitamin A

Stabilising and suspending agents
Ceratonia, methylcellulose

Supplementary drugs and other substances
Phosphoric acid, sodium phenylbutyrate, thalidomide, ursodeoxycholic acid

Thyroid and antithyroid drugs
Carbimazole, iodine, potassium iodide, potassium perchlorate

Urological drugs
Sildenafil citrate

The active substances dispensed by most hospitals were: hydrocortisone and spironolactone (all participant hospitals, n=7); hydrochlorothiazide, morphine and propranolol HCl (n=6).

Almost all compounded medicines included just 1 active substance (single-drug) in their composition. In fact, only 6 compounded medicines included more than 1 active substance (multi-drug), in combinations of up to 4 different active substances, as follows:

- 2 active substances (n=4): ergocalciferol and vitamin A; iodine and potassium iodide (Lugol's Solution, Appendix 16); mannitol and ceratonia (Appendix 14); miconazole and lidocaine.
- 3 active substances (n=1): dibasic sodium phosphate, monobasic sodium phosphate and sodium fluoride.
- 4 active substances (n=1): lidocaine, hydroxyzine HCl, aluminium hydroxide and magnesium hydroxide.

Multi-drugs were dispensed as oral liquids and oromucosal preparations (all oral solids included 1 active substance only), by a total of 4 participant hospitals.

In total, 13 proprietary medicines were reported by 2 hospitals, both as oral solids and oromucosal preparations, as follows:

- Oral solids (n=2,649 individual units): Adursal (ursodeoxycholic acid); Cordarone (amiodarone HCl); Frisium (clobazam); Insomin (nitrazepam); Kalcipos (calcium carbonate); Nifangin (nifedipine); Orfiril (sodium valproate); Resonium (sodium polystyrene sulfonate); Rivatril (clonazepam); and Topimax (topiramate).
- Oromucosal preparations (n=9 multidose units): Daktarin (miconazole); Jekovit (ergocalciferol); and Vitol (vitamin A and ergocalciferol).

10.4.2 **Oral solids**

Oral solid dosage forms were reported by all participant hospitals and included oral powders (6 hospitals) and capsules (4 hospitals). In total, 6 hospitals shared quantitative datasets, whereas 1 hospital disclosed only semi-quantitative data with regards to the oral powders dispensed, which was processed and analysed accordingly (Section 2.4).

The quantities of oral solids were provided as the number of individual units and/or the number of packs dispensed, which are shown separately below (Figure 10.4). A total of 3 hospitals provided both figures whereas 3 hospitals provided the number of packs and 1 hospital provided the number of units only. The number of packs of oral solids dispensed varied from 25 to 1,423 packs, whereas the number of units varied from 2,500 to 6,700 units. In total, 2,363 packs and 18,605 units of oral solids were reported.

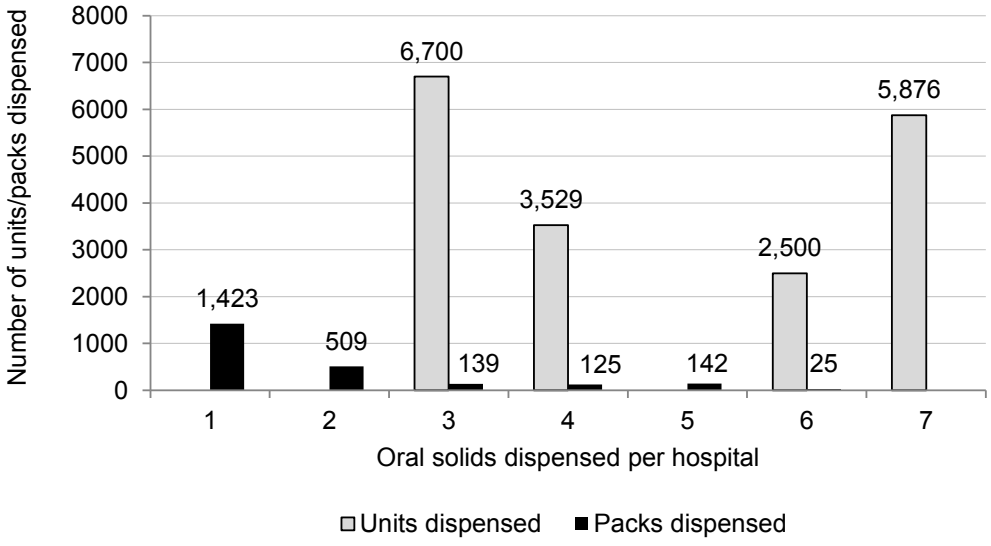


Figure 10.4 Oral solids dispensed by number of units and number of packs, per hospital.

The top 10 active substances dispensed as oral solids by number of units and by number of packs (and ranked by number of units) are listed in Figure 10.5. A total of 16 active substances are shown; hydrocortisone, propranolol HCl, potassium perchlorate, hydrochlorothiazide, ursodeoxycholic acid and spironolactone are part of both top 10 active substances by number of units and by number of packs.

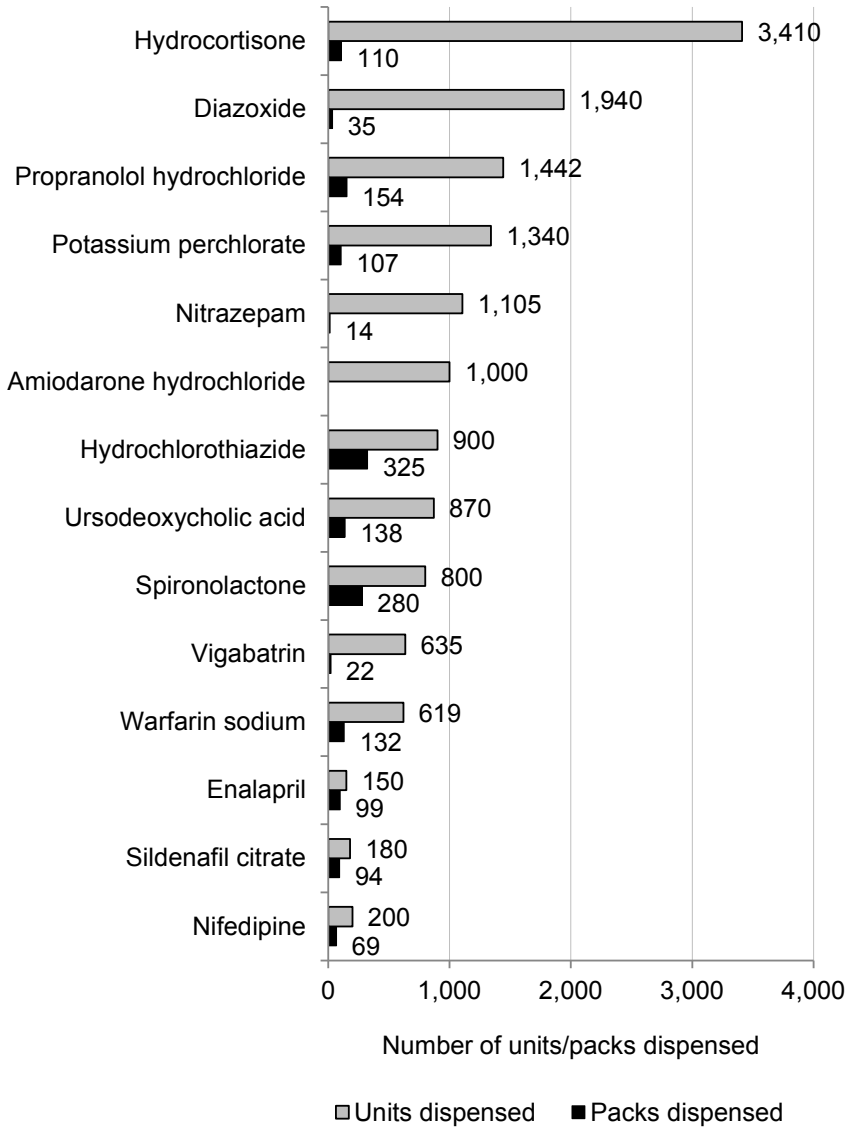


Figure 10.5 Top 10 active substances dispensed, by number of units and number of packs of oral solids (ranked by number of units).

The top therapeutic groups, ranked by number of units of the corresponding oral solids, are listed in Figure 10.6. The most frequent therapeutic group was cardiovascular drugs, which comprised 12 different active substances that were dispensed in a total of 7,751 units and 1,201 packs of oral solids. Cardiovascular drugs represented 42% of the individual units dispensed and 65% of the packs of oral solids dispensed. The active substances most frequently dispensed as cardiovascular drugs are displayed in Figure 10.7.

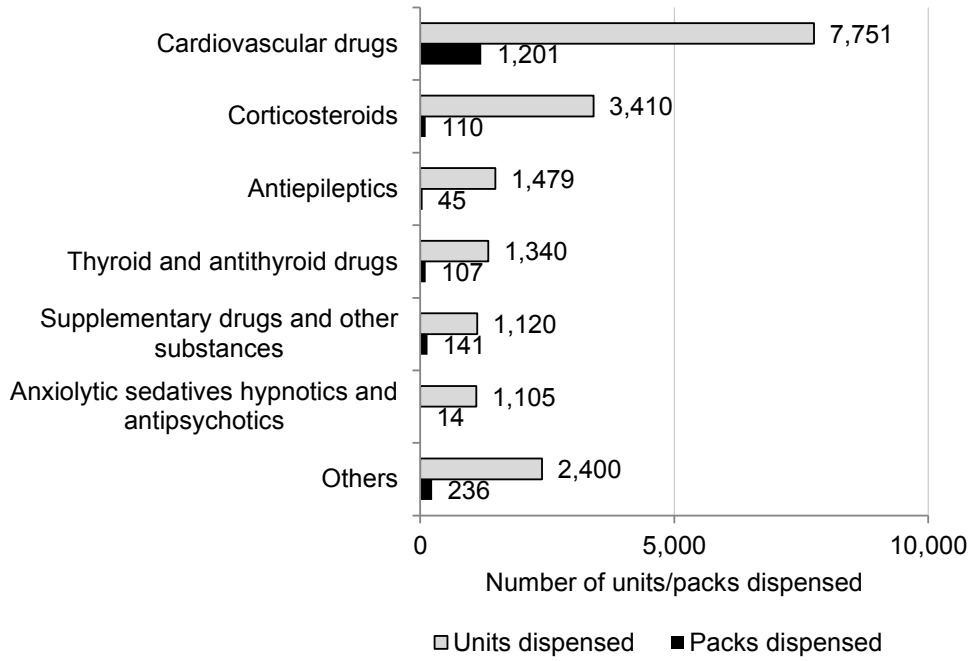


Figure 10.6 Dispensed oral solids classified by therapeutic groups, by number of units/packs.

The next most frequent therapeutic groups were corticosteroids and antiepileptics (Figure 10.6). In total, oral solids corresponding to 20 therapeutic groups (out of the 25 outlined in Table 10.1) were dispensed in Finland. The last category “others” included 14 therapeutic groups, as follows: analgesics, anti-inflammatory drugs and antipyretics; antibacterials; antihistamines; antineoplastics; antiprotozoals; chelators, antidotes and antagonists; dermatological drugs and sunscreens; disinfectants and preservatives; GI drugs; hypothalamic and pituitary hormones; local anaesthetics; muscle relaxants; nutritional agents and vitamins; and urological drugs.

The majority of participant hospitals did not specify the strength of the oral solids dispensed. In fact, only 1 hospital provided detailed information, whereas all other hospitals provided either an interval of strengths (i.e. hydrochlorothiazide 1-10 mg) or no information at all.

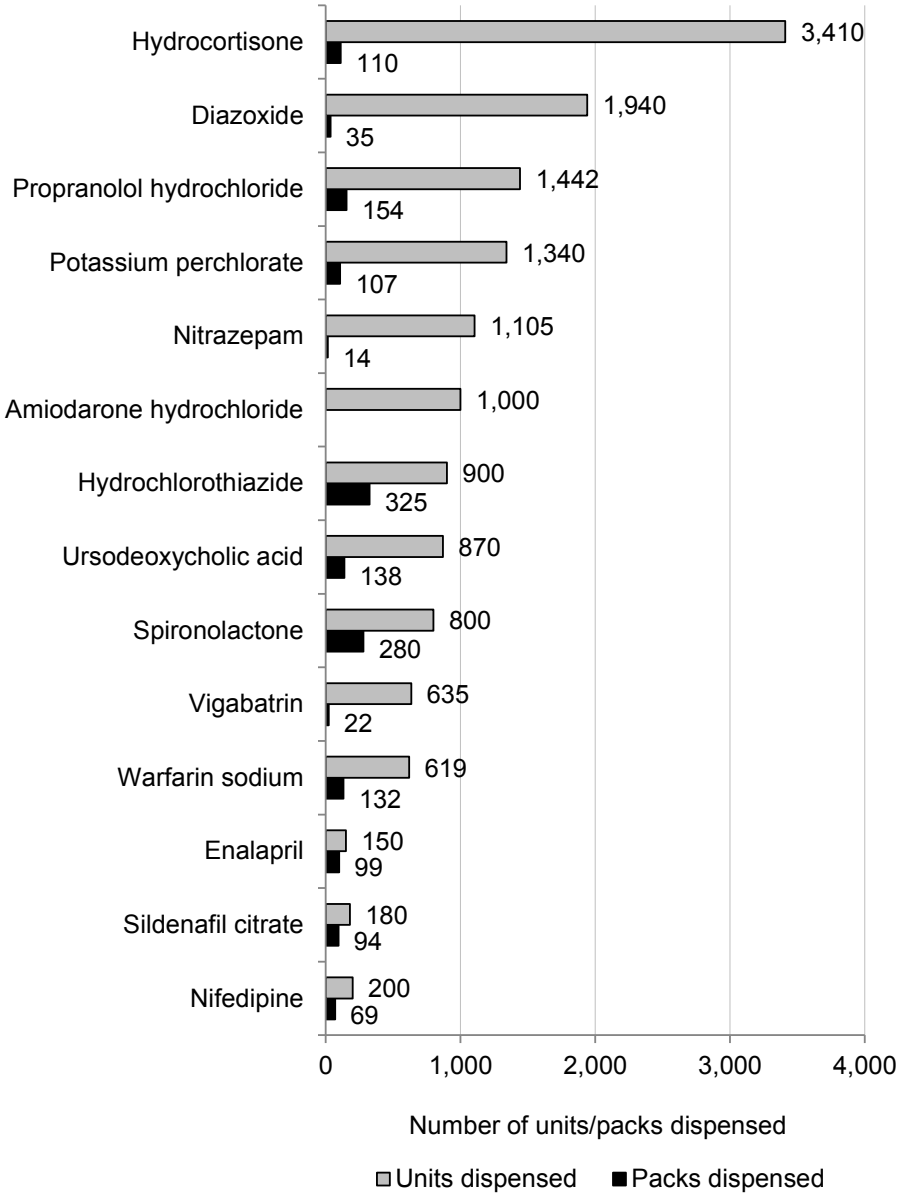


Figure 10.7 Top 10 active substances dispensed as cardiovascular drugs (oral solids), by number of units/packs.

In 2005, the number of patients discharged from all hospitals (including through death) in Finland was highest for diseases of the circulatory system (3,121 patients / 100,000 population) (Figure 10.8) (WHO Regional Office for Europe, 2008). It was to be expected then that cardiovascular drugs were the most frequent oral solids dispensed by the participant hospitals (Figure 10.6).

Oral powders were dispensed in larger quantities than capsules, both by number of units and by number of packs dispensed (Figure 10.9). A total of

2,198 (93%) packs and 10,305 (55%) units of oral powders were reported, which is in accordance with Koskinen and Kela (2009) and Eronen *et al.* (2005), who stated that a large number of compounded medicines are prepared in Finland, particularly oral powders for paediatrics (Section 10).

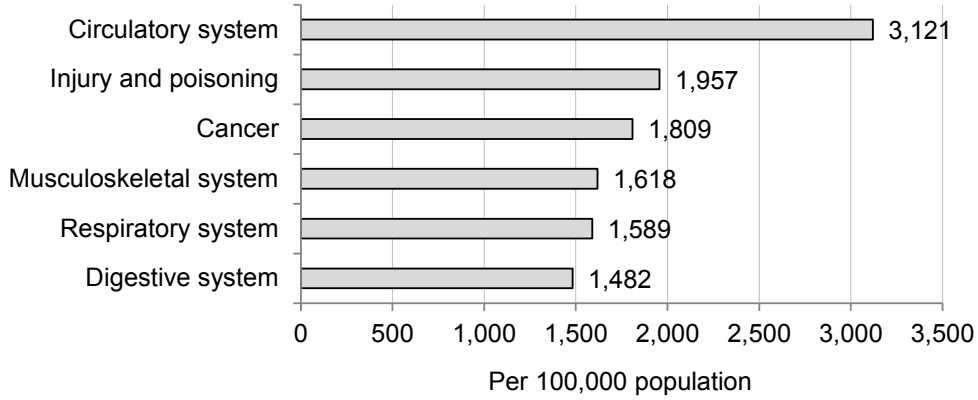


Figure 10.8 Number of patients per 100,000 population discharged from all hospitals (including through death) in Finland during 2005 (latest available year), categorised by principal diagnosis (adapted from WHO Regional Office for Europe, 2008).

Oral powders were reported by 6 (86%) of hospitals (only 1 participant hospital did not report oral powders) and, considering the number of units dispensed, the top 5 active substances were: hydrocortisone, diazoxide, potassium perchlorate, amiodarone HCl and ursodeoxycholic acid; which were all included in the top 10 oral solids, dispensed by number of units and packs, displayed in Figure 10.5. Only 1 participant hospital classified the oral powders dispensed as sachets.

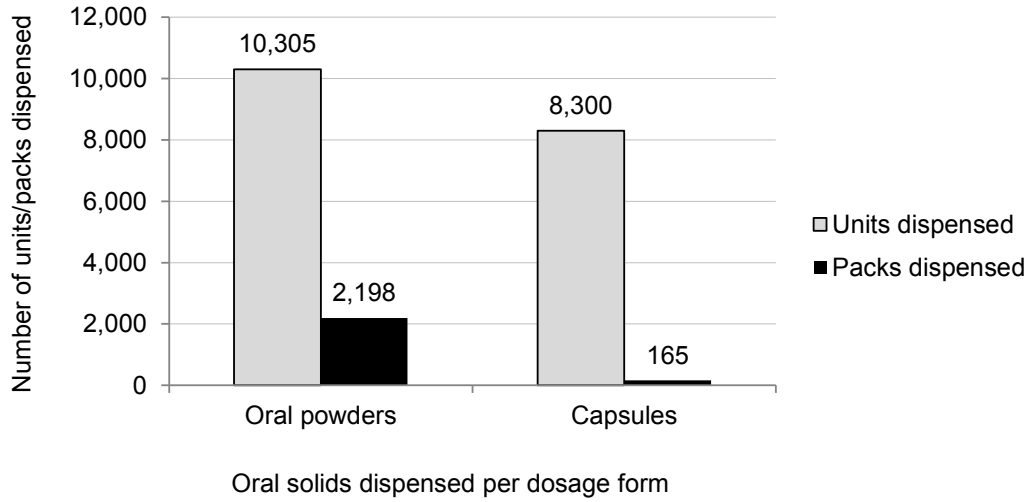


Figure 10.9 Oral solids dispensed by number of units/packs, per dosage form.

Considering the capsules, a total of 8,300 (45%) units and 165 (7%) packs were reported. The top 5 active substances were also included in the top 10 oral solids, dispensed by number of units and packs, displayed in Figure 10.5, and corresponded to the following substances: hydrocortisone, ursodeoxycholic acid, propranolol HCl, nitrazepam and warfarin sodium.

10.4.3 **Oral liquids**

Oral liquid dosage forms were reported by all participant hospitals and included solutions and suspensions. The majority of oral liquids were reported as solutions (91.5%) but it is likely that the classification of some oral liquids was not accurate (Section 2.1.3). The volumes reported ranged from 0.4 mL to 1,000 mL, which corresponded to both multidose and unidose oral liquids. Only 1 hospital distinguished some oral liquids dispensed as (unidose) oral syringes but it was assumed that a total of 2 hospitals dispensed unidose oral liquids in Finland (Section 2.1.3). Only 5 active substances were dispensed as unidose (n=8,130 units), in limited strengths and in volumes of 0.4 mL to 32 mL, as displayed in Table 10.2.

Table 10.2 Compounded medicines dispensed as unidose oral liquids.

Active substances	Strengths	Volumes	Number of units
Methadone HCl	5 mg/mL	8-32 mL	4,304
Glucose	300 mg/mL	2 mL	2,300
Hydrochlorothiazide	1-3 mg/mL	0.4-2 mL	790
Spironolactone	2-10 mg/mL	0.5-2 mL	470
Nimodipine	7.5 mg/mL	8 mL	266
Total			**8,130**

Multidose oral liquids were reported by all participant hospitals, in a total of 16,948 units, from 171 to 8,336 units per hospital, as displayed in Figure 10.10. Multidose oral liquids were dispensed in larger quantities than unidose oral liquids. Hospitals 1 to 4 are university hospitals, whereas hospitals 5 to 7 are central hospitals. All unidose oral liquids and 90% of the multidose oral liquids were dispensed in university hospitals, whereas no unidose and only 10% of the multidose liquids were dispensed in central hospitals. According

to Puumalainen (2009), university hospitals dispense the largest variety of compounded medicines in Finland. It is concluded that compounding practices vary within university and central hospitals, as previously anticipated (Section 10.3.2).

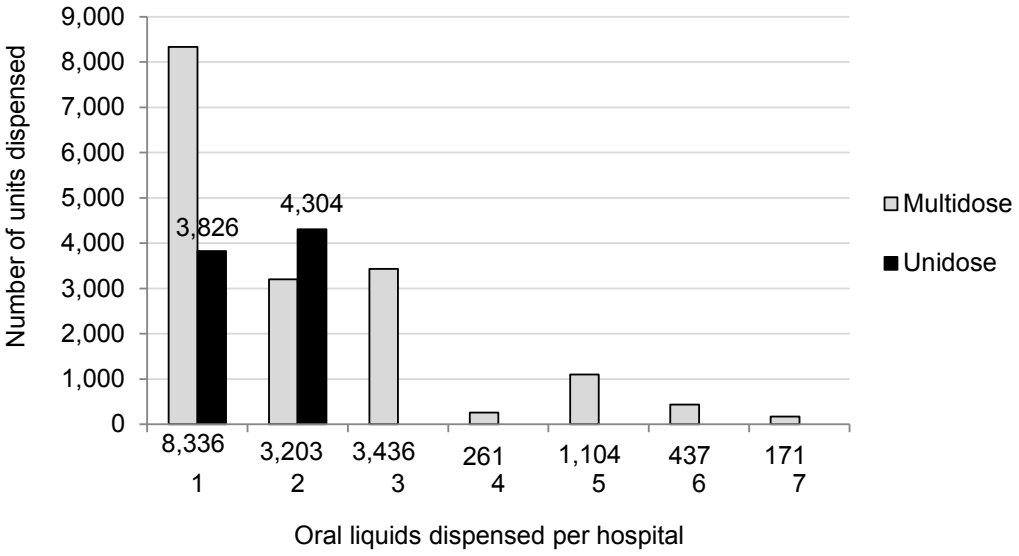


Figure 10.10 Number of units of oral liquids (unidose and multidose) dispensed per hospital.

The compounded medicines most frequently dispensed as multidose oral liquids are displayed in Table 10.3. Methadone HCl and glucose are also active substances which are most frequently dispensed as unidose oral liquids (Table 10.2).

Table 10.3 Compounded medicines dispensed as multidose oral liquids.

Active substances	Strengths	Volumes	Number of units
Methadone HCl	5 and 10 mg/mL	20-500 mL	10,094
Sodium citrate	0.3 M	30-500 mL	2,587
Glucose	200-300 mg/mL	20-500 mL	1,666
Morphine HCl	0.4-10 mg/mL	20-300 mL	1,328
Others			1,273
Total			**16,948**

Methadone HCl was the active substance most frequently dispensed both as a unidose and multidose oral liquid. It was reported in the strengths of 5 mg/mL and 10 mg/mL, and in the volumes of 8 mL to 500 mL. Methadone

HCl is an opioid analgesic commonly used in the treatment of severe pain and in the management of opioid dependence. For pain relief, usual doses range from 5 mg to 10 mg every 6-8 hours; for opioid withdrawal, daily doses range from 10 mg to 60 mg but there are reports of patients receiving 120 mg (or even more) daily (*Martindale 35*, 2007), which is in accordance with the strengths reported by Finnish hospitals. In 2009, it was estimated that approximately 1800 patients were receiving opioid substitution treatment in Finland, of whom 720 (40%) were on methadone (EMCDDA, 2012).

Glucose was also frequently dispensed both as unidose and multidose oral liquids. It was reported in strengths of 200-300 mg/mL, and in volumes of 2 mL to 500 mL. Glucose is a monosaccharide commonly used in the treatment of carbohydrate and fluid depletion, and also in the treatment of hypoglycaemia; the doses vary in accordance with the individual patient needs (*Martindale 35*, 2007).

The top 5 therapeutic groups, ranked by number of units of the corresponding oral liquids, are listed in Figure 10.11. The most frequent therapeutic group was analgesics, anti-inflammatory drugs and antipyretics, which comprised the following active substances (in decreasing order): methadone HCl, morphine, morphine HCl and ethylmorphine HCl.

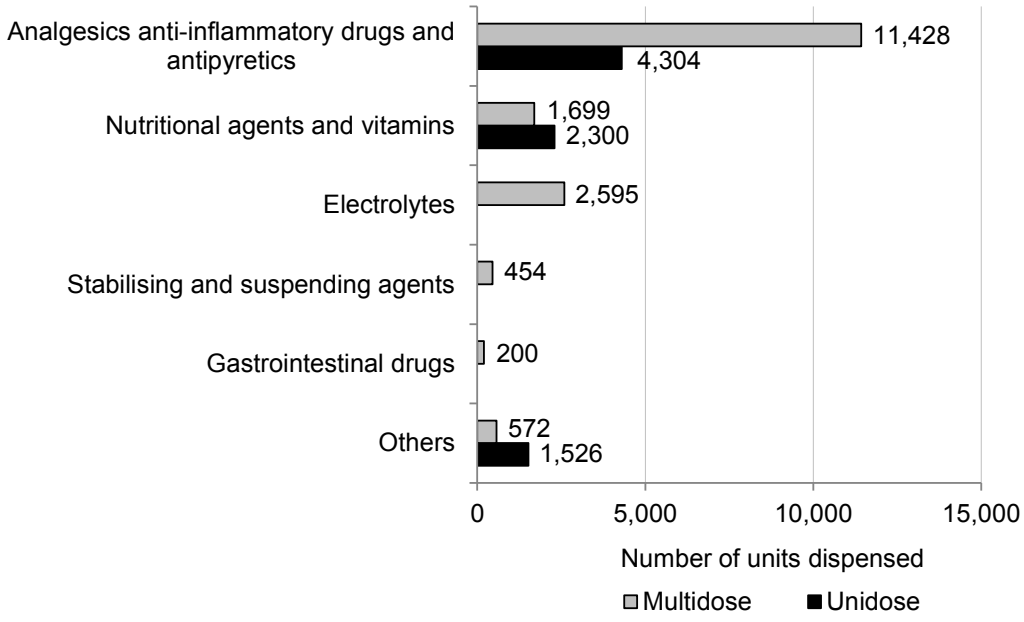


Figure 10.11 Oral liquids classified by therapeutic groups and dispensed by number of units (unidose and multidose).

The last column “others” included the following therapeutic groups:

- Multidose: antidiabetics; antiepileptics; antihistamines; antineoplastics; antiprotozoals; anxiolytic, sedatives, hypnotics and antipsychotics; cardiovascular drugs; contrast media; corticosteroids; local anaesthetics; supplementary drugs and other substances; thyroid and antithyroid drugs; and urological drugs;
- Unidose: antineoplastics and cardiovascular drugs.

The multidose oral liquids may be quantitatively compared to the oral solids dispensed (in packs). Considering that oral powders were dispensed in packs of 13 units (Section 2.1.3), the 10,305 individual units of oral powders corresponded approximately to 793 packs of oral powders (of 13 units each).

Assuming that capsules were dispensed in packs of 50 units (Section 2.1.3), the 8,300 individual units of capsules corresponded approximately to 166 packs of oral capsules (of 50 units each). Therefore, when the 16,948 units of multidose oral liquids are compared to the 2,363 packs of oral solids, and the estimation of 959 packs (793+166 packs of oral powders/capsules), it is concluded that oral liquids were dispensed in larger quantities than oral solids. This fact is not in accordance with Brion *et al.* (2003), who concluded that oral powders were the most frequently dispensed oral dosage forms in Finland but their findings related to only 1 Finnish hospital.

When further comparing oral solids and oral liquids, the top 5 therapeutic groups (Figures 10.6 and 10.11) were all different, which suggests that active substances in Finland are preferably dispensed either as solid or liquid dosage forms; i.e. cardiovascular drugs are preferably dispensed as oral solids whereas analgesics, anti-inflammatory drugs and antipyretics are preferably dispensed as oral liquids. This is likely to be related with the physiochemical properties of the active substances.

10.4.4 **Oromucosal preparations**

In Finland, oromucosal preparations were reported by 2 hospitals (29% of all participants) and, in total, 5 different compounded medicines were dispensed, in a sum of 835 multidose containers, namely: miconazole and lidocaine gel (20 g); sodium hypochlorite solutions 0.5% and 1% (100 mL); and 2 mouthwashes for CIOM: ergocalciferol solution (100 mL) and ergocalciferol and vitamin A solution (200 g)

10.5 **Summary**

- Compounded medicines are commonly prepared in community and hospital pharmacies in Finland. The university hospitals dispense the largest quantities and variety of compounded medicines.
- Finnish pharmacies are allowed to prepare their own compounded medicines and also to dispense compounded medicines prepared in other pharmacies (contract manufacturing).
- A purposive sample of 8 hospitals was included in the research and a response rate of 88% was obtained. A total of 85 different active substances (including 4 NTI drugs) were reported corresponding to 25 different therapeutic groups. The top 3 therapeutic groups were cardiovascular drugs (n=19), nutritional agents and vitamins (n=10) and antiepileptics (n=8).
- Oral solid dosage forms were reported by all participant hospitals and included oral powders and capsules. Oral powders were dispensed in a total sum of 10,305 (55%) units and the top 5 active substances were: hydrocortisone, diazoxide, potassium perchlorate, amiodarone HCl and ursodeoxycholic acid. Capsules were dispensed in a total sum of 8,300 units (45%) and the top 5 active substances were: hydrocortisone, ursodeoxycholic acid, propranolol HCl, nitrazepam and warfarin sodium.
- Oral liquid dosage forms were reported by all participant hospitals and included solutions and suspensions (multidose and unidose). Multidose oral liquids were dispensed in a total sum of 16,948 containers and the top 5 active substances were: methadone HCl, sodium citrate, glucose, morphine (HCl) and methylcellulose. Unidose oral liquids were dispensed in a total sum of 8,130 units and the top 5 active substances were: methadone HCl, glucose, hydrochlorothiazide, spironolactone and nimodipine. Multidose oral liquids were dispensed in larger quantities than unidose oral liquids.
- Oral liquids were dispensed in larger numbers than oral solids.
- Oromucosal preparations were reported in a total sum of 835 multidose containers and corresponded to the following: miconazole and lidocaine gel, sodium hypochlorite solutions and mouthwashes for CIOM.

11. **Compounding in Spain**

Spain joined the EU in 1986 and its official language is Spanish (*Europa*, 2009). The country is constituted by the mainland and 2 archipelagos - the Balearic Islands in the Mediterranean Sea and the Canary Islands in the Atlantic Ocean - plus the cities of Ceuta and Melilla, located on the coast of Africa. Spain is divided in 17 autonomous communities[40]: *Andalucía, Aragón, Asturias, Islas Baleares, Islas Canarias, Cantabria, Castilla-La Mancha, Castilla y León, Cataluña, Comunidad Valenciana, Extremadura, Galicia, Comunidad Madrid, Murcia, Navarra, País Vasco* and *La Rioja* (Turespaña, 2011). Spain is the second largest EU country, having an area of 506,000 Km^2 and is the 5^{th} most populated, with a population of 44.5 million in 2007 (Figure 2.2) (*Europa*, 2008).

In 2006, there were 746 hospitals in Spain (ratio of 1.72 hospitals per 100,000 population) and a total of 146,202 hospital beds (ratio of 337.03 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2006, there were 39,900 pharmacists in Spain (ratio of 91.98 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4). According to the EAHP survey, the average number of pharmacists in Spanish hospitals is 5.0, similar to the European average of 4.7 pharmacists per European hospital. In addition, Spanish hospitals have an average of 5.3 qualified pharmacy technicians/assistants per hospital, similar to the European average of 6. Spain also has an average of 7.3 non-qualified pharmacy assistants per hospital (EAHP, 2005; Hartmann, 2010).

Pharmaceutical compounding has a long tradition in Spain and is currently a common practice in both hospital and community pharmacies (CGCOF, 2010). Sterile and non-sterile compounded medicines are prepared in both settings, although sterile compounding is more frequent in hospital pharmacies.

[40]Spain is divided into 17 regional governments, which are designated by autonomous communities (regions) (*Europa*, 2009).

Of the 1,295 community pharmacies in the region of Madrid, certified by the respective board of pharmacy[41] for the preparation of compounded medicines (Section 11.1), only 3 pharmacies (less than 0.5%) prepare sterile compounded medicines (COFM, 2011). On the other hand, non-sterile compounded medicines are prepared by the majority of the community pharmacies in Spain accounting, on average, for approximately 2% of all prescriptions dispensed (Baixauli, 2008a; Marro, 2008).

In the hospital setting, pharmaceutical compounding is an important practice to meet patients' therapeutic needs with customised medicines (CGCOF, 2010). At *Hospital Infantil Universitario Niño Jesús*, a paediatric hospital located in Madrid, the compounded medicines dispensed from January to October 2007 were retrospectively analysed and it was concluded that 89 active substances were dispensed, in a total of 142 different compounded medicines. The majority was prepared from proprietary medicines and only 35% were prepared from raw materials. The most frequently dispensed dosage forms prepared from proprietary medicines were sachets (60%) and capsules (15%), whereas the most frequently dispensed dosage forms prepared from raw materials were sachets (52%) and solutions (27%). The majority of capsules and sachets were dispensed to neurology (43.66%), followed by the intensive care unit (15.47%), oncology (12.24%) and cardiology (9.56%) departments (Díaz *et al.*, 2007).

11.1 **Legislation**

According to Spanish legislation, there are 4 types of legally recognised medicines, namely: medicines for human and veterinary use produced by industry; magistral formulae and officinal preparations (both compounded medicines); and special medicines foreseen by the legislation (Ministerio de Sanidad y Consumo, 2006a).

Magistral formulae (*formulas magistrales*) correspond to medicines for a specific patient, prepared by the pharmacist, or under his/her supervision, to expressly comply with the detailed medical substances included in the doctor's prescription, in accordance with the established "norms for the

[41] In Spain, each autonomous community is represented by a board of pharmacy, which corresponds to a regional pharmaceutical society.

correct preparation and QC of compounded medicines". They are dispensed in a community or hospital pharmacy together with the respective necessary information for the patient (Ministerio de Sanidad y Consumo, 2006a). Therefore, magistral formulae are prescription-only (compounded) medicines, prepared in accordance with a doctor's prescription. These may be prepared in accordance with the Spanish official national formulary - *Formulario Nacional* - which includes a total of 21 standardised ("typified") magistral formulae, corresponding to long-established formulae frequently prescribed in Spain (Section 11.2.2). According to Cortina *et al.* (2009a), the majority (81.74%) of compounded medicines dispensed in community pharmacies correspond to magistral formulae.

Officinal preparations (*preparados oficinales*) are medicines prepared in accordance with the established "norms for the correct preparation and QC of compounded medicines" guaranteed by a pharmacist, or under his/her supervision, dispensed in a community or hospital pharmacy, numbered and described in the national formulary (Section 12.2.2), to be directly dispensed to the patients assisted by that pharmacy. Therefore, officinal preparations are compounded medicines described in the Spanish official national formulary and do not require a doctor's prescription. It has been suggested (Marro, 2008), that the majority of these officinal preparations correspond to "old topical preparations of little interest in today's therapeutic setting". According to Cortina *et al.* (2009b), the most frequently dispensed officinal preparations in community pharmacies are for dermatological use, in particular "Water Paste" (Appendix 16) and "Salicylate Vaseline".

Community and hospital pharmacies that do not meet all necessary requirements may outsource the preparation and/or QC of compounded medicines from an entity authorised by the Spanish agency of medicines and sanitary products (AEMPS) (Ministerio de Sanidad y Consumo, 2006a). Pharmacies may lack facilities, equipment or even the skills to prepare a given compounded medicine, and third-party compounding allows patients to receive virtually all compounded medicines at their nearest local pharmacy (Marro, 2008). In practice, this authorised entity includes not only hospital and community pharmacies but also other organisations, for instance, the

Board of Pharmacy in Valencia and the Board of Pharmacy in Zaragoza. In these 2 autonomous communities, in particular, local community and hospital pharmacies have lost a considerable part of their compounding requests, since the regional Boards of Pharmacy represent a powerful and influential competitor. The ethics of having the regional Boards of Pharmacy as a competitor have been questioned in Spain (AEFF, 2012).

In order to guarantee the quality of compounded medicines, the pharmacist must follow the "norms for the correct preparation and QC of compounded medicines" (*Normas de correcta elaboración y control de calidad de fórmulas magistrales y preparados oficinales*), established by law (Ministerio de Sanidad y Consumo, 2001). These norms corresponding to GCP comprise 6 components, namely: personnel; facilities and equipment; documentation; raw materials and packaging materials; preparation; and dispensing; these norms are very similar to the Portuguese guidelines (Section 3.1). In Spain, QC must be performed on all compounded medicines prepared, and the minimum QC tests required depend on the type of compounded medicines, as follows:

- Magistral formulae: verification of organoleptic characteristics.
- Standardised "typified" magistral formulae and officinal preparations: all QC tests outlined in the *Formulario Nacional* (Ministerio de Sanidad y Consumo, 2001).

According to Díaz *et al.* (2007), these norms have resulted in considerable change in the hospital compounding practices throughout Spain, in particular with regards to paediatric hospitals, which are nowadays characterised by rigour and quality with respect to pharmaceutical compounding. According to the latest EAHP survey, SOP (for compounding) are nowadays used in more than 90% of hospital pharmacies in Spain (EAHP, 2005).

The raw materials included in the preparation of compounded medicines must be substances with legally recognised actions and indications in Spain (Ministerio de Sanidad y Consumo, 2001). Nevertheless, there are restrictions for the use of certain raw materials in pharmaceutical compounding, namely: human and animal organs or glands (and their

respective derivatives). Plus, raw materials with the following actions: anorexic, psychotropic, hormonal, laxative and diuretic, used in combination; 2 of these raw materials may be exceptionally used in combination provided that the prescriber justifies the need, efficacy and safety of such combination (Ministerio de Sanidad y Consumo, 1997). These restrictions were introduced after the massive expansion of the market for slimming products in Spain, and the consequent misuse of such drugs by means of pharmaceutical compounding.

In Spain, each autonomous community is responsible for the adaptation and enforcement of pharmaceutical legislation in the corresponding region, which results in different criteria with regards to the practice of pharmacy (and pharmaceutical compounding) within each community. For instance, the use of proprietary medicines in compounding is subject to varying restrictions. In some autonomous communities, the use of proprietary medicines is not allowed, though in others, Madrid, for example, a paediatric hospital reported that the majority of the compounded medicines dispensed were indeed prepared from proprietary medicines (Díaz *et al.*, 2007). Furthermore, community pharmacies in the region of Madrid require specific certification from the respective Board of Pharmacy to prepare compounded medicines based on the criteria sterile/non-sterile and on the dosage forms prepared, whereas in other regions the same criteria may not apply. These differences in criteria within Spanish autonomous communities are bureaucratic (Marro, 2006) and contribute to heterogeneous requirements and practices throughout the country (Rodríguez, 2005).

11.2 **Professional organisations and information sources**

11.2.1 **Spanish professional organisations**

- *Asociación Española de Farmacéuticos Formulistas* (AEFF): is the Spanish association of compounding pharmacists, an organisation that promotes pharmaceutical compounding in Spain and helps pharmacists install and develop compounding laboratories in community pharmacies. The AEFF is steadily growing and has now over 400 members (AEFF, 2010). The AEFF organises a scientific congress every year and other compounding

events throughout the country. The International Society of Pharmaceutical Compounding (ISPhC) (Section 14.2.1) was officially constituted in Spain during the annual congress of the AEFF in 2004 (ISPhC, no date).

- *Asociación Profesional Independiente de Farmacéuticos Formuladores* (Aprofarm): is the independent professional association of compounding pharmacists, an organisation created in 1996 in Barcelona that promotes individualised medicines; researches, develops and publicises pharmaceutical compounding; supports compounding pharmacists; establishes contacts and links between compounders; criticises, informs and collaborates with changes in legislation; and educates pharmacists and health professionals (Aprofarm, 2011). Aprofarm also organises compounding events in Spain. Aprofarm and AEFF are currently working together on "Formula 2015", a 5-year project that aims to develop and promote pharmaceutical compounding in collaboration with doctors in hospitals and other health centres throughout Spain. A team of 35 compounding experts is responsible for providing informative sessions to doctors, developing compounding formularies and undertaking research studies (Aprofarm and AEFF, 2010).
- *Asociación de Formulistas de Andalucía* (AFA): is the association of compounding pharmacists from *Andalucía* (autonomous community), an association that includes 212 members (of which 40 members are from outside *Andalucía*), that promotes pharmaceutical compounding and represents the interests of compounding pharmacists in Spain (AFA, 2009). Since 2009, AFA organises an annual symposium - *Rafael Alvarez Colunga* - on compounding for paediatric patients (standardisation of criteria), where current compounding practices are discussed.
- *Instituto Tecnologico del Medicamento Individualizado* (ITMI): is the technological institute of individualised medicine, an organisation promoted by AFA which collaborates with Spanish Universities (*Granada*, *Seville* and *La Laguna*) in the investigation and development of compounded medicines for paediatric patients. ITMI was constituted in 2009 and aims to promote pharmaceutical compounding in community and hospital pharmacies by providing consultancy on all technical aspects related to the practice of compounding (ITMI, no date).

- *Sociedad Española de Farmacia Hospitalaria* (SEFH): is the Spanish society of hospital pharmacy, a scientific, private, active and professional organisation dedicated to promoting knowledge about hospital pharmacy and whose actions aim to increase the appropriate and safe use of medicines (SEFH, no date). The SEFH has a working group dedicated specifically to pharmaceutical compounding - *Farmacotecnia* - which coordinates several compounding-related projects, for example, the development of a hospital pharmacy formulary, SOP and a manual with norms and procedures adapted to compounding legislation (Ministerio de Sanidad y Consumo, 2001; Vila and Martínez, 2009).
- *Sociedad Valenciana de Farmacia Hospitalaria* (SVFH): is the hospital pharmacy society of the autonomous community of Valencia, a scientific non-profit association that promotes and supports hospital pharmacy in the region of Valencia (SVFH, no date), including the practice of pharmaceutical compounding.
- *Consejo General de Colegios Oficiales de Farmacéuticos:* is the general council of the official boards of pharmacy in Spain, an entity that brings all regional boards of pharmacy together. Although pharmaceutical compounding is relevant for all boards of pharmacy, their activities vary from region to region. For instance, some boards of pharmacy have a compounding laboratory and prepare compounded medicines for pharmacies within the region. Others offer only consultancy services and compounding courses to affiliated members. The *Colegio Oficial de Farmacéuticos de Madrid* (COFM), corresponding to the Board of Pharmacy from Madrid, has a department specifically dedicated to the practice of compounding and the COFM newsletter “practice of pharmacy” includes, in each publication, a revised monograph for a compounded medicine of interest (COFM, 2010). Other boards of pharmacy have also published compounding-specific formularies (Section 11.2.2).

11.2.2 **Spanish information sources**

- *Formulario Nacional:* is the Spanish national formulary, the official reference for pharmaceutical compounding in this country. It was initially published in 2003 (Ministerio de Sanidad y Consumo, 2003) and was first

updated in 2007 (Ministerio de Sanidad y Consumo, 2006b). This formulary is divided in 2 parts: Part I includes all relevant legislation for the practice of compounding in Spain. Part II includes 25 SOP (general; preparation of dosage forms; pharmaceutical operations and QC); 66 monographs for raw materials (active substances and excipients/vehicles); 63 monographs for long-established standardised ("typified") magistral preparations and officinal preparations; and a separate chapter dedicated to phytotherapy (30 monographs for active substances and officinal preparations). This formulary includes monographs for oral, oromucosal, topical and rectal compounded medicines; in liquid, semi-solid and solid dosage forms. According to Cristina Avendaño Solá[42], the galenic and pharmacological information included in the national formulary is essential for the preparation (in community or hospital pharmacies) of medicines with appropriate quality, safety and efficacy (Comité del Formulario Nacional, 2007). Whilst this formulary is the official Spanish reference which compiles monographs for the long-established standardised "typified" magistral preparations and officinal preparations, the Spanish Pharmacopoea (*Real Farmacopea Española*) is the official reference which contains monographs for medical substances and excipients for human and veterinary use, as well as the respective analytical control methods (Ministerio de Sanidad y Consumo, 1995).

- Formularies established by the official boards of pharmacy: some boards of pharmacy have published compounding-specific formularies (Section 11.2.1). For instance, the *Formulario Regional* (regional formulary) from the region of *Murcia* and the *Guía de Calidad en Formulación Magistral* (compounding quality guide) from the community of *Valencia*.
- *Formulario Básico de Medicamentos Magistrales:* is a non-official Spanish formulary, published by Clavijo and Comes (2009), which includes complete monographs for vehicles/bases and raw materials (active substances and excipients) frequently used in pharmaceutical compounding in Spain.
- *Formulación en Farmacia Pediátrica:* is another non-official Spanish formulary, published by Fernández *et al.* (2011), which includes detailed

[42]Director of AEMPS in 2007.

procedures and patient information leaflets for more than 100 compounded medicines frequently used in paediatric patients in Spain.

- *Preparación de Medicamentos. Formulación Magistral*: is a reference manual for pharmaceutical compounding in hospital pharmacy in Spain, published by Maria Eugenia Méndez Esteban[43] in 2 large volumes as a result of her practice and expertise in pharmaceutical compounding at *Hospital Universitario 12 de Octubre* (Madrid) (Esteban, 2010).

As shown in Table 11.1 (below), formularies for pharmaceutical compounding have been published, regularly in Spain, over the past years.

Table 11.1 Formularies published in Spain from 1995-2008 (adapted from Baixauli, 2008b).

Years	Published formularies
1995	5
1997	5
1998	4
2002	1
2003	3
2004	1
2007	1
2008	1

11.3 **Methods**

The research project was initiated in 2006 by consulting representatives of the AEFF. In a second approach, the SEFH was contacted several times by email and telephone, and also the SVFH, but no response was provided. In a third approach, personal approaches were made by email and Diego Marro[44], in particular, provided invaluable help by identifying and contacting directly José María Alonso Herreros[45], who identified the purposive sample of hospitals based on his knowledge and expertise as a member of SEFH.

[43]Pharmacist responsible for the compounding department at *Hospital Universitario 12 de Octubre* (*Comunidad de Madrid*).
[44]Diego Marro is a pharmacist at *Farmacia Marro* in *Huesca* and director of the Master in Pharmaceutical Care and Pharmacotherapy at the University *San Jorge* in *Zaragoza*.
[45]José Maria Alonso Herreros is a hospital pharmacist at *Hospital Reina Sofía* in *Murcia* and member of the working group on pharmaceutical compounding at SEFH (Section 11.2.1).

This list was further complemented by Manuela Atienza Fernández[46], on the basis of her practice and expertise in paediatric hospital pharmacy in Spain. Vicente Baixauli Comes[47] also contributed with the suggestion of 1 hospital. As a result, a purposive sample of 40 hospitals was established, including general hospitals, university hospitals and paediatric-specialist hospitals.

No fieldwork was undertaken in Spain, nor it was necessary to request specific advice on the Spanish questionnaire, because of the expertise of MC in the field of pharmaceutical compounding in this country.

11.3.1 **Country-specific questionnaire**

The research instrument developed to collect information regarding oral compounded medicines most frequently dispensed in Spanish hospital pharmacies was a self-completion questionnaire (main heading in Figure 11.1), based on the template established for Portugal (Section 3.3.1) and adapted to the practice of pharmaceutical compounding in Spain. This customised questionnaire comprised 1 table only and was developed in Spanish by MC. Data collection in Spain was undertaken in the year 2009 and, therefore, the questionnaire addressed information relating to 2008.

Compounded medicines were defined as “magistral formulae and/or officinal preparations prepared at the hospital pharmacy” because, although magistral formulae and officinal preparations are commonly distinguished in Spain (Section 11.1), both categories should be considered altogether when establishing the most frequently dispensed oral compounded medicines.

[46]Manuela Atienza Fernández is a specialist in hospital pharmacy in Spain and author of the paediatrics formulary *Formulación en Farmacia Pediátrica* (Fernández *et al.*, 2011) (Section 11.2.2).
[47]Vicente Baixauli Comes is a community pharmacist specialist in pharmaceutical compounding and author of the Spanish formulary *Formulario Básico de Medicamentos Magistrales* (Clavijo and Comes, 2009) (Section 11.2.2).

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PROYECTO DE DOCTORADO

MEDICAMENTOS MAGISTRALES EN FARMACIA HOSPITALARIA EN EUROPA

ESPAÑA

Por favor completar la siguiente información:

Teniendo en cuenta los MEDICAMENTOS MAGISTRALES ORALES más frecuentemente dispensados por vuestros Servicios Farmacéuticos en 2008

MEDICAMENTOS MAGISTRALES son definidos para el propósito de este estudio como fórmulas magistrales y/o preparados oficinales elaborados en la farmacia hospitalaria

	Principio Activo	Dosis	Forma Farmacéutica	Cantidad	Número de veces dispensado en 2008
Ejemplos	Captopril	1 mg / mL	Solución	50 - 250 mL	75
	Hidrato de Cloral	100 mg / mL	Jarabe	100 - 300 mL	67
	Bicarbonato de Sodio	500 mg	Cápsulas	30 - 300 caps	45
1					
2					
3					

Figure 11.1 Country-specific questionnaire (Spain).

11.3.2 **Purposive sample of hospitals**

A purposive sample of 40 hospitals was selected across Spain, from the cities of: *A Coruña*, *Alicante*, *Almería*, *Badajoz*, *Baracaldo*, *Barcelona, Cádiz*, *Córdoba*, *Donostia-San Sebastián*, *Getafe*, *Granada*, *Guadalajara*, *Huelva*, *Jaén*, *Las Palmas de Gran Canaria* (not included in the map), Madrid (capital), *Murcia*, *Oviedo*, *Palma de Mallorca*, *Salamanca*, *San Sebastián de los Reyes*, *Santander*, *Sevilla*, *Toledo*, *Valencia*, *Vigo* and *Zaragoza* (Figure 11.2). A total of 9 hospitals were from Madrid, 4 from *Barcelona*, 2 from *Seville* and 2 from *Valencia*. The 40 hospitals selected were identified by the stakeholders as the ones in which the largest quantities of compounded medicines were likely to be dispensed in Spain.

Figure 11.2 Map of Spain (mainland) adapted from National Geographic Society (1998h); indicating the location of the purposive sample of hospitals (●).

11.3.3 **Data collection**

Two hospitals were contacted directly by Manuela Atienza Fernández and all other 38 hospitals were contacted by MC by email (in Spanish) with the request to share data regarding the oral compounded medicines most frequently dispensed in 2008 (or the latest available year). A brief introductory email was then sent to the key contact person with the questionnaire attached as well as an electronic copy of the IJPC article

(Carvalho *et al.*, 2008). Non-respondents were sent periodical email reminders (average of 3 emails per hospital pharmacy). All persistent non-respondents were then contacted by MC by telephone (in Spanish), followed by a maximum of 4 additional email reminders. Data were collected by the hospital pharmacy's staff and none of the Spanish hospitals were visited by MC.

11.4 **Results and discussion**

Of the 40 hospitals contacted, 31 hospital pharmacies responded to the request for collaboration and 9 were non-respondents, resulting in a response rate of 78%. From the 31 respondents, 30 contributed data regarding the oral compounded medicines most frequently dispensed by their pharmacies and 1 hospital pharmacy was a non-participant (Figure 11.3); the reason stated for not collaborating was that they did not dispense any compounded medicines.

Of the 30 participant hospitals, 77% (n=23) shared quantitative and complete datasets. Other replies were distributed as follows: 1 hospital shared quantitative but incomplete data; another hospital provided semi-quantitative data; and 5 hospitals provided qualitative data only.

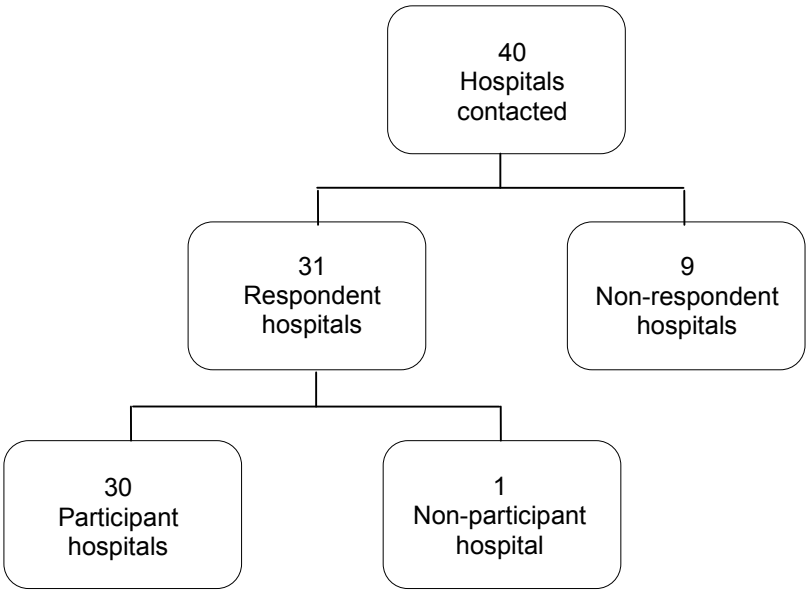


Figure 11.3 Purposive sample distributed by respondent and participant hospitals.

The main reasons stated for not sharing quantitative and complete datasets were that data were not readily accessible and that no records were kept with regards to specific data. Only 1 hospital stated that they dispensed few oral compounded medicines.

The majority of hospitals shared data in their own formats and only 43% used the questionnaire provided, which may result from the fact that the majority of hospital pharmacies in Spain have a software application for compounding. For instance, the SEFH collaborated with TECNO[48] to develop the *Formulario Magistral COPA*, a Microsoft Access application for pharmaceutical compounding in Spanish hospital pharmacies (Vila and Martínez, 2009). One hospital provided the required data by telephone.

The participant hospitals provided data mainly from 2008 and 2009; only 1 hospital shared data from 2007 and 4 hospitals from 2 consecutive years.

The research project undertaken in Spain was the second largest, after Portugal, and corresponded to a complex and time-consuming process. A total of 40 telephone calls were made to Spanish hospitals and a total of 152 emails were sent with requests for collaboration.

11.4.1 **Active substances**

A complete list of the active substances most frequently dispensed as oral compounded medicines in Spain is shown in Table 11.2. Active substances were grouped according to their respective therapeutic classification (*Martindale 35*, 2007), giving a total of 35 therapeutic groups and 281 different active substances, which is considerably more than the 89 active substances identified by Díaz *et al.* (2007) but this study related to only 1 Spanish hospital (Section 11).

Cardiovascular drugs was the group with the greatest number of different active substances (n=39), followed by nutritional agents and vitamins (n=34) and antibacterials (n=31).

[48]TECNO is the acronym given to the committee within the SEFH that evaluates new technology relevant to hospital pharmacists (both software and hardware that is used in the care of patients at any phase of the medication process).

Table 11.2 Active substances most frequently dispensed as oral compounded medicines in Spain (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aspirin, benzydamine HCl, celecoxib, codeine, dexketoprofen trometamol, dipyrone, ibuprofen, indometacin, ketorolac trometamol, meloxicam, methadone HCl, morphine, morphine HCl, paracetamol, tolmetin sodium, tramadol HCl

Antihelmintics
Levamisole, praziquantel

Antibacterials
Aminosalicylic acid, amoxicillin, ampicillin, cefaclor, cefalexin, chloramphenicol, ciprofloxacin, clindamycin, colistin sulfate, cycloserine, doxycycline, doxycycline hyclate, erythromycin, ethambutol HCl, gentamicin sulfate, isoniazid, levofloxacin, linezolid, neomycin, oxytetracycline, penicillin, pyrazinamide, rifabutin, rifampicin, sodium aminosalicylate, sulfadiazine, sulfamethoxazole, tobramycin, tobramycin sulfate, trimethoprim, vancomycin

Antidementia drugs
Idebenone

Antidepressants
Amitriptyline, doxepin HCl, duloxetine HCl, oxitriptan

Antidiabetics
Acarbose, metformin HCl

Antiepileptics
Carbamazepine, clobazam, ethosuximide, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, phenytoin sodium, topiramate, vigabatrin, zonisamide

Antifungals
Amphotericin B, fluconazole, flucytosine, nystatin, terbinafine, voriconazole

Antigout drugs
Allopurinol, colchicine, probenecid

Antimalarials
Chloroquine, chloroquine phosphate, hydroxychloroquine sulfate, pyrimethamine, quinine, quinine HCl, quinine sulfate

Antimyasthenics
3,4-Diaminopyridine, fampridine, pyridostigmine bromide

Antineoplastics
Busulfan, cyclophosphamide, hydroxycarbamide, irinotecan HCl, lomustine, mercaptopurine, procarbazine HCl, sunitinib malate, temozolomide, tioguanine, topotecan HCl

Antiparkinsonian drugs
Carbidopa, entacapone, levodopa

Antiprotozoals
Benznidazole

Antivirals
Abacavir, abacavir sulfate, aciclovir, entecavir, lamivudine, nevirapine, oseltamivir phosphate, ribavirin, valaciclovir HCl, valganciclovir HCl, zidovudine

Anxiolytic, sedatives, hypnotics and antipsychotics
Alprazolam, chloral hydrate, clorazepate, diazepam, dipotassium clorazepate, levomepromazine, lorazepam, lormetazepam, midazolam, nitrazepam, zolpidem tartrate

Bronchodilators and anti-asthma drugs
Caffeine, caffeine citrate, sodium cromoglicate, theophylline

Cardiovascular drugs
Acenocoumarol, amiloride HCl, amiodarone, amlodipine besilate, atenolol, atropine sulfate, bisoprolol fumarate, bosentan, captopril, carvedilol, clonidine, clopidogrel bisulfate, colestipol hydrohloride, colestyramine, diazoxide, diltiazem HCl, dipyridamole, doxazosin mesilate, enalapril, enalapril maleate, flecainide acetate, furosemide, hydralazine HCl, hydrochlorothiazide, labetalol HCl, losartan potassium, mannitol, metoprolol, mexiletine HCl, minoxidil, nadolol, nifedipine, nimodipine, propafenone HCl, propranolol HCl, sotalol HCl, spironolactone, verapamil HCl, warfarin sodium

Chelators, antidotes and antagonists
Calcium polystyrene sulfonate, methionine, sevelamer HCl, sodium polystyrene sulfonate, trientine dihydrochloride

Contrast media
Barium sulfate, meglumine amidotrizoate, sodium amidotrizoate

Corticosteroids
Beclometasone dipropionate, dexamethasone, dexamethasone phosphate, fludrocortisone acetate, hydrocortisone, methylprednisolone, prednisone, triamcinolone, triamcinolone acetonide

Cough suppressants, expectorants, mucolytics and nasal decongestants
Ephedrine, ipecacuanha

Dermatological drugs and sunscreens
Acitretin, tretinoin

Disinfectants and preservatives
Chlorhexidine, chlorhexidine gluconate, hexetidine, metabisulfite, sodium benzoate, sodium metabisulfite

Electrolytes
Bicarbonate, calcium, dibasic sodium phosphate, magnesium lactate, magnesium sulfate, monobasic sodium phosphate, potassium chloride, potassium citrate, sodium bicarbonate, sodium chloride, sodium citrate, sodium phosphate

GI drugs
Calcium carbonate, omeprazole, ondansetron, ranitidine, ranitidine HCl, sodium sulfate

Immunosuppressants
Azathioprine, mycophenolate mofetil, tacrolimus

Local anaesthetics
Lidocaine, lidocaine HCl, mepivacaine HCl

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide

Muscle relaxants
Baclofen, tizanidine HCl

Nutritional agents and vitamins
Alanine, arginine, ascorbic acid, biotin, calcitriol, calcium folinate, citrulline, copper sulfate, folic acid, folinic acid, fructose, glucose, glutamine, isoleucine, lactose, maltodextrin, maltose, mecobalamin, nicotinamide, phenylalanine, pyridoxal phosphate, pyridoxine HCl, riboflavin, serine, sorbitol, sucrose, sucralose, thiamine, tocopherol, valine, vitamin E, zinc aspartate, zinc acetate, zinc sulfate

Stabilising and suspending agents
Methylcellulose, microcrystalline cellulose

Supplementary drugs and other substances
Belladonna, bethanechol chloride, borax, cellulase, citric acid, glycerol, melatonin, nitisinone, pancreatin, phosphoric acid, phosphorus, quercetin, sodium phenylbutyrate, taurine, thalidomide, ubidecarenone, ursodeoxycholic acid, xylose

Thyroid and antithyroid drugs
Iodine, levothyroxine sodium, potassium iodide, potassium perchlorate

Urological drugs
Finasteride, sildenafil citrate

Although the active substances listed were reported as oral compounded medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: dermatological drugs and sunscreens (Appendix 11); disinfectants and preservatives (Appendix 12); stabilising and suspending agents (Appendix 14); and supplementary drugs and other

substances (Appendix 15). The active substances included in these groups are described in the respective appendixes.

A total of 9 NTI drugs (ANVISA, 2007; Appendix 1), were dispensed as oral compounded medicines (underlined in Table 11.2).

The active substances dispensed by most hospitals were: ranitidine (n=21); captopril, furosemide, hydrochlorothiazide, omeprazole, phenobarbital, spironolactone and ursodeoxycholic acid (n=16-20); chloral hydrate, dexamethasone, ipecacuanha, methadone HCl, midazolam, propranolol HCl, sildenafil citrate and tacrolimus (n=10-15).

All active substances reported were included in *Martindale 35* (2007) with the exception of 4 that were dispensed by 3 hospitals in a total of 21,969 units of capsules (Appendix 26), as follows:

- Ambrisentan (5 mg): an orphan drug for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (Committee for Orphan Medicinal Products, 2008).
- Darunavir (150 mg): an oral HIV-1 (human immunodeficiency virus) protease inhibitor indicated in antiretroviral therapy (McKeage *et al.*, 2009).
- Detrothyronine (25 µg): the D-isomer of liothyronine that has been used as a lipid-regulating drug but is now part of the "Archive of deleted monographs" of *Martindale 35* (2007), which includes substances that are no longer in use nor of general interest.
- Maraviroc (150 mg): an oral HIV-1 drug (CCR5 receptor antagonist) indicated in multi-resistant antiretroviral therapy (SEFH, 2005).

The majority of compounded medicines dispensed included 1 active substance only. Nevertheless, combinations of up to 4 different active substances were also dispensed both as solid and liquid dosage forms (Sections 11.4.1 and 11.4.2).

Placebo was reported by 14 hospitals in a total of 27,703 units of capsules containing lactose or starch and dispensed in several sizes (0-3) and colours. Placebo capsules are indicated when a placebo effect is particularly beneficial for the therapeutic outcome and these are frequently used in different hospital services across the country. In Spain, placebo capsules

may also be indicated in protocols for the withdrawal of opioids and in clinical trials (Esteban, 2010).

Compounded medicines were also reported by given titles, namely: Joulie's Solution, Lugol's Solution and Shohl's Solution (Section 11.4.2).

In addition, 9 proprietary medicines were reported as oral compounded medicines (solid and liquid dosage forms) by a total of 8 hospitals (Sections 11.4.2 and 11.4.3). Finally, 2 hospitals reported nutritional supplements in a total of 4,314 units of capsules and sachets.

11.4.2 **Oral solids**

Oral solid dosage forms were reported by 93% (n=28) of all participant hospitals and included capsules (n=26), oral powders (n=17) and powders for oral liquids (n=2). In total, 20 hospitals shared complete (quantitative) data with regards to the oral solids dispensed; 4 hospitals disclosed qualitative data only; 3 hospitals disclosed semi-quantitative data; and 1 hospital reported partial data only. Qualitative, semi-quantitative and partial data were processed and analysed accordingly (Section 2.4). The quantities of oral solids were provided as the number of packs and/or the number of individual units dispensed, which are shown separately below (Figure 11.4).

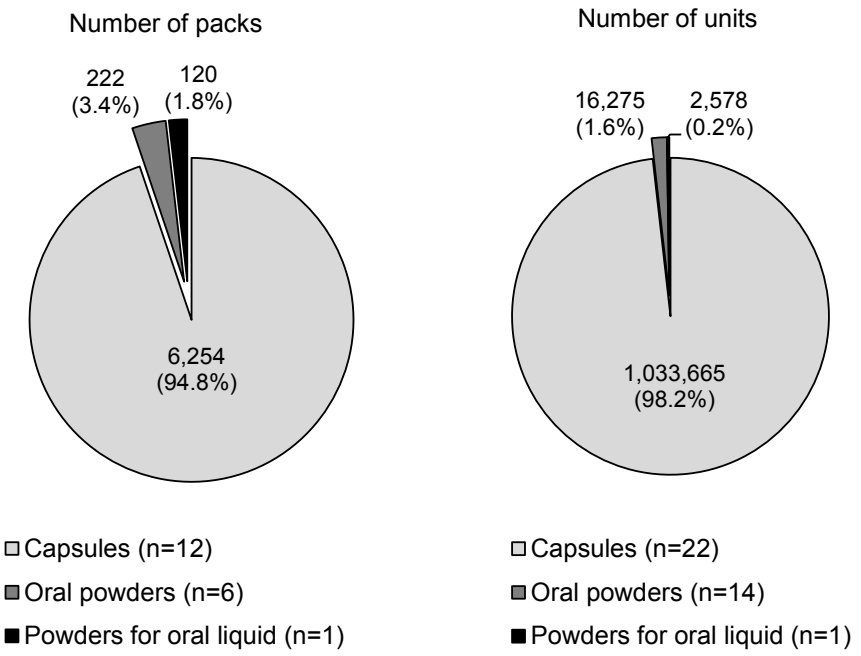


Figure 11.4 Oral solids dispensed per number of packs and number of individual units.

The top 20 active substances dispensed as oral solids and ranked by number of individual units are shown in Figure 11.5. Ribavirin, dexamethasone, clopidogrel bisulfate, 3,4-diaminopyridine, fampridine, chloramphenicol and potassium perchlorate are also part of the top 20 active substances ranked by number of packs.

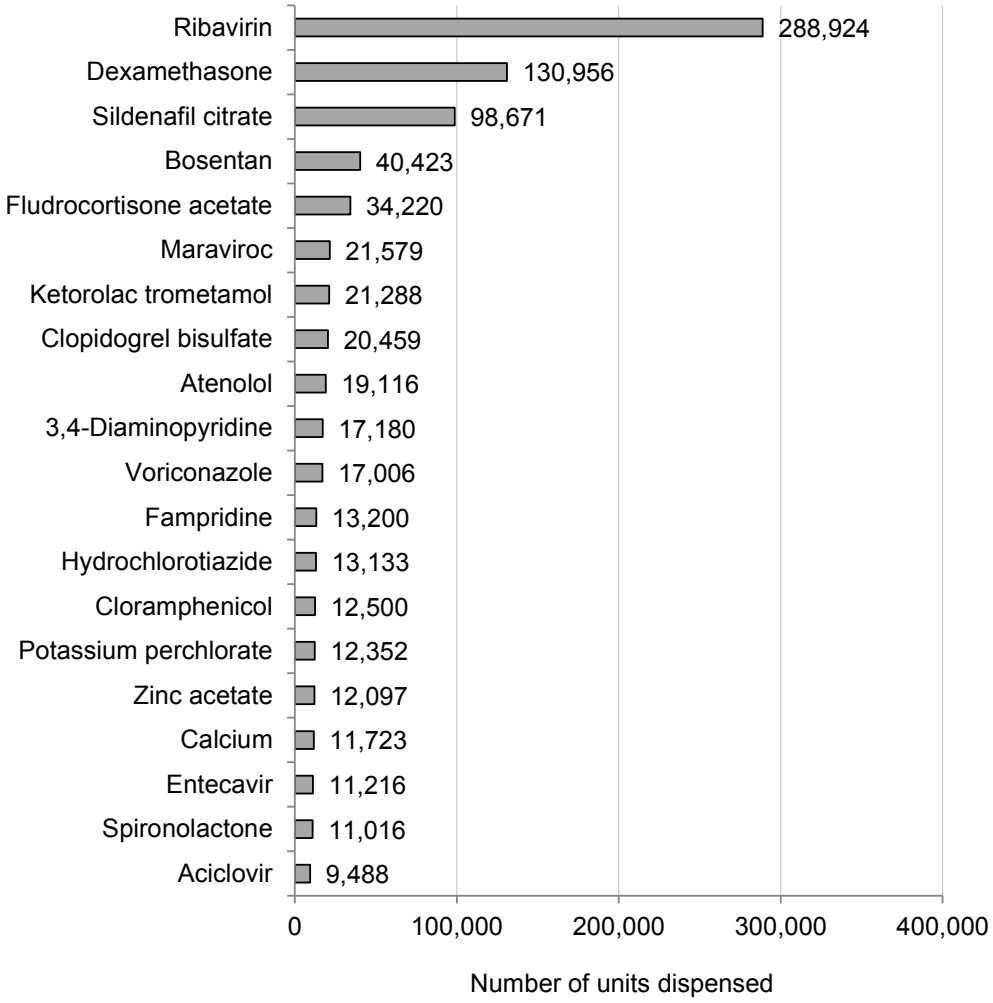


Figure 11.5 Top 20 active substances dispensed as oral solids (ranked by number of units).

The top 5 therapeutic groups, ranked by the number of units of the corresponding oral solids, are shown in Table 11.3. The most frequent therapeutic group was antivirals, which comprised 8 different active substances that were dispensed in a total of 312,329 units of oral solids. All 5 groups included active substances that were part of the top 20 shown in Figure 11.5. The therapeutic group containing the most active substances was nutritional agents and vitamins (n=26).

Table 11.3 Top 5 therapeutic groups ranked by number of units of oral solids dispensed.

Therapeutic groups	Number of active substances	Active substances included in top 20	Number of units
Antivirals	8	Ribavirin Entecavir Aciclovir	312,329
Corticosteroids	6	Dexamethasone Fludrocortisone acetate	170,026
Cardiovascular drugs	18	Bosentan Clopidogrel bisulfate Atenolol Hydrochlorothiazide Spironolactone	116,195
Urological drugs	2	Sildenafil citrate	99,971
Analgesics, anti-inflammatory drugs and antipyretics	12	Ketorolac trometamol	41,539

Capsules were dispensed in much larger quantities than oral powders and represented over 90% of all oral solids dispensed, both in number of packs and number of units dispensed (Figure 11.4). A total of 6,254 packs and 1,033,665 units of capsules were reported but these figures are not directly comparable as 11 hospitals did not provide the number of packs and 1 hospital did not provide the number of units of capsules dispensed. According to several participant hospitals, capsules were prepared in packs of 100 units and were dispensed individually, depending on the posology and duration of treatment. Capsules were reported by 87% of hospitals and, considering the number of units dispensed, the top 5 active substances are shown in Table 11.4, which corresponded to the top 5 active substances dispensed as oral solids (as shown in Figure 11.5).

Table 11.4 Compounded medicines most frequently dispensed as capsules.

Active substances	Strengths	Number of hospitals	Number of units
Ribavirin	300 mg 400 mg	3	288,924
Dexamethasone	4-40 mg	13	130,956
Sildenafil citrate	5-50 mg	3	98,581
Bosentan	5-62.5 mg	5	40,385
Fludrocortisone acetate	5-12.5 µg	2	34,220

None of these active substances have a monograph in the Spanish national formulary, which confirms the proposition that this formulary does not include monographs of interest in today's therapeutic setting (Marro, 2008).

Ribavirin is commercially available both as capsules and tablets of 200 mg and also as an oral solution of 40 mg/mL (AEMPS, 2011). Nevertheless, it was reported as capsules including higher strengths but these are still within the recommended dose for adults of 400 mg twice a day (*Martindale 35*, 2007).

Bosentan is commercially available as tablets of 62.5 mg and 125 mg (AEMPS, 2011) and was reported as capsules of variable strengths from 5 mg up to 62.5 mg. The most frequently dispensed strength was 62.5 mg, which corresponded to 70% of all strengths dispensed. Bosentan is recommended in pulmonary hypertension and is given orally in an initial dose of 62.5 mg twice a day (*Martindale 35*, 2007). The fact that bosentan was dispensed as a compounded medicine in the same strength of the commercially available tablets may be explained by one of the following reasons: the patient was unable to swallow solid dosage forms and the capsules were meant to be opened prior administration; the patient was intolerant to one or more excipients included in the tablets; or the proprietary tablets were commercially unavailable.

The top 5 active substances described were reported as capsules only, with the exception of sildenafil citrate and bosentan which were also reported as oral powders, but in much smaller quantities.

Capsules including more than one active substance were dispensed by 4 hospitals in a total of 5,693 units, which corresponded to only 0.6% of all capsules dispensed. In decreasing order, the combinations of 2 active substances dispensed as capsules were: carbidopa and levodopa; gentamicin sulfate and nystatin; abacavir and lamivudine; zidovudine and lamivudine. Likewise, the combinations of 3 active substances were the following: abacavir, lamivudine and zidovudine; methionine, ascorbic acid and tocopherol (named as "antioxidant capsules"); rifampicin, isoniazid and pyrazinamide; levodopa, carbidopa and entacapone. All these combinations

are therapeutically coherent as the active substances combined are part of the same therapeutic group or, alternatively, are included in therapeutic groups likely to be combined (i.e. antibacterials and antifungals).

Placebo was also reported as capsules (Section 11.4.1).

Resincalcio (calcium polystyrene sulfonate) was the only proprietary medicine reported quantitatively as capsules. A total of 243 units were dispensed by 1 hospital. Furthermore, a total of 48 proprietary medicines were reported qualitatively by another hospital as capsules and oral powders (sachets).

Oral powders represented less than 5% of all oral solids dispensed, both in number of packs and number of units dispensed (Figure 11.4). A total of 222 packs and 16,275 units of oral powders were reported but these figures are not directly comparable as 9 hospitals did not provide the number of packs and 1 hospital did not provide the number of units of oral powders dispensed. The majority of oral powders were reported as sachets (94%) (Figure 3.6) and only 6% were dispensed in flasks, which are usually reserved for larger quantities of powders. Oral powders were dispensed by 57% of hospitals and, considering the number of units dispensed, the top 5 active substances are shown below (Table 11.5).

Table 11.5 Compounded medicines most frequently dispensed as oral powders.

Active substances	Strengths	Number of hospitals	Number of units dispensed
Hydrochlorothiazide	1-5 mg	1	1,342
Calcium polystyrene sulfonate	4 mg - 15 g	3	1,195
Aspirin	5-450 mg	3	1,090
Sucrose	1.2-2.4 g	2	909
Monobasic sodium phosphate	0.5-3 g	2	855

Hydrochlorothiazide, although reported by only 1 hospital, was the active substance most frequently dispensed as oral powders and the only active substance included in the top 20 active substances dispensed as oral solids.

Calcium polystyrene sulfonate is a cation-exchange resin used in the treatment of hyperkalaemia. The usual doses are 15 g, 3 to 4 times a day and, in children, the maintenance dose is 500 mg/kg a day in divided doses (*Martindale 35*, 2007), which explains the wide range of strengths encountered.

Aspirin was reported by 3 hospitals in the strengths of 5 mg up to 450 mg. Since aspirin tablets are commercially available in the strengths of 100 mg and 500 mg (AEMPS, 2011), the evidence base for prescribing aspirin 450 mg oral powders may be questionable. The most frequently dispensed strengths were 5 mg and 10 mg. Although aspirin is not licensed for use in children under 16 years, low doses of aspirin (1-5 mg/kg) are indicated in neonates and child (1 month - 12 years) as an antiplatelet agent in the prevention of thrombus formation after cardiac surgery (Paediatric Formulary Committee, 2008).

A total of 4 proprietary medicines were reported as oral powders: Ammonaps (sodium phenylbutyrate); Lamisil (terbinafine); Resincalcio (calcium polystyrene sulfonate) and Resincolestiramina (colestyramine) in a total of 962 units dispensed by 4 hospitals. Only 1 combination of 2 different active substances was dispensed as oral powders, namely maltodextrin and sucralose (sweetening agent), which was dispensed by 1 hospital in a total of 35 units of sachets (correspondent to 0.2% of all oral powders dispensed).

Powders for oral liquids represented less than 2% of all oral solids dispensed, both in number of packs and number of units dispensed (Figure 11.4), and were reported by only 2 hospitals. A total of 120 packs and 2,578 units were reported but these figures are not directly comparable as 1 hospital did not provide the number of packs dispensed. Powders for oral liquids including more than 1 active substance were dispensed by only 1 hospital, in a total of 393 units, and corresponded to the following combinations: codeine, aspirin and dipotassium clorazepate; codeine, aspirin, dipotassium clorazepate and levomepromazine. Both compounded medicines included the combination of “analgesics, anti-inflammatory drugs and antipyretics” with “anxiolytic, sedatives, hypnotics and antipsychotics” and were indicated in emergency withdrawal syndrome protocols.

11.4.3 **Oral liquids**

Oral liquid dosage forms were reported by 90% (n=27) of all participant hospitals and included both multidose and unidose containers, as follows:

- Multidose: solutions and suspensions (n=26), syrups (n=19), elixirs[49] (n=2), oral drops (n=1) and tinctures[50] (n=1).
- Unidose: oral syringes (n=4).

In total, 24 hospitals shared complete (quantitative) data with regards to the oral liquids dispensed; 1 hospital reported partial data; 1 hospital disclosed semi-quantitative data; and another hospital disclosed qualitative data only. Partial, semi-quantitative and qualitative data were processed and analysed accordingly (Section 2.4). The majority of hospitals reported the volumes dispensed per container and only 4 hospitals reported total volumes. The volumes dispensed ranged from 1 mL up to 4,000 mL, which corresponded to both multidose and unidose oral liquids. Although not all hospitals distinguished multidose from unidose, it was assumed that quantities <10 mL corresponded to unidose, whereas quantities >10 mL corresponded to multidose containers. For quantities of 10 mL, each data entry was considered individually regarding the strengths reported (Section 2.1.3). As a result, it was concluded that 9 hospitals dispensed unidose oral liquids in Spain.

Multidose oral liquids were dispensed in a total of 60,117 containers and the most frequently reported dosage forms were solutions and suspensions (80.4%), followed by syrups (7.2%), tinctures, elixirs and oral drops (0.2%). Over 12% of oral liquids were not classified with regards to the specific dosage form, as shown in Figure 11.6.

The top 20 active substances dispensed as multidose oral liquids are displayed in Figure 11.7. Dexamethasone and sildenafil citrate are also part of the top 20 active substances dispensed as oral solids.

[49]Although elixirs are not an official PhEur dosage form, these are subject of an individual monograph in the BP (Oral Liquids of the BP) and correspond to clear and flavoured oral liquids containing 1 or more active substances dissolved in a vehicle that usually contains a high proportion of sucrose, or a suitable polyhydric alcohol or alcohols, and may also contain ethanol (96% or diluted) (BP Commission, 2008a).

[50]Tinctures are extracts of liquid consistency, usually obtained using 1 part of herbal drug / animal matter and either 10 or 5 parts of extraction solvent (EDQM, 2007).

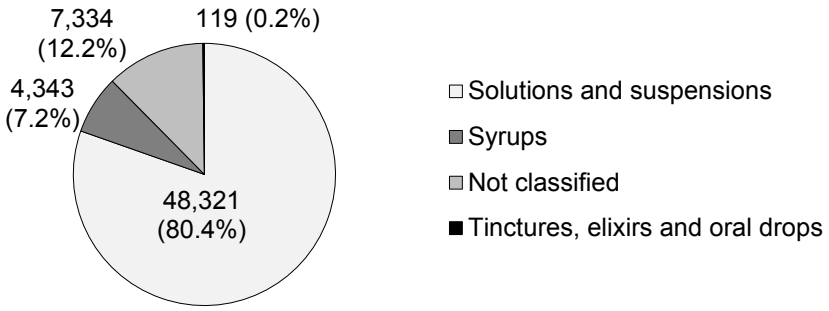


Figure 11.6 Multidose oral liquid dosage forms dispensed per number of containers.

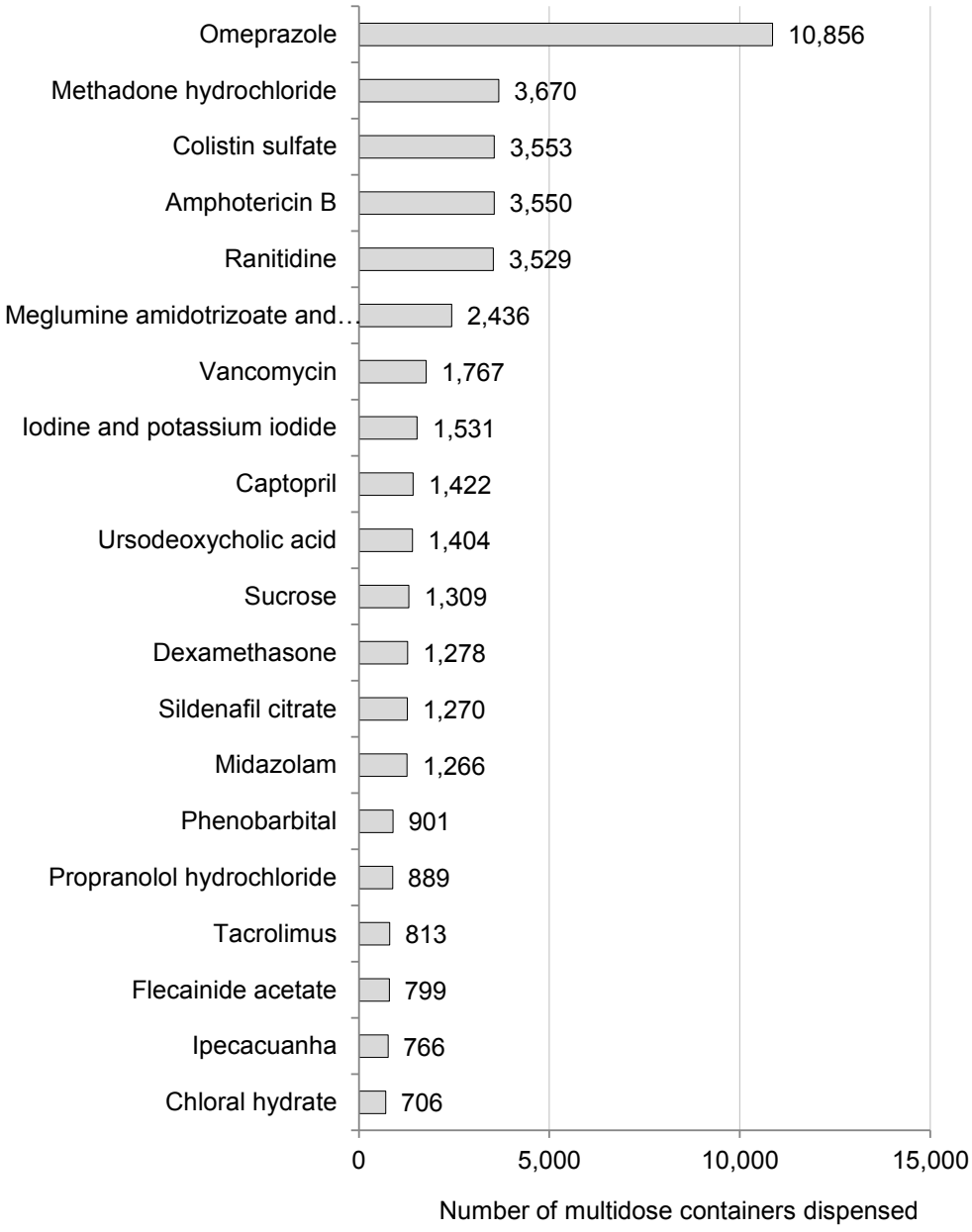


Figure 11.7 Top 20 active substances dispensed as multidose oral liquids and ranked by number of containers dispensed.

The top 5 active substances (Table 11.6) represented 42% of the active substances dispensed as multidose oral liquids. Of these, only methadone HCl is included in the Spanish national formulary.

Table 11.6 Compounded medicines most frequently dispensed as multidose oral liquids.

Active substances	Strengths	Number of hospitals	Number of containers
Omeprazole	2 mg/mL 10 mg/mL	19	10,856
Methadone HCl	0.1-10 mg/mL	11	3,670
Colistin sulfate	*not specified*	3	3,553
Amphotericin B	*not specified*	1	3,550
Ranitidine	5-20 mg/mL	19	3,529

Omeprazole is not commercially available in Spain as an oral liquid dosage form (AEMPS, 2011) and was reported as solutions, suspensions and syrups by 63% of hospitals (n=19). Omeprazole is indicated mainly in dyspepsia, gastro-oesophageal reflux disease and peptic ulcer disease, in daily doses of 10 mg or 20 mg (*Martindale 35*, 2007). The most frequently dispensed strength was 2 mg/mL, which corresponds to a daily dose of 5 mL or 10 mL.

Methadone HCl is commonly prepared in Spanish hospital (and community) pharmacies as oral solutions of variable strengths for the managed withdrawal of narcotics and treatment of acute pain. It was reported by 11 hospitals as solutions and syrups of 10 mL to 4,000 mL; the preparation of large volumes suggests that methadone HCl is not always dispensed to individual patients. According to 1 participant, the hospital pharmacy established a protocol with several care centres for drug addicts and, therefore, they prepared methadone solution in large batches (Herreros, 2010). The strengths reported varied from 0.1 mg/mL to 10 mg/mL; the most frequently dispensed strength was 3 mg/mL. The Spanish national formulary includes a monograph for an oral solution of methadone HCl 1% and suggests doses are adapted to the clinical outcome with a maximum of 200 mg (20 mL) (or more) per day (Comité del Formulario Nacional, 2007). At *Hospital Universitario 12 de Octubre* (Madrid), methadone HCl is prepared as

an oral solution of 1 mg/mL (100 mL), which corresponds to the necessary quantity for a 4-day treatment (Esteban, 2010).

Colistin sulfate and amphotericin B were both reported as solutions but the respective strength(s) were not specified.

Ranitidine is not commercially available in Spain as an oral liquid dosage form (AEMPS, 2011) and it was reported as solutions, suspensions and syrups by 63% of hospitals. Ranitidine is indicated mainly in gastric and duodenal ulceration and also in gastro-oesophageal reflux disease, in a usual dose of 150 mg twice a day (*Martindale 35*, 2007). The most frequently dispensed strengths were 5 mg/mL and 15 mg/mL, which would correspond to dose volumes 30 mL and 10 mL respectively. This fact suggests that lower doses than 150 mg twice a day were administered, probably to paediatric patients, since volumes >10 mL are too large for a single dose.

Iodine and potassium iodide were dispensed as Lugol's Solution in a total of 1,531 multidose containers (Figure 11.7) of 10 mL to 100 mL, by 13 hospitals. The Spanish national formulary includes 2 monographs for Lugol's Solution: Lugol's Solution Weak (0.015%) and Lugol's Solution Strong (5%) (Comité del Formulario Nacional, 2007), which are shown in Appendix 16. The Lugol's Solution Strong is indicated, in combination with other antithyroid medicines, in the pre-operative treatment of hyperthyroidism (2-6 drops, 3 times daily, for 7-14 days); thyrotoxic crisis; neonatal thyrotoxicosis; and in thyroids protection during nuclear emergencies (15 drops daily) (Comité del Formulario Nacional, 2007). The Lugol's Solution Weak is indicated in the prophylaxis and treatment of disorders caused by lack of iodine (Comité del Formulario Nacional, 2007). The majority of the Lugol's Solutions dispensed were not classified (76%) whereas 20% corresponded to Lugol's Solution Strong and 4% were classified as Lugol's Solution Weak. Apart from the Lugol's Solution, 2 more compounded medicines were reported by given title: Shohl's Solution (n=594; 2 hospitals); and Joulie's Solution (n=4; 1 hospital). A formulary for the compounded medicines reported by given title is shown in Appendix 16.

Oral liquids including more than 1 active substance were dispensed by 6 hospitals in a total of 2,979 multidose containers, which corresponded to only 5% of all oral liquids. In decreasing order, the active substances dispensed in combination were: meglumine amidotrizoate and sodium amidotrizoate (Gastrografin, see below); levodopa and carbidopa; hydrochlorothiazide and spironolactone; amiloride HCl and hydrochlorothiazide; isoniazid and pyridoxine HCl; and colistin sulfate, tobramycin and nystatin.

A total of 5 proprietary medicines, in a sum of 2,444 multidose containers, were reported by 4 hospitals as part of the multidose oral liquids dispensed, as follows: CellCept (mycophenolate mofetil); Colimicina (colistin sulfate); Gastrografin (meglumine amidotrizoate and sodium amidotrizoate); Kreon (pancreatin) and Vibracina (doxycycline hyclate).

The top 5 therapeutic groups are listed in Table 11.7. The most frequent therapeutic group was GI drugs, which was constituted by 4 different active substances, dispensed in a total of 14,749 multidose containers. All 5 groups included active substances that were part of the top 20 shown above (Figure 11.7). The group represented by most active substances was cardiovascular drugs which included 31 active substances dispensed as multidose oral liquids. Cardiovascular drugs and "analgesics, anti-inflammatory drugs and antipyretics" were also part of the top 5 therapeutic groups in oral solids (Table 11.3). The top 5 therapeutic groups represented almost 60% of all multidose oral liquids dispensed, which suggests that there is a demand for compounded medicines in Spain particularly for these 5 groups.

Table 11.7 Top 5 therapeutic groups ranked by number of multidose oral liquids dispensed.

Therapeutic groups	Number of active substances	Active substances included in top 20	Number of containers
GI drugs	4	Omeprazole Ranitidine	14,749
Cardiovascular drugs	31	Captopril Propranolol HCl	7,427
Antibacterials	12	Colistin sulfate Vancomycin	5,387
Analgesics, anti-inflammatory drugs and antipyretics	6	Methadone HCl	4,339
Antifungals	2	Amphotericin B	3,557

GI drugs and cardiovascular drugs were the most frequent therapeutic groups, which is consistent with the fact that diseases of the circulatory system and digestive system corresponded to the major causes of discharge from all Spanish hospitals, as shown in Figure 11.8.

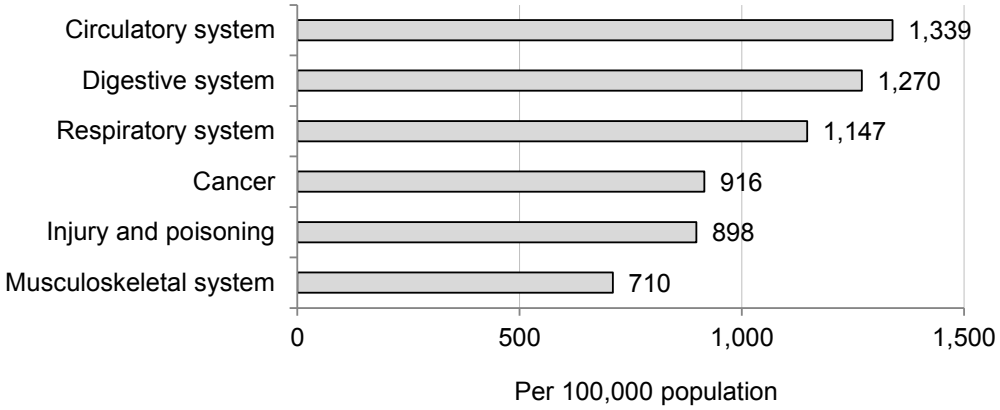


Figure 11.8 Number of patients per 100,000 population discharged from all hospitals (including through death) in Spain during 2005 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

Solutions and suspensions were reported by 26 hospitals, in a total of 48,321 multidose containers, corresponding to the most frequently reported oral liquids. Solutions and suspensions were reported in almost equal quantities but it is likely that classification errors occurred (Section 2.1.3). Furthermore, it is likely that the majority of the "not classified" (Figure 11.6) were also solutions or suspensions and, in this case, over 90% of solutions and suspensions were dispensed. The top 5 active substances dispensed as solutions and suspensions corresponded to the top 5 active substances dispensed as multidose oral liquids (Table 11.6).

Syrups were dispensed both as multidose and unidose oral liquids. Multidose syrups were reported by 19 hospitals in a total of 4,343 containers, which represented only 7.24% of all oral liquids (Figure 11.6), though there may have been classification errors (Section 2.1.3). The top 5 active substances accounted for 70% of all syrups dispensed and corresponded to (in decreasing order): midazolam, ranitidine, chloral hydrate, dexamethasone and potassium iodide. These are all part of the top 20 active substances dispensed as multidose oral liquids (Figure 11.7). Unidose syrups were

reported by 1 hospital, in a total sum of 3,263 oral syringes (5 mL) of propranolol HCl 1 mg/mL.

Tinctures (Belladonna Tincture) were reported by 1 hospital, in a sum of 106 containers of 10 mL each. Considering that therapeutic doses of Belladonna Tincture range from 0.5 mL to 2 mL (Marriott *et al.*, 2010), the 10 mL containers dispensed were assumed multidose. Elixirs (cyclophosphamide 10 mg/mL and 20 mg/mL) were reported by 2 hospitals, in a total of 12 multidose containers. Finally, oral drops were reported by 1 hospital and only 1 container of atropine sulfate (20 mL) was dispensed. However, oral drops may have been classified as solutions or suspensions instead (Section 2.1.3). The tinctures, elixirs and oral drops accounted for only 0.2% of all multidose oral liquids (Figure 11.6).

Multidose oral liquids may be quantitatively compared to the oral solids dispensed (in packs). Assuming all oral solids were dispensed in packs of 100 units (Section 11.4.1), the 1,052,518 individual units of oral solids corresponded approximately to 10,525 packs of oral solids. Therefore, when the 60,117 units of multidose oral liquids are compared to the 10,525 packs of oral solids, it is concluded that oral liquids were dispensed in larger quantities than oral solids. This finding clarifies the conclusion of Brion *et al.* (2003) that, in Spain, a "non-well defined combination of liquids, powders and capsules is dispensed". However, it disagrees with Díaz *et al.* (2007), who concluded in 2007 that the most frequently dispensed dosage form at their hospital was sachets.

Unidose oral liquids were dispensed in a total of 59,142 units (from 1 mL to 30 mL) by 9 hospitals. In fact, only 4 hospitals reported oral syringes but, considering the quantities dispensed for selected compounded medicines, it was assumed that 9 hospitals dispensed unidose oral liquids. In total, 20 active substances from 12 therapeutic groups were reported. The top 5 active substances (shown in Table 11.8) represented 74% of the active substances dispensed as unidose oral liquids. Of these, only barium sulfate and nystatin were not included in the top 5 active substances dispensed as multidose oral liquids. Therefore, it is concluded that methadone HCl,

omeprazole and ranitidine were the active substances most frequently dispensed as oral liquids (both unidose and multidose).

Table 11.8 Compounded medicines most frequently dispensed as unidose oral liquids.

Active substances	Strengths	Number of hospitals	Number of units
Barium sulfate	*not specified*	1	11,448
Nystatin	1,000,000 IU/mL	1	10,448
Ranitidine	5 mg/mL	3	8,856
Methadone HCl	1-20 mg/mL	2	8,400
Omeprazole	2 mg/mL 20 mg/mL	2	4,793

The multidose oral liquids dispensed may be quantitatively compared to the unidose oral liquids (in packs). Considering that the unidose (oral syringes) were dispensed in packs of 12 units (Section 2.3.1), the 59,142 individual units corresponded approximately to 4,929 packs of oral liquids (of 12 units each). Therefore, when the 60,117 multidose containers are compared to the 4,929 packs of unidose oral liquids, it is concluded that multidose containers were clearly dispensed in larger quantities than the unidose/oral syringes.

11.4.4 **Oromucosal preparations**

In Spain, oromucosal preparations were reported by 8 hospitals (27% of all participants) and these were reported as solutions, suspensions, gels, ointments and gargles, in a total of 4,531 multidose containers. The most frequently dispensed oromucosal preparations are shown in Table 11.9, which corresponded to 88% of all oromucosal preparations reported.

Table 11.9 Oromucosal preparations most frequently dispensed in Spain.

Oromucosal preparations	Number of hospitals	Number of containers
Anaesthetic solution	1	1,453
Oral decontamination preparation	1	1,015
Mouthwash for CIOM	6	984
Gargle solution	2	539

- The anaesthetic solution was reported by only 1 hospital and included nystatin, mepivacaine HCl, sodium bicarbonate and hexetidine, in 500 mL containers.
- The oral decontamination preparation was reported by another hospital and included tobramycin sulfate, amphotericin B and colistin sulfate. It was dispensed both as suspensions (2-6 L) and ointments (100-500 g); the large quantities reported suggest that these were not prepared for individual patients but to the hospitals' wards instead.
- The mouthwash for CIOM was reported by 6 hospitals and was also prepared in large scale to be dispensed to the wards. The composition of this mouthwash varied slightly within hospitals and corresponded to a sodium bicarbonate solution (in most cases) including 1 or more of the following active substances: gentamicin sulfate (antibacterials); nystatin (antifungals); hydrocortisone and methylprednisolone (corticosteroids); chlorhexidine (disinfectants and preservatives); and lidocaine and mepivacaine HCl (local anaesthetics).

These 3 oromucosal preparations are very similar in their composition and are mainly constituted by a combination of antibacterials, antifungals, disinfectants and preservatives and/or local anaesthetics. In total, these were dispensed in a sum of 3,452 multidose containers, which represented 76% of all oromucosal preparations.

- The gargle solution[51] was reported by 2 hospitals in a sum of 539 multidose containers and was prepared on large scale to be dispensed to the wards. This solution is included in the Spanish national formulary and it is indicated as a mouth antiseptic for aphthous ulcers and stomatitis (Comité del Formulario Nacional, 2007). The composition of this officinal preparation includes borax in glycerol (Appendix 16), which was formerly used as paints for the throat, tongue and mouth but should no longer be used because of toxicity risks (*Martindale 35,* 2007). Since the Spanish national formulary is the official reference for pharmaceutical compounding in this country (Section 12.2.2), this formula in particular should be revised.

[51]Gargles are aqueous solutions intended for gargling to obtain local effect and are not meant to be swallowed (EDQM, 2007).

11.5 **Summary**

- Compounded medicines (both sterile and non-sterile) are commonly prepared in hospital and community pharmacies in Spain. Apart from these, compounded medicines may also be prepared by other "entities previously authorised" which, so far, correspond to the regional boards of pharmacy of selected autonomous communities.
- Legislation on pharmaceutical compounding is detailed and includes GCP. Professional organisations are common across the country and numerous compounding courses and events are organised throughout the year. Information sources, including an official national formulary, are frequent in Spain.
- A purposive sample of 40 hospitals was included in the research and a response rate of 78% was obtained. A total of 281 different active substances (including 9 NTI drugs) was reported, corresponding to 35 different therapeutic groups. The top 3 therapeutic groups were cardiovascular drugs (n=39), nutritional agents and vitamins (n=34) and antibacterials (n=31). Placebo was dispensed in a total sum of 27,703 units of capsules (n=14).
- Oral solid dosage forms were reported by 93% of all participant hospitals and included capsules, oral powders and powders for oral liquids. Capsules were dispensed in a total of 1,033,665 units (over 90% of all oral solids) and the top 5 active substances were: ribavirin, dexamethasone, sildenafil citrate, bosentan and fludrocortisone acetate. Oral powders (mainly sachets) were dispensed in a total of 16,275 units (less than 5% of all oral solids) and the top 5 active substances were: hydrochlorothiazide, calcium polystyrene sulfonate, aspirin, sucrose and monobasic sodium phosphate. Powders for oral liquids were dispensed in a total sum of 2,578 units (less than 2% of all oral solids).
- Oral liquid dosage forms were reported by 90% of all participant hospitals and included solutions and suspensions, syrups, tinctures, oral drops and elixirs (multidose); oral syringes (unidose). Multidose oral liquids were dispensed in a total sum of 60,117 containers and the top 5 active substances were: omeprazole, methadone HCl, colistin sulfate, amphotericin B and ranitidine.
- Solutions and suspensions were dispensed in a total of 48,321 multidose containers (over 80% of all multidose oral liquids) and the top 5 active substances corresponded to the top 5 of multidose oral liquids. Syrups were dispensed in 4,343 multidose containers (over 7% of all multidose oral liquids) and the top 5 active substances were: midazolam, ranitidine, chloral hydrate, dexamethasone and potassium iodide. Tinctures, elixirs and oral drops accounted for only 0.2% of all multidose oral liquids dispensed. Unidose oral liquids were dispensed in a total of 59,142 units and the top 5 active substances correspond to the top 5 of multidose oral liquids, with the exception of nystatin and barium sulfate. Oral liquids were dispensed in larger quantities than oral solids.
- Oromucosal preparations were reported in a total of 4,531 multidose containers and the most frequently dispensed preparations included a combination of antibacterials, antifungals, disinfectants and preservatives and/or local anaesthetics.

12. **Compounding in France**

France is one of the 6 founding member states of the EU and its official language is French (*Europa*, 2009). France is the largest EU country, with a surface area of 544,000 Km^2, and is the second most populated EU country, with a population of 63.4 million in 2007 (Figure 2.2) (*Europa*, 2008).

In 2005, there were 2,856 hospitals in France (ratio of 4.68 hospitals per 100,000 population) and, in 2006, there were a total of 439,765 hospital beds (ratio of 716.78 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2007, there were 70,498 pharmacists in France (ratio of 113.82 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4). According to the EAHP survey, the average number of pharmacists in French hospitals is 3.3 pharmacists per hospital, which is lower than the European average of 4.7. According to Cornette and Jolivet (2007), although the number of hospital pharmacists in France has greatly increased over the past decade, this number is still insufficient considering the responsibilities and duties of hospital pharmacists. French hospitals have an average of 7.7 qualified pharmacy technicians/assistants per hospital, which is higher than the European average of 6. Regarding non-qualified pharmacy assistants, France has an average of 0.7 (EAHP, 2005; Hartmann, 2010). Qualified pharmacy technicians/assistants must have at least a bachelor's degree and 2 years of training, plus a 3rd year of hospital specialisation for a permanent job in a French hospital pharmacy (Cornette and Jolivet, 2007).

Prot-Labarthe *et al.* (2007) compared pharmacy practices at the French maternal and children's teaching hospital in Paris - *Hôpital Robert Debré* - with a similar institution in Canada. According to their findings, the practice in France seems to be more product-oriented whereas in Canada it seems more patient-oriented. The French hospital prepared annually a total of approximately 95,000 compounded medicines: 3.5% oral preparations; 78.8% other non-sterile preparations; 3.9% sterile preparations; 10.9% TPN infusion bags; and 2.9% sterile cytotoxic preparations. A test for uniformity of

content is performed for each batch of capsules in this hospital; and both sterile and non-sterile compounded medicines are identified with patient-specific labels (Prot-Labarthe *et al.*, 2007).

Fontan *et al.* (2000) identified the compounded medicines prepared and dispensed for paediatric patients in 53 French hospital pharmacies in 1997. According to their findings, oral dosage forms were more frequently dispensed than sterile dosage forms. Capsules were the most frequently dispensed oral dosage form (97%) and were dispensed by 96% of the participant hospitals. A total of 220 active substances were dispensed as capsules and the top 10 (and the respective number of strengths) were as follows: diphemanil (n=38), captopril (n=36), fludrocortisone (n=21), hydrocortisone (n=25), ranitidine (n=36), spironolactone (n=46), ursodeoxycholic acid (n=19), capsules for decontamination (n=1), caloreen (dextrin; n=2) and phenytoin (n=26). Oral liquids, on the other hand, were dispensed by 62% of the participant hospitals and represented only 3% of all oral compounded medicines dispensed. This study demonstrated the need and importance of oral compounded medicines, in particular capsules, for paediatric patients in France (Fontan *et al.*, 2000). Storme (2010) also stated that capsules were the most frequently compounded medicines in France. When administered to children, capsules are opened just before administration and their contents added to liquids or food. Although this administration is complicated, capsules are very popular in France because of their likely stability and easy preparation (Storme, 2010).

12.1 **Legislation**

According to the French legislation, compounded medicines may be classified into 4 categories, as follows:

1. *Préparation Magistrale* (magistral preparation): any medicine prepared according to a medical prescription intended for a specific disease and prepared extemporaneously in a pharmacy (*Legifrance*, 2010a). Magistral preparations are prepared individually.
2. *Préparation Hospitalière* (hospital preparation): any medicine prepared according to the indications of the French Pharmacopoeia and in conformity

with GCP. Hospital preparations are dispensed by the hospital pharmacy to one or more patients according to a medical prescription, and these preparations must be declared to the AFSSAPS (Section 12.2.1) (*Legifrance*, 2010a). Hospital preparations are usually prepared in batches.

3. *Préparation Officinale* (officinal preparation): any medicine prepared in a pharmacy that is included in the French Pharmacopoeia or in the national formulary and is intended to be directly dispensed to patients assisted by that pharmacy (*Legifrance*, 2010a).

4. *Produit Officinal Divisé* (POD) (divided officinal product): any chemical product or medicine included in the French Pharmacopoeia that is prepared and packaged in advance by a pharmaceutical institution, the community pharmacy that sells it, or a hospital pharmacy (*Legifrance*, 2010a).

In France, hospital pharmacies are named "*pharmacies à usage intérieur*" and hospitals may have one or more pharmacies (*Legifrance*, 2010b). The duties of these pharmacies are divided into compulsory duties and optional duties (performed if needed, but only after a special authorisation). Part of the compulsory duties is to compound magistral preparations (from bulk raw materials or proprietary medicines) and PODs (*Legifrance*, 2010c). Optional duties may only be authorised if the hospital pharmacy meets the necessary requirements in terms of facilities, personnel, equipment and information systems. If hospital pharmacies do not have the necessary resources, another institution may be subcontracted to perform the optional duties. Part of the list of optional duties is to compound hospital preparations (*Legifrance*, 2010d). Since 2004, all hospital pharmacies that are authorised to compound hospital preparations must report electronically the medicines prepared to AFSSAPS (Section 12.2.1). The aim of this declaration is to gather complete information regarding compounded medicines prepared in large quantities so that essential and non-essential medicines are identified. Essential hospital preparations could then be developed commercially, if pharmaceutical companies are interested; otherwise, AFSSAPS would standardise their preparation and QC through the PUI-DLC department (Section 12.2.1) (Cornette and Jolivet, 2007; Crauste-Manciet, 2007; Storme, 2010). French legislation states that the preparation of compounded medicines must be in accordance with the GCP - *"bonnes pratiques de préparation"* - established

by the AFSSAPS (Section 12.2.1) (*Legifrance*, 2010e). The GCP (published in December 2007) is a legally binding document for the preparation of compounded medicines; it is based on industrial GMP (Storme, 2010) and aims to guarantee the quality of the medicines prepared in hospital and community pharmacies (Chauvé, 2007). This reference document is divided into 4 parts: part 1 is composed of 5 general chapters (including preparation, QC and documentation); part 2 is composed of specific guidelines common to community and hospital pharmacies (e.g. preparation of sterile compounded medicines); part 3 is composed of specific guidelines for hospital pharmacies only (e.g. preparation of radiopharmaceuticals); and part 4 comprises annexes (Crauste-Manciet, 2007; AFSSAPS, 2010b). Adverse compounding incidents have happened in France, which raise the awareness for good quality compounding, such as the intoxication of 48 patients with capsules containing an overdose of thyroid extracts prepared at a community pharmacy (Perez, 2007). In the opinion of Chauvé (2007), GCP is a complete, precise and realistic document that does not represent an obstacle to compounding but, instead, represents a means to guarantee health safety.

12.2 **Professional organisations and information sources**

12.2.1 **French professional organisations**

- *Agence Française de Sécurité Sanitaire des Produits de Santé (*AFSSAPS): is the French Medicines Agency, a public institution guided by the Ministry of Health that was created in 1999 with the mission to guaranty the quality and safe use of health products, including medicines and raw materials. This institution performs activities of evaluation, control and inspection; it employs nearly 1,000 professionals and is an important component of the public health system (AFSSAPS, 2010a).
- *Pharmacies à Usage Intérieur - Département des Laboratoires de Contrôles* (PUI-DLC): is the department of AFSSAPS responsible for laboratory control of batch preparations. It was founded in 2008 with the main goal to improve the quality of batch preparations and to standardise their preparation and QC throughout France. Monographs for batch preparations may be submitted to this department and, once approved, are published in

the French national formulary (Section 12.2.2), setting the standards for future preparations (Storme, 2010).

- *Societe des Officinaux sous-Traitants en Preparations* (SOTP): is a society of community pharmacists that prepare compounded medicines for other pharmacies (third-party) (SOTP, no date). According to Fabien Bruno[52], the SOTP is constituted by approximately 40 community pharmacists and aims to promote and support pharmaceutical compounding in France (Bruno, 2011).

12.2.2 **French information sources**

- *Pharmacopée Française*: is the French Pharmacopoeia, an official publication for health professionals that includes the texts of the PhEur and also nation-specific texts (*Legifrance*, 2010f). It was first published in 1983 and is now in its 10th edition The French Pharmacopoeia currently contains part XI - *Formulaire National* - that aims to replace the national formulary published in 1974 (now obsolete) (AFSSAPS, 2010e).
- *Formulaire National:* is the French national formulary, established by the national commission of the French Pharmacopoeia, which corresponds to a collection of the standardised formulae from the pharmacopoeia. This formulary comprises 50 complete monographs that not only include the pharmaceutical product's formula and preparation method but also the QC method, storage conditions and labelling. Potential new formulae for the national formulary include formulae with demonstrated clinical effect; formulae currently prepared in community pharmacies; and formulae reported to AFSSAPS by hospital pharmacies. When a preparation is included in the national formulary, the pharmacist must comply with the monograph as described (Chaumeil, 2007; AFSSAPS, 2010b; 2010c).
- *Défense de la Préparation Officinale*: is a report that was developed by French compounding stakeholders, working in different professional activities, and aimed to promote and support pharmaceutical compounding in France. Fabien Bruno was part of this working group (Bruno, 2011; Laurent *et al.,* 2011).

[52]Fabien Bruno is the vice-president of the SOTP and responsible pharmacist for *Pharmacie / Laboratoire Delpeche*, in Paris.

12.3 **Methods**

France was the first European country, to be included in the research, whose data on pharmaceutical compounding had already being collected by another institution. Hospital preparations must be reported periodically to AFSSAPS by all hospital pharmacies that are authorised to compound hospital preparations. Since magistral preparations are prepared individually and hospital preparations are usually prepared in larger quantities, data on the hospital preparations most frequently dispensed by the French hospitals was precisely the relevant data envisaged for this study. Consequently, and to avoid duplication of data collection, it was decided not to develop a customised questionnaire but, instead, to request the relevant data from AFSSAPS. Therefore, AFSSAPS was first contacted by email in August 2007 and by telephone in January 2008, with the request for them to supply the list of oral hospital preparations most frequently dispensed by the French hospital pharmacies, in the latest available year.

In May 2008, AFSSAPS agreed to share the requested data for analysis and inclusion in the Europe-wide study. In France, the research project consisted then in analysing the data received electronically by AFSSAPS and not, as in all previous European countries, in collecting comparable data by means of a country-specific questionnaire.

12.4 **Results and discussion**

The “List of oral hospital preparations declared electronically to AFSSAPS by the hospital pharmacies between 23 November 2004 and 7 May 2008” was received by post in June 2008, and soon after by email, from the AFSSAPS: *Direction de l’Evaluation des Médicaments et des Produits Biologiques*, *Département de l’Evaluation des Essais Cliniques et des Médicaments à Statut Particulier* and *Cellule Préparations Hospitalières*. The complete list included the oral hospital preparations reported to AFSSAPS by 60 French hospital pharmacies, in a total of 3,704 data entries. According to Dichou (2008), there were 2,700 hospital pharmacies in France but only 200 were in fact authorised to compound hospital preparations. However, only 140 declared the hospital preparations to AFSSAPS and, of these, only 60

agreed with AFSSAPS to share their data. As a result, the purposive sample in France was constituted by 60 hospital pharmacies.

For each European country, the objective was to identify the purposive sample of hospitals that dispensed the largest quantities of compounded medicines throughout the country. In France, however, it was not possible to conclude that the 60 hospitals were the ones that dispensed the most. In addition, the names and location of the hospitals were not disclosed and, hence, it was not possible to identify their distribution across the country.

The participant hospitals shared their data in different periods of time as, for example, 25 July 2005 - 24 January 2006 (hospital X); 10 August 2006 - 9 February 2007 (hospital Y); 25 July 2007 - 24 January 2008 (hospital Z). For this reason, it was not possible to extract the data relative to one complete year only. Consequently, the list provided was analysed as a whole, from the 23 November 2004 to the 7 May 2008, as opposed to the one-year studies undertaken in the previous EU countries.

AFSSAPS acknowledges that the electronic input of hospital preparations by the pharmacies is subject to error (Belorgey-Bismut, 2008). In fact, when the list provided was processed and analysed, it was found that some data entries were indeed incomplete or inaccurate as, for example, capsules of ursodeoxycholic acid being reported as 50 mg and 51 mg, in the same data entry (hospital X); capsules of 3,4-diaminopyridine 10 mg being reported as a gel, also in the same data entry (hospital Y); potassium chloride 0.7 mg oral solution (hospital Z). Since the identification of the hospital pharmacies was not disclosed by AFSSAPS, it was not possible to check the data entries with the pharmacies that dispensed the respective compounded medicines. However, the complete list of hospital preparations provided was thoroughly and carefully processed and analysed, taking into account the exclusion criteria in Section 2.4.1.

12.4.1 **Active substances**

A list of the active substances dispensed as oral hospital preparations is presented in Table 12.1. Active substances were grouped by therapeutic classification (*Martindale 35*, 2007), giving a total of 34 therapeutic groups

and 197 different active substances, similar to the 220 active substances identified by Fontan *et al.* (2000) in a study of 53 hospitals (Section 12). Cardiovascular drugs was the group with the greatest number of different active substances (n=39), followed by antibacterials (n=22) and nutritional agents and vitamins (n=18). Although these active substances were all reported as oral hospital preparations, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: colouring agents (Appendix 25); disinfectants and preservatives (Appendix 12); and supplementary drugs and other substances (Appendix 15). The active substances included in these groups are described in the respective appendixes.

The group “general anaesthetics” included ketamine HCl, which is commonly given by IV injection, infusion or intramuscular injection (*Martindale 35*, 2007). However, it was reported as syrup by 1 hospital and, therefore, it was exceptionally included as for oral use.

A total of 7 NTI drugs (ANVISA, 2007; Appendix 1), were dispensed as oral hospital preparations (underlined in Table 12.1).

The active substances dispensed by most hospitals were: sodium bicarbonate (n=24); captopril, carmine, dexamethasone and spironolactone (n=16-20); 3,4-diaminopyridine, amiodarone, hydrocortisone and sodium chloride (n=10-15).

All active substances reported were included in *Martindale 35* (2007) with the exception of the following:

- Nickel sulfate: reported as capsules (2.5 mg and 11.2 mg) by 2 hospitals (Appendix 26) (Section 4.4.1).
- Potassium dichromate: reported as capsules (7.1 mg) by 1 hospital (Appendix 26). Since chromate is a common cause of contact allergy, it is likely that it was indicated for oral hyposensitization therapy or allergy testing (Rui *et al.*, 2010).

Table 12.1 Active substances dispensed as oral hospital preparations in France (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aspirin, codeine, codeine phosphate, ethylmorphine HCl, indometacin, morphine, morphine HCl, morphine sulfate, paracetamol, sulindac

Anthelmintics
Levamisole HCl

Antibacterials
Amoxicillin, cefuroxime, clavulanic acid, clindamycin, colistin sulfate, demeclocycline HCl, erythromycin, ethambutol HCl, framycetin sulfate, gentamicin sulfate, isoniazid, norfloxacin, ofloxacin, phenoxymethylpenicillin, pristinamycin, pyrazinamide, rifampicin, roxithromycin, sulfadiazine, telithromycin, vancomycin HCl

Antidementia drugs
Donepezil HCl

Antidepressants
Mianserin HCl, paroxetine HCl, paroxetine mesilate, tianeptine sodium, venlafaxine HCl, viloxazine HCl

Antidiabetics
Metformin HCl

Antiepileptics
Clobazam, levetiracetam, phenobarbital, phenytoin, topiramate, vigabatrin

Antigout drugs
Allopurinol

Antihistamines
Alimemazine tartrate

Antimalarials
Pyrimethamine, quinine

Antimyasthenics
3,4-diaminopyridine, fampridine, pyridostigmine bromide

Antineoplastics
Busulfan, hydroxycarbamide, mercaptopurine, methotrexate, tioguanine

Antiparkinsonian drugs
Benserazide, bromocriptine mesilate, levodopa

Antivirals
Valganciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Alprazolam, chloral hydrate, lorazepam, meprobamate, midazolam, oxazepam, pentobarbital, tiapride HCl, zolpidem tartrate, zopiclone

Bronchodilators and anti-asthma drugs
Bambuterol HCl, caffeine, caffeine citrate

Cardiovascular drugs
Acenocoumarol, altizide, amiodarone HCl, amlodipine besilate, atenolol, betaxolol HCl, bisoprolol fumarate, buflomedil HCl, captopril, carvedilol, celiprolol HCl, clonidine, clopidogrel bisulfate, diazoxide, disopyramide, enalapril maleate, flecainide acetate, fluindione, furosemide, hydrochlorothiazide, irbesartan, labetalol HCl, lercanidipine HCl, lisinopril, losartan potassium, mannitol, metoprolol, nadolol, nicardipine HCl, nifedipine, perindopril erbumine, pravastatin sodium, propranolol HCl, quinidine, ramipril, sotalol HCl, spironolactone, verapamil HCl, warfarin sodium

Chelators, antidotes and antagonists
Activated charcoal, calcium polystyrene sulfonate, methionine, methylthioninium chloride, sodium polystyrene sulfonate

Colouring agents
Carmine, carmoisine, erythrosine, ponceau 4R, sunset yellow FCF, tartrazine

Contrast media
Barium sulfate

Corticosteroids
Dexamethasone, dexamethasone acetate, fludrocortisone acetate, hydrocortisone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Ipecacuanha

Disinfectants and preservatives
Alcohol, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite

Electrolytes
Bicarbonate, potassium bicarbonate, potassium chloride, sodium bicarbonate, sodium chloride, sodium citrate

GI drugs
Calcium carbonate, kaolin, lactilol, lactulose, magnesium hydroxide, omeprazole, ranitidine HCl

General anaesthetics
Ketamine HCl

Immunosuppressants
Azathioprine, tacrolimus

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide, pilocarpine

Muscle relaxants
Baclofen, dantrolene sodium

Nutritional agents and vitamins
Ascorbic acid, dextrin, ferrous fumarate, ferrous sulfate, folic acid, folinic acid, fructose, glucose, glutamine, iron, lactose, maltodextrin, maltose, menadione, nicotinamide, sucrose, vitamin B, vitamin E

Prostaglandins
Misoprostol

Supplementary drugs and other substances
Bethanechol chloride, calcium hydroxide, cinchona bark, cobalt chloride, diphemanil metilsulfate, glycerol, indigo carmine, melatonin, menthol, papain, patent blue V, phosphoric acid, riluzole, tolonium chloride, ursodeoxycholic acid, xylose

Thyroid and antithyroid drugs
Carbimazole, iodine, potassium iodide, potassium perchlorate

Urological drugs
Alfuzosin HCl, sildenafil citrate

The majority of oral hospital preparations included 1 active substance only. Multi-drugs were thus uncommon and these included the combination of 2 (mainly) or 3 active substances, as follows:

- 2 active substances (n=12): alcohol and menthol (Appendixes 12 and 15); altizide and spironolactone; amoxicillin and clavulanic acid; butylated hydroxyanisole and butylated hydroxytoluene (Appendix 12); calcium hydroxide and barium sulfate; codeine and ethylmorphine HCl; folic acid and vitamin E; iodine and potassium iodide (Lugol's Solution, Appendix 16); iron and vitamin C; lactilol and mannitol; lactulose and mannitol; and pyrimethamine and sulfadoxine.
- 3 active substances (n=1): quinine, quinidine and cinchona bark (Appendix 15).

Placebo was reported by 8 hospitals, exclusively capsules, in a total of 53,460 units. The French national formulary (Section 12.2.2) comprises a monograph for placebo capsules - Capsules of Placebo for Therapeutic Use - comprising microcrystalline cellulose (diluent) and silica colloidal anhydrous (lubricant) (AFSSAPS, 2010c). According to the French GCP, when a

preparation is included in the national formulary, the pharmacist must comply with formula described (AFSSAPS, 2010b) and, therefore, the placebo capsules reported should have complied with the corresponding monograph in the national formulary.

Oral hospital preparations were also reported by the respective given titles but, since the identification of the hospital pharmacies was not disclosed by AFSSAPS, it was not possible to check their composition. Each given title was reported by only 1 hospital, as follows:

- Capsules: Decontamination Capsules named “Kachouga”; Trimetallic Capsules; Capsules 89 CGV3; and Capsules 555.
- Powders for oral liquids: Powder for Syrup “Kachouga”.
- Oral liquids: Composed Oil; Mixture of Three Oils; Potion “Charrier”; Potion Paregoric; Solute Pectoral for Diabetics; Syrup of “Docteur Blayac” and Treatment of Adult Growth Hormone Deficiency.
- Oral drops: Tincture of “Jaborandi” Solution diluted to ¼ and Tincture of “Laudanum de Sydenham” diluted to ¼.

Capsules for the selective decontamination of the digestive tract (SDD) were also reported (Section 12.4.2).

In addition, 16 hospitals reported proprietary medicines as part of the oral hospital preparations dispensed (both solid and liquid dosage forms). In total, almost 80 different proprietary medicines were reported but, since hospital preparations are usually prepared in large scale (as opposed to magistral preparations that are prepared individually), these should preferably include raw materials in bulk instead (Section 1.1.2.2).

12.4.2 **Oral solids**

Oral solid dosage forms were dispensed by 58 (97%) of the participant hospitals and included capsules, oral powders, powders for oral liquids and tablets. Capsules were the most frequently dispensed dosage form (total of 3,873,453 units) and represented 99.1% of all oral solid hospital preparations. These figures are in accordance with the study undertaken by Fontan *et al.* (2000), in which capsules were dispensed by 96% of the hospitals studied and were also the most frequently dispensed dosage form.

The top 5 hospital preparations dispensed as oral solids are shown in Table 12.2 and corresponded to capsules only. Capsules for SDD, captopril and hydrocortisone were also included in the top 10 identified by Fontan *et al.* (2000). In general, the number of strengths encountered is considerably lower than in their study (e.g. captopril 15 vs 36 strengths; hydrocortisone 12 vs 25 strengths), which may be due to improved standardisation of hospital preparations from 1997 (Fontan *et al.*, 2000) to 2004/2008 (AFSSAPS).

Table 12.2 Top 5 hospital preparations dispensed as oral solids (capsules).

Active substances	**Strengths** (number of strengths)	**Number of hospitals**	**Number of units**
3,4-Diaminopyridine	5-50 mg (5)	15	558,209
Capsules for SDD	n/a	5	473,902
Sodium bicarbonate	125-1,000 mg (4)	24	219,978
Captopril	0.5-25 mg (15)	16	199,862
Hydrocortisone	0.5-9 mg (12)	10	184,817

Capsules for SDD were reported for both adult and paediatric patients by a total of 5 hospitals. The selective decontamination of the digestive tract is an infection-prevention regimen used in critically ill patients that aims to eradicate aerobic (potentially pathogenic) microorganisms from the oropharynx, stomach and gut. The SDD regimen includes the oral administration of antibiotics such as polymyxin E, tobramycin and amphotericin B (Jonge *et al.*, 2003).

Sodium bicarbonate (capsules) is included in the French national formulary (Section 12.2.2) and the monograph states the same 4 strengths reported here: 125 mg, 250 mg, 500 mg and 1,000 mg. The excipient (diluent) stated in the monograph is microcrystalline cellulose (AFSSAPS, 2010c). Because these capsules are included in the French national formulary, the hospital preparations reported should have complied with corresponding monograph (AFSSAPS, 2010b).

In France, conditions of the digestive and circulatory systems were the major causes of discharge from all hospitals (including through death) during 2005

(Figure 12.1), which is consistent with the fact that capsules for SDD and captopril are part of the top 5 hospital preparations.

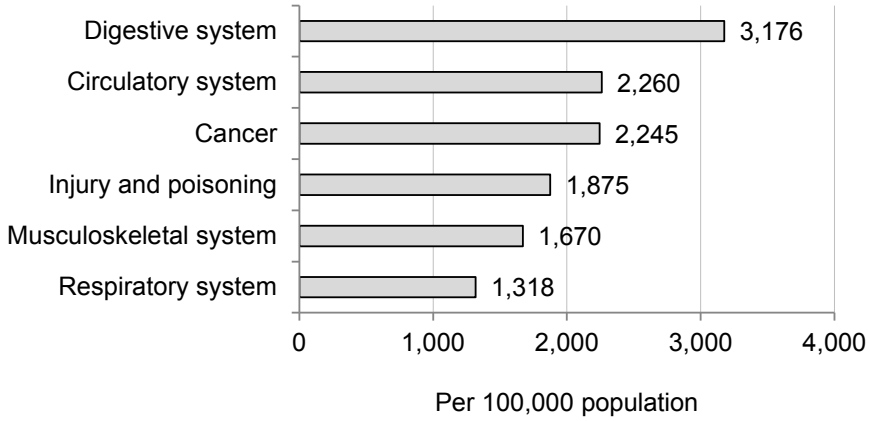


Figure 12.1 Number of patients per 100,000 population discharged from all hospitals (including through death) in France during 2005 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

Tablets were the next most frequently dispensed oral solids (total of 23,996 units; 0.6%) and these were reported by 6 (10%) participant hospitals. The top 5 active substances dispensed were, in decreasing order: sodium chloride (500 mg), calcium carbonate (500 mg), celiprolol HCl (100 mg), spironolactone (1 mg, 2.5 mg and 5 mg) and amiodarone HCl (5 mg). Spironolactone was also part of the top 10 identified by Fontan *et al.* (2000) but in fewer strengths compared to their study. The French national formulary includes monographs for tablets of both sodium chloride and calcium carbonate (AFSSAPS, 2010d).

Powders for oral liquids were reported by 5 (8%) hospitals, in a sum of 8,688 units (0.2%). In total, only 5 different hospital preparations were reported and these corresponded (in decreasing order) to the following: sodium polystyrene sulfonate (15 g), Powder for Syrup “Kachouga”, pentobarbital (100 mg), sucrose (3.75 g) and sodium metabisulfite (25 mg; Appendix 12). Oral powders were reported by 5 (8%) of participant hospitals, in a sum of 4,484 units (0.1%). The top 5 active substances dispensed were, in decreasing order: caffeine (150 mg), glucose (50 g and 75 g), lactose (50 g), erythromycin (500 mg and 1,000 mg) and xylose (25 g; Appendix 15).

The oral solids dispensed were reported by number of individual units only, in a total of 3,910,621 units. The number of packs of oral solids was not

provided and, therefore, it was not possible to conclude the number of times each hospital preparation was dispensed (as a pack). Nevertheless, since capsules corresponded to 99.1% of all oral solids dispensed, it is possible to estimate that each oral solid hospital preparation was dispensed, on average, as packs of 50 individual units (Section 2.1.3). Consequently, it is possible to estimate that oral solids were dispensed in a total of 78,212 packs (of 50 individual units).

12.4.3 **Oral liquids**

Oral liquid dosage forms were reported by 34 (54%) hospitals, which is similar to the results by Fontan *et al.* (2000), in which oral liquids were dispensed by 62% participant hospitals. The oral liquids dispensed included multidose and unidose dosage forms, as follows: solutions, suspensions, syrups and oral drops (multidose) and oral syringes (unidose). The most frequently dispensed dosage forms were solutions and suspensions (total of 29,475 units), which represented 62% of all multidose oral liquids dispensed (Figure 12.2). The top 5 hospital preparations dispensed as solutions and suspensions were, in decreasing order: sucrose (4 hospitals), mannitol and lactulose (1 hospital), vitamin E (1 hospital), folinic acid (1 hospital) and Potion “Charrier” (1 hospital). As previously stated, many data entries were incomplete or inaccurate (Section 12.4) and, therefore, the individual strengths and pack sizes of oral liquids will not be addressed in detail.

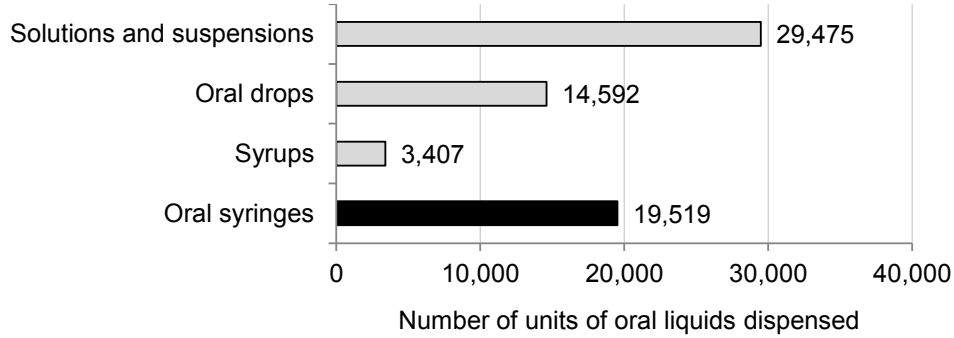


Figure 12.2 Oral liquid dosage forms dispensed per number of units.

Oral drops were the next most frequently dispensed dosage forms (total of 14,592 units), which represented 31% of all multidose oral liquids dispensed (Figure 12.2) and these were reported by 5 hospital pharmacies. In total, only

4 different hospital preparations were reported, namely (in decreasing order): Tincture of “Laudanum de Sydenham” diluted to ¼ (1 hospital); Tincture of “Jaborandi” Solution diluted to ¼ (1 hospital); iodine and potassium iodide (3 hospitals); and codeine and ethylmorphine HCl (1 hospital). It was not possible to check the composition of the oral hospital preparations reported by given titles since the identification of the hospital pharmacies was not disclosed by AFSSAPS (Section 12.4.1).

Syrups were reported by 15 participant hospitals, in a total of 3,407 multidose units, which represented 7% of all multidose oral liquids dispensed (Figure 12.2). The top 5 hospital preparations dispensed as syrups were (in decreasing order): sodium citrate (1 hospital); chloral hydrate (5 hospitals); ketamine HCl (1 hospital); ipecacuanha (6 hospitals); and Syrup of “Docteur Blayac” (1 hospital). The French national formulary includes a monograph for “Syrup of Ipecacuanha” (AFSSAPS, 2010d). As mentioned in Section 2.1.3, classification of some oral liquids by the hospital pharmacies may not have been accurate.

Oral syringes were reported as unidose oral liquids, in a total of 19,519 individual units (Figure 12.2), by 2 hospital pharmacies. Only 2 active substances were dispensed as oral syringes, namely (in decreasing order): alimemazine tartrate (30-100 mg/5 mL, 5 strengths) and sucrose (1 strength).

In total, hospital pharmacies dispensed 47,474 multidose oral liquids and 19,519 unidose oral liquids. The quantities of multidose and unidose oral liquids cannot be directly compared as 1 syringe (unidose) is equivalent only to one dose of the multidose oral liquids. Nevertheless, when both figures are compared to the estimation of 78,212 oral solids (packs of 50 units) (Section 12.4.2), it is possible to conclude that oral solids (capsules) were more frequently dispensed than oral liquid dosage forms (Figure 12.3). This fact is in accordance with Brion *et al.* (2003), who also concluded that capsules were the most frequently dispensed oral dosage forms in France.

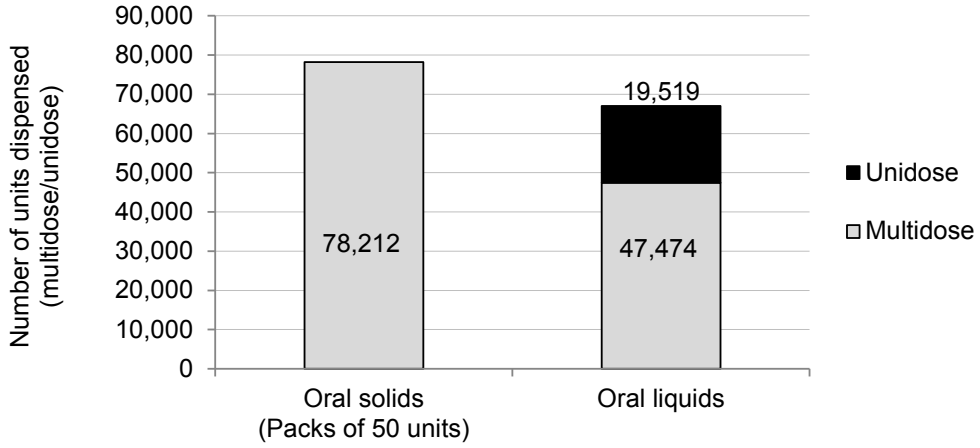


Figure 12.3 Number of units of oral solid and oral liquid dosage forms (unidose and multidose) dispensed by the participant hospitals.

12.4.4 **Oromucosal preparations**

In France, the "List of oral hospital preparations" shared by AFSSAPS included only 2 hospital preparations classified as oromucosal, namely: methylthioninium chloride solution 1% and Lugol's Solution 2%. Since the French database included inaccurate entries (Section 12.4), it was assumed that these 2 oromucosal preparations corresponded, instead, to oral hospital preparations (as shared by AFSSAPS). Therefore, no oromucosal preparations were considered in France.

12.5 **Summary**

- Compounded medicines in France may be classified into 4 categories: magistral preparations, hospital preparations, officinal preparations and divided officinal products. Hospital preparations must be declared to AFSSAPS and are usually prepared in batches. The preparation of compounded medicines must be in accordance with French GCP.
- PUI-DLC (AFSSAPS), SOTP and *Défense de la Préparation Officinale* represent 3 professional organisations that support pharmaceutical compounding in France. The national formulary is part of the French Pharmacopoeia and includes 50 standardised formulae.
- Data collection was not undertaken in France. Instead, the "List of oral hospital preparations declared electronically to AFSSAPS by the hospital pharmacies between 23 November 2004 and 7 May 2008" was shared by AFSSAPS for analysis. A total of 60 French hospitals were included in the research.
- According to the data shared, a total of 197 active substances (including 7 NTI drugs) were dispensed as oral hospital preparations, corresponding to 34 therapeutic groups.
- The therapeutic groups with the greatest number of different active substances were: cardiovascular drugs (n=39), antibacterials (n=22) and nutritional agents and vitamins (n=18). Placebo was dispensed in a total sum of 53,460 units of capsules (n=8).
- Oral solid dosage forms were dispensed in 97% of hospitals and included capsules, tablets, powders for oral liquids and oral powders. Capsules were dispensed in a total of 3,873,453 units (99.1% of oral solids) and the top 5 active substances were: 3,4-diaminopyridine, *capsules for SDD*, sodium bicarbonate, captopril and hydrocortisone. Tablets were dispensed in a total of 23,996 units (0.6% of oral solids) and the top 5 active substances were: sodium chloride, calcium carbonate, celiprolol HCl, spironolactone and amiodarone HCl. Powders for oral liquids were dispensed in a total of 8,688 units (0.2%) and oral powders in a total of 4,484 units (0.1% of oral solids).
- Oral liquid dosage forms were dispensed in 54% of hospitals and included solutions and suspensions, oral drops and syrups (multidose) and oral syringes (unidose).
- Solutions and suspensions were dispensed in a total of 29,475 containers (62% of multidose oral liquids) and the top 5 active substances were: sucrose, mannitol and lactulose, vitamin E, folinic acid and *Potion "Charrier"*. Oral drops were dispensed in a total of 14,592 containers (31% of multidose oral liquids) and the top 3 hospital preparations were: Tincture of "Laudanum de Sydenham" diluted to ¼; Tincture of "Jaborandi" Solution diluted to ¼; iodine and potassium iodide. Syrups were dispensed in a total of 3,407 containers (7% of multidose oral liquids) and the top 5 active substances were: sodium citrate, chloral hydrate, ketamine HCl, ipecacuanha and Syrup of "Docteur Blayac". Oral syringes (alimemazine tartrate and sucrose) were dispensed in a total of 19,519 unidose oral liquids.
- Oral solids were dispensed in larger quantities than oral liquids.

13. **Compounding in Germany**

Germany is one of the 6 founding member states of the EU and its official language is German (the most widely spoken first language in the EU). Germany is the most populated country in the EU, with a population of 82.4 million in 2007 (Figure 2.2), and is physically the 4th largest EU country, occupying a surface area of 357,000 Km^2 from the North Sea and the Baltic in the North, to the alps in the South (*Europa*, 2008; 2009).

In 2006, there were 3,359 hospitals in Germany (ratio of 4.07 hospitals per 100,000 population) and a total of 683,484 hospital beds (ratio of 829.09 hospital beds per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 3).

In 2007, there were 49,528 pharmacists in Germany (ratio of 59.87 pharmacists per 100,000 population) (WHO Regional Office for Europe, 2010) (Appendix 4). In total, only 3.2% of German pharmacists work in hospital pharmacy (ABDA, 2010). According to the EAHP survey, the average number of pharmacists per German hospital is 4.0, which is lower than the European average of 4.7. Moreover, German hospitals have an average of 5.0 qualified pharmacy technicians/assistants per hospital, which is also lower than the European average of 6. Regarding non-qualified pharmacy assistants per hospital, Germany has an average of 4.3 (EAHP, 2005; Hartmann, 2010).

In Germany, pharmaceutical compounding is part of pharmacists' activity in both community (Zueck, 2008) and hospital pharmacies (Ohem, 2007) and is considered an indispensable part of therapy (Kinget, 2009). Upon a compounding prescription, pharmacists have to prepare the respective compounded medicine(s) and all 21,500 community pharmacies in Germany are capable of performing, at least, basic compounding for their patients. It has been estimated that around 25 million compounded medicines are prepared in the community setting every year (around 1,100 compounded medicines per pharmacy per year) (Zueck, 2008; Kinget, 2009). The quality of the compounded medicines prepared is of major concern in Germany and community pharmacies regularly participate in quality testing by submitting

selected compounded medicines, on a voluntary basis, to the "Central Laboratory of German Pharmacists" (*Zentrallaboratorium Deutscher Apotheker e.V.*). Quality testing in Germany is recommended at least once a year so that pharmacists assess and optimise their compounding practices (Zueck, 2008; Kinget, 2009).

Hospitals in Germany are not obliged to have their own hospital pharmacy as medicines may be supplied by the hospital pharmacy of another hospital or even by a community pharmacy (EAHP and HOPE, 2002; Amann and Hoppe-Tichy, 2007). In fact, 78% of German hospitals do not have a pharmacy of their own (61% are supplied by other hospitals and 39% by community pharmacies). Considering the German hospitals that do have a pharmacy on their own, 71% of the hospital pharmacies supply not only their own hospital but also other hospitals (Amann and Hoppe-Tichy, 2007). The total number of German hospitals has been decreasing and more and more hospitals are being supplied by other hospital pharmacies; the larger hospitals in Germany are the ones most likely to have a pharmacy on their own (EAHP and HOPE, 2002; Krämer, 2007).

Hospital pharmacy in Germany is traditionally a manufacturing and supply-based activity and pharmaceutical compounding is still one of the core areas of hospital pharmacists' activities and responsibilities; together with pharmaceutical logistics, pharmacoeconomics and clinical pharmacy (Gessel, 2006; Krämer, 2007).

13.1 **Legislation**

In accordance with the German Medicinal Products Act (*Gesetz über den Verkehr mit Arzneimitteln*), medicinal products prepared according to a prescription for an individual patient are exempt from needing a marketing authorisation (Bundesministerium der Justiz, 2009). These medicines may be considered in 3 different categories, as follows: compounded medicines prepared extemporaneously for an individual patient (*rezeptur*); compounded medicines prepared in advance as batches up to a maximum of 100 packs (of the same compounded medicine) per day (*defektur*); and compounded medicines prepared in larger quantities (more than 100 packs per day)

(*großherstellung*). For each category, different requirements apply with regards to compounding records and testing (among others) (EAHP and HOPE, 2002; Ohem, 2007; Bundesministerium der Justiz, 2008).

Guidelines for the practice of pharmaceutical compounding have been developed (and updated) by ABDA (Section 13.2.1) and, although not legally binding, these guidelines are the foundation for GCP in Germany. A total of 23 guidelines have been developed, covering all relevant steps of the practice of compounding, from checking the prescription and testing the raw materials to the QC of the final compounded medicines (Kinget, 2009; ABDA, 2011a).

13.2 **Professional organisations and information sources**

13.2.1 **German professional organisations**

- *Bundesverband Deutscher Krankenhausapotheker e.V.* (ADKA): is the German Society of Hospital Pharmacists, the only organisation in Germany that represents hospital pharmacy and supports pharmacists working in German hospitals. This nation-wide society is constituted by 8 special interest groups, from drug production to QA, which comprise its scientific and professional foundation (Amann, 2007; 2011; ADKA, no date). According to the president of ADKA: “Drug manufacturing is to be performed in the hospital pharmacy department considering state-of-the-art processes. Facilities and equipment should correspond with the type and amount of products manufactured” (Krämer, 2011).
- *Bundesvereinigung Deutscher Apothekerverbände* (ABDA): is the Federal Union of German Associations of Pharmacists, the main organisation of German pharmacists, which aims to join together and bring forward the common interests of its 34 member organisations, namely: 17 State level councils of pharmacists (confederated to the National Council of Pharmacists) and 17 State level associations of pharmacists (confederated to the German Pharmacists’ Association (DAV) - *Deutscher Apotheker Verlag*) (ABDA, 2011b). ABDA is the editor organisation of the German national formulary (Section 13.2.2).

13.2.2 **German information sources**

- *Deutscher Arzneimittel-Codex - Neues Rezeptur-Formularium* (DAC-NRF): is the German drug-codex, which includes the national formulary - know in short as NRF (New Recipe-Formulary) - a loose-leaf reference source comprising 3 volumes and divided into 5 parts, as follows: (I) General notices; (II) Individualised processing pattern; (III) References for starting material; (IV) 239 standardised formulae; (V) 23 stock preparation monographs (ABDA, 2008). Standardised Recipes (*Standardisierte Rezepturen*) is the corresponding reference for doctors, known as the doctor's NRF (Reimann, 2007). The formulae in the NRF are based on real prescriptions and were designed for the preparation of standardised individual compounded medicines. The development of NRF formulae is undertaken in collaboration with several German pharmaceutical institutions and also with the LNA in the Netherlands (Section 7.2.1) (Kinget, 2009). There is cooperation between the Dutch formulary (FNA, Section 7.2.2) and the German formulary in relation to "formulations, procedures and guidelines", which is gradually developing into harmonisation of both (Bouwman, 2007). The DAC-NRF is available online (for subscribers only) at the *Pharmazeutische Zeitung* (2011), together with additional compounding information and technological support (Reimann, 2007).
- *Herstellungsvorschriften aus Krankenhausapotheken*: is a formulary for hospital compounding, edited by the DAV (Section 13.2.1), also in a loose-leaf format and comprising monographs for the preparation of compounded medicines specially needed in the hospital setting (Kinget, 2009; DAV, no date).

13.3 **Methods**

Germany was the second European country to be included in the research whose data on hospital pharmaceutical compounding was previously collected by another institution. Barnscheid (2008) at the "Institute of Pharmaceutics and Biopharmaceutics (IPB)" (*Institut für Pharmazeutische Technologie und Biopharmazie*) from the *Heinrich Heine* University in *Düsseldorf* (Heinrich Heine Universität Düsseldorf, 2011), undertook PhD research on "Child-appropriate drug formulations including diuretic drugs"

(*Kindgerechte Arzneizubereitungen mit diuretischen Wirkstoffen*), supervised by Jörg Breitkreutz and supported by the *Hexal-Initiative Kinderarzneimittel.* For this reason, and so that data collection would not be duplicated, it was decided not to develop a customised questionnaire for German hospitals but, instead, to request the relevant data from the IPB. Therefore, Jörg Breitkreutz was contacted by email in May 2009 with the request for the list of oral compounded medicines most frequently dispensed by the German hospitals included in their research. In July 2009, the required data was shared during a 2-day visit to *Düsseldorf.*

During his PhD research, Barnscheid (2008) contacted all German hospitals that had a paediatric department (including all paediatric hospitals) with the request to participate in his study. A total of 234 hospitals were initially contacted and the hospitals willing to participate were sent an introductory letter, a collection box and a few prescription notebooks, as illustrated in Figure 13.1.

The prescription notebooks were to be distributed to all hospital paediatricians[53] to record all their prescriptions for compounded medicines (only) during a 6-month period (2005/2006). Each prescription notebook was made up of prescription sheets (in white) and the respective carbon copies (in yellow). The carbon copies included all the information from the prescription sheets, with the exception of the patient name and respective location, the date and the doctor's signature; this information was omitted for blinding purposes (Figure 13.1) (Breitkreutz, 2006; 2009; Hermes *et al.*, 2010). The prescription sheets were to be used in the hospital and the respective carbon copies were to be put inside the collection box, which was to be sent back to the IPB at the end of the study period (Breitkreutz, 2006; 2009). Once received, the carbon copies (inside the collection box) were analysed and all relevant data inserted in an Excel database.

[53]If more prescription notebooks were required these would be sent by post (as many as necessary) at anytime and free of charge (Breitkreutz, 2009).

Figure 13.1 Collection box (left), prescription notebook and inside contents (right).

The complete Excel database was shared including data regarding all oral and non-oral compounded medicines prescribed to paediatric patients during the study period but, for comparative purposes, data regarding non-oral compounded medicines was excluded from the database. Furthermore, the database was not formatted and some data entries were missing key information such as the dosage form and the quantities prescribed. Other data entries were not clearly identified in terms of the respective active substances. Since the identification of the hospital pharmacies was not disclosed, all data entries that were missing key information and also those not clearly identified were excluded from the database for this study.

13.4 **Results and discussion**

A total of 40 hospitals participated in the research study and these were distributed throughout Germany, as shown in Figure 13.2 (Breitkreutz, 2006; 2009; Hermes *et al.*, 2010). A total of 4,895 carbon copies of the prescriptions for paediatric patients were received and analysed. The majority of the compounded medicines were for oral administration (87%), followed by parenteral (5%) and rectal administration (4%) (Barnscheid, 2008). Unfortunately, only a few prescriptions sheets were fully completed by paediatricians (Breitkreutz, 2009). The Excel database shared included data regarding 37 German hospitals and, since 1 hospital did not provide any

quantities of the medicines prescribed, only 36 German hospitals were considered for analysis.

Figure 13.2 Map of Germany adapted from National Geographic Society (1998i); indicating the location of the 40 participant hospitals (●).

13.4.1 **Active substances**

A complete list of the active substances prescribed as oral (and oromucosal) compounded medicines in Germany (for paediatric patients) is shown in Table 13.1. All active substances were included in *Martindale 35* (2007) and these were grouped according to the respective therapeutic classification, giving a total of 147 different active substances and 32 therapeutic groups. Cardiovascular drugs was the group with the greatest number of different active substances (n=26), followed by supplementary drugs and other substances (n=14) and antiepileptics / nutritional agents and vitamins (n=11).

Although these active substances were all prescribed as oral (and oromucosal) compounded medicines, the title of some therapeutic groups suggested non-oral (therapeutic) indications, namely: colouring agents (Appendix 25); disinfectants and preservatives (Appendix 12); nonionic surfactants (Appendix 25); and supplementary drugs and other substances (Appendix 15). The active substances included in these groups were described in the respective appendixes.

Table 13.1 Active substances prescribed as oral (and oromucosal) compounded medicines in Germany (for paediatric patients) (NTI drugs underlined).

Analgesics, anti-inflammatory drugs and antipyretics
Aspirin, celecoxib, flupirtine maleate, indometacin, morphine, morphine HCl, morphine sulfate, naproxen, opium

Antibacterials
Cefuroxime, colistin sulfate, nitrofurantoin, protionamide, pyrazinamide, roxithromycin, sultamicillin, trimethoprim, vancomycin

Antiepileptics
Clobazam, lamotrigine, levetiracetam, mesuximide, phenobarbital, phenytoin, sodium valproate, sultiame, topiramate, vigabatrin, zonisamide

Antifungals
Ciclopirox, fluconazole, itraconazole, miconazole, nystatin

Antigout drugs
Allopurinol, probenecid

Antihistamines
Flunarizine HCl, pheniramine maleate

Antimalarials
Hydroxychloroquine sulfate

Antiparkinsonian drugs
Bromocriptine mesilate

Antiprotozoals
Emetine HCl, metronidazole

Antivirals
Aciclovir, ganciclovir, oseltamivir phosphate, valganciclovir HCl

Anxiolytic, sedatives, hypnotics and antipsychotics
Chloral hydrate, midazolam, midazolam HCl, tetrazepam

Bronchodilators and anti-asthma drugs
Caffeine, caffeine citrate, ipratropium bromide, orciprenaline sulfate, theophylline

Cardiovascular drugs
Amiodarone, atenolol, bosentan, captopril, carvedilol, clonidine, clonidine HCl, diazoxide, dihydralazine sulfate, enalapril, enalapril maleate, furosemide, hydrochlorothiazide, irbesartan, metoprolol, mexiletine HCl, nifedipine, phenprocoumon, potassium canrenoate, propafenone HCl, propranolol HCl, ramipril, sotalol HCl, spironolactone, verapamil HCl, warfarin sodium

Chelators, antidotes and antagonists
Sevelamer HCl

Colouring agents
Carmine

Corticosteroids
Betamethasone, budenoside, dexamethasone, fludrocortisone acetate, hydrocortisone

Cough suppressants, expectorants, mucolytics and nasal decongestants
Ipecacuanha

Disinfectants and preservatives
Acriflavinium chloride

Electrolytes
Calcium, calcium gluconate, calcium glycerophosphate, calcium hydrogen phosphate, calcium lactate, calcium phosphate, dibasic sodium phosphate, sodium chloride, sodium citrate, sodium phosphate

GI drugs
Aluminium hydroxide, dronabinol, esomeprazole magnesium, mesalazine, omeprazole, ranitidine, sulfasalazine, tegaserod maleate

General anaesthetics
Ketamine HCl

Hypothalamic and pituitary hormones
Desmopressin acetate

Immunosuppressants
Azathioprine

Local anaesthetics
Procaine HCl

Miotics, mydriatics and antiglaucoma drugs
Acetazolamide, pilocarpine HCl

Muscle relaxants
Baclofen

Nonionic surfactants
Polysorbate 80

Nutritional agents and vitamins
Calcitriol, calcium folinate, ferrous sulfate, folic acid, fructose, glucose, iron, lactose, maltodextrin, pyridoxine HCl, sucrose

Sex hormones
Estradiol valerate

Supplementary drugs and other substances
Dexpanthenol, macrogols, macrogol 4000, melatonin, orotic acid, pancreatin, phosphorus, potassium bromide, taurine, thyme, tormentil, ursodeoxycholic acid, vanillin, xylose

Thyroid and antithyroid drugs
Levothyroxine sodium, propylthiouracil

Urological drugs
Oxybutynin HCl, sildenafil citrate, tamsulosin HCl

With reference to the official list provided by ANVISA (2007) (Appendix 1), a total of 6 NTI drugs were prescribed as oral compounded medicines (underlined in Table 13.1).

The active substances prescribed in most hospitals were: spironolactone (n=30); hydrochlorothiazide (n=28); caffeine citrate (n=18); chloral hydrate (n=16) and theophylline (n=15).

Almost all medicines prescribed included just 1 active substance and only 4 compounded medicines contained up to 3 different active substances, which were dispensed both as oral solid and liquid dosage forms, and also as oromucosal preparations (described below).

13.4.1 **Oral solids**

Oral solid dosage forms were prescribed in 97% of the hospitals (only 1 hospital did not report oral solids) and included capsules (n=33), oral powders (n=13), tablets (n=3) and pellets (n=2). The quantities of oral solids were provided as the number of individual units prescribed, which may not correspond to the exact number of units dispensed by the hospital pharmacy; compounding records identify the compounded medicines dispensed more accurately than the respective prescriptions (Giam and McLachlan, 2008). Therefore, in accordance with the data shared, the most frequent dosage forms were capsules (92.36%), followed by oral powders (7.39%) and, in a minority, pellets and tablets (Figure 13.3). Since all compounded medicines prescribed were for the paediatric population, it is likely that part of the

capsules prescribed were opened before administration and given to paediatric patients with liquids or food.

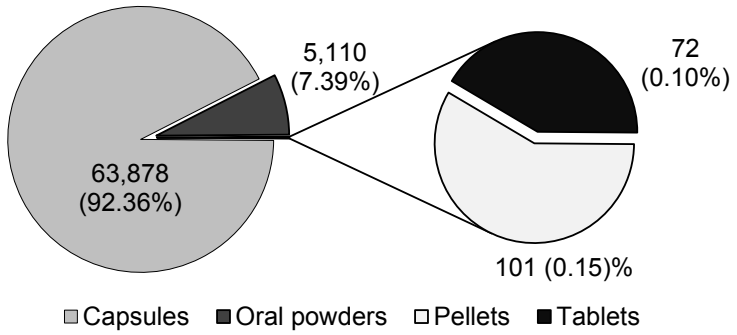


Figure 13.3 Number of units of oral solids prescribed per dosage form.

The top 20 active substances prescribed as oral solids and ranked by number of units are listed in Figure 13.4. Hydrochlorothiazide was the most frequently prescribed active substance (10.5%), followed by calcium gluconate (10.1%) and spironolactone (9.5%). Hydrochlorothiazide and spironolactone were also the active substances prescribed by most hospitals.

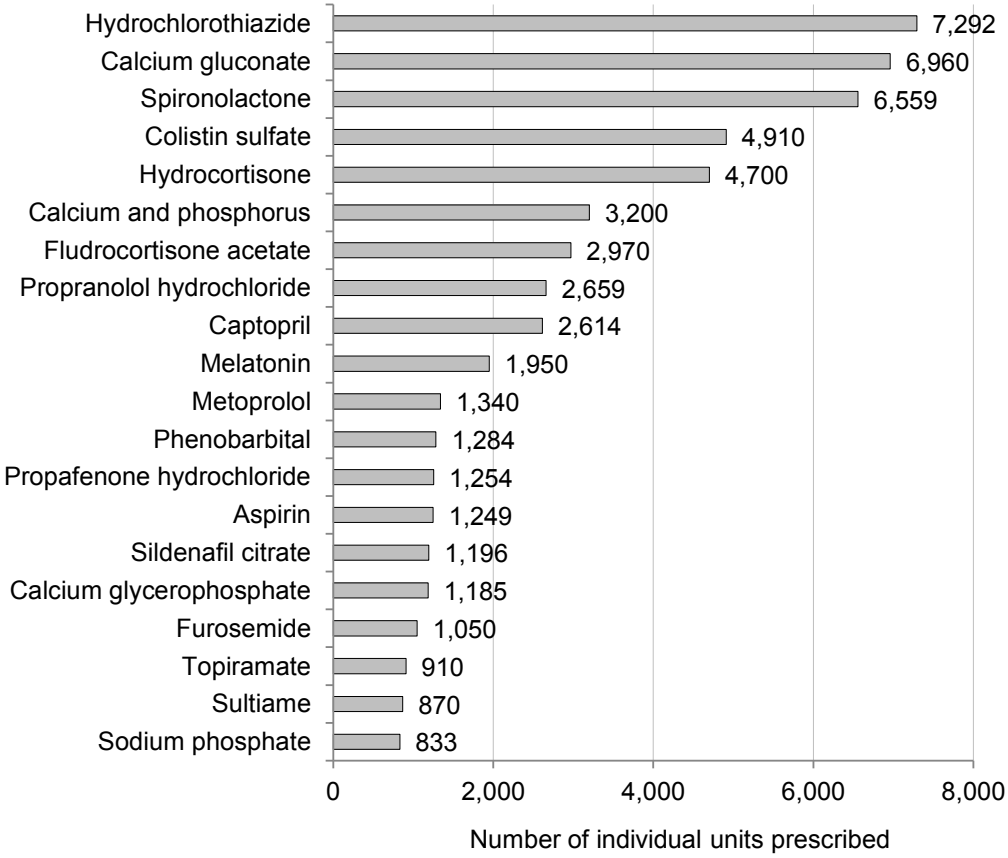


Figure 13.4 Top 20 active substances prescribed as oral solids and ranked by units.

The top 10 active substances represented over 60% of all active substances prescribed as oral solids, which indicates that these are the active substances most highly demanded as compounded medicines for paediatric patients in Germany.

The top 5 therapeutic groups, ranked by number of units prescribed of the corresponding oral solids, are listed below in Table 13.2. All 5 groups included active substances that were part of the top 20 (Figure 13.4).

Table 13.2 Top 5 therapeutic groups ranked by number of units of oral solids prescribed.

Therapeutic groups	Number of active substances	Active substances included in top 20	Number of units prescribed
Cardiovascular drugs	26	7	26,361
Electrolytes	9	4	10,793
Corticosteroids	3	2	7,855
Antibacterials	9	1	5,795
Antiepileptics	11	3	5,018

The most frequent therapeutic group was cardiovascular drugs, which is consistent with the fact that conditions of the circulatory system are the major cause of discharge from all German hospitals (including through death) (Figure 13.5). Cardiovascular drugs was also the therapeutic group constituted by most active substances dispensed as oral solids and included all active substances shown in Table 13.1.

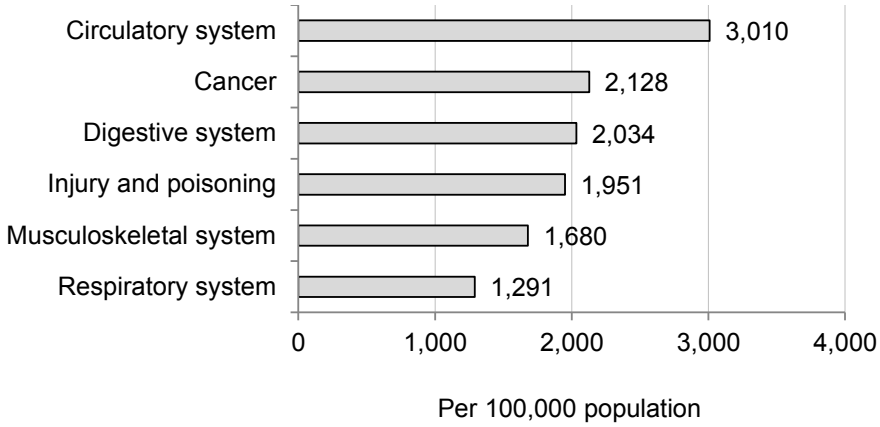


Figure 13.5 Number of patients per 100,000 population discharged from all hospitals (including through death) in Germany during 2005 (latest available year), categorised by principal diagnosis (WHO Regional Office for Europe, 2008).

Capsules were prescribed in 92.4% of the hospitals and the top 20 active substances corresponded to the top 20 prescribed as oral solids, with the exception of calcium hydrogen phosphate and dibasic sodium phosphate (Figure 13.4), which is consistent with the fact that capsules were the most frequently prescribed oral solid dosage forms. Capsules including more than 1 active substance were prescribed by 3 hospitals, in a total of 3,990 units, as follows: calcium and phosphorous; calcium hydrogen phosphate and dibasic sodium phosphate; and spironolactone and hydrochlorothiazide.

Because only a few prescriptions were fully completed by paediatricians (Breitkreutz, 2009), the majority of the data entries were incomplete and, therefore, the individual strengths and pack sizes of oral solids will not be addressed in detail.

Oral powders were prescribed by only 36% of the hospitals and the top 5 active substances (spironolactone, caffeine citrate, hydrochlorothiazide, topiramate and furosemide) were part of the top 20 prescribed as oral solids, with the exception of caffeine citrate. These top 5 active substances accounted for almost 60% of all active substances prescribed as oral powders. Oral powders were prescribed comprising 1 active substance only.

Pellets represented less than 0.2% of all oral solids and were prescribed in only 2 hospitals, as follows: theophylline (75 mg and 100 mg) and topiramate (30 mg). Tablets, on the other hand, represented only 0.1% of all oral solids and were prescribed in 3 hospitals, as follows: nitrofurantoin (20 mg); hydrochlorothiazide and spironolactone (1.8 mg and 1 mg); and metronidazole (50 mg).

13.4.2 **Oral liquids**

Oral liquid dosage forms were prescribed in 89% of the hospitals and included solutions and suspensions (n=31), oral drops (n=14), syrups (n=7), tinctures (n=2) and mixtures (n=2). Oral syringes were not prescribed in Germany and it was assumed that all oral liquids were multidose. Nevertheless, it is possible that part of the oral liquids prescribed were actually unidose but, since the majority of data entries were incomplete, this information could not be accurately retrieved from the database. In addition, it

is possible that the dosage forms and quantities prescribed did not always correspond to that actually dispensed by the hospital pharmacy. Some interchange might have occurred, particularly between solutions, suspensions, syrups and mixtures since the distinction between these dosage forms is not always clear to all health care professionals (Section 2.1.3).

The most frequent dosage forms were solutions and suspensions (87.8%), followed by oral drops (10.9%), syrups (1%) and, in a minority, tinctures and mixtures (Figure 13.6).

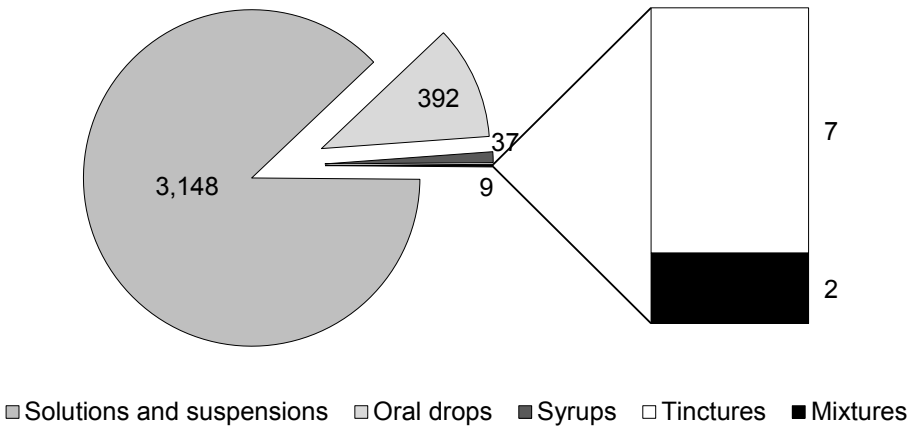


Figure 13.6 Number of multidose containers of oral liquids prescribed per dosage form.

The top 10 active substances dispensed as oral liquids and ranked by number of multidose containers are listed below (Figure 13.7). Caffeine citrate was the most frequently prescribed active substance (39.7%), followed by midazolam (19.1%) and the combination of calcium hydrogen phosphate with dibasic sodium phosphate (11.2%), which was the only oral liquid prescribed including more than 1 active substance.

Caffeine citrate (bronchodilators and anti-asthma drugs) is commonly used in the short-term treatment of neonatal apnoea[54] as it has been found to reduce the number and severity of apnoeic episodes (*Martindale 35*, 2007). Caffeine citrate was also part of the top 5 active substances prescribed as oral

[54]Neonatal apnoea corresponds to the cessation of breathing either lasting 20 seconds or more or associated with bradycardia, cyanosis, pallor and hypotonia, for which no specific cause can be identified (*Martindale 35*, 2007).

powders (Section 13.4.2). Hydrochlorothiazide, spironolactone and furosemide were also included in the top 20 active substances prescribed as oral solids (Figure 13.4). The active substances prescribed by most hospitals (spironolactone, hydrochlorothiazide, caffeine citrate, chloral hydrate and theophylline) are all included in the top 10 oral liquids.

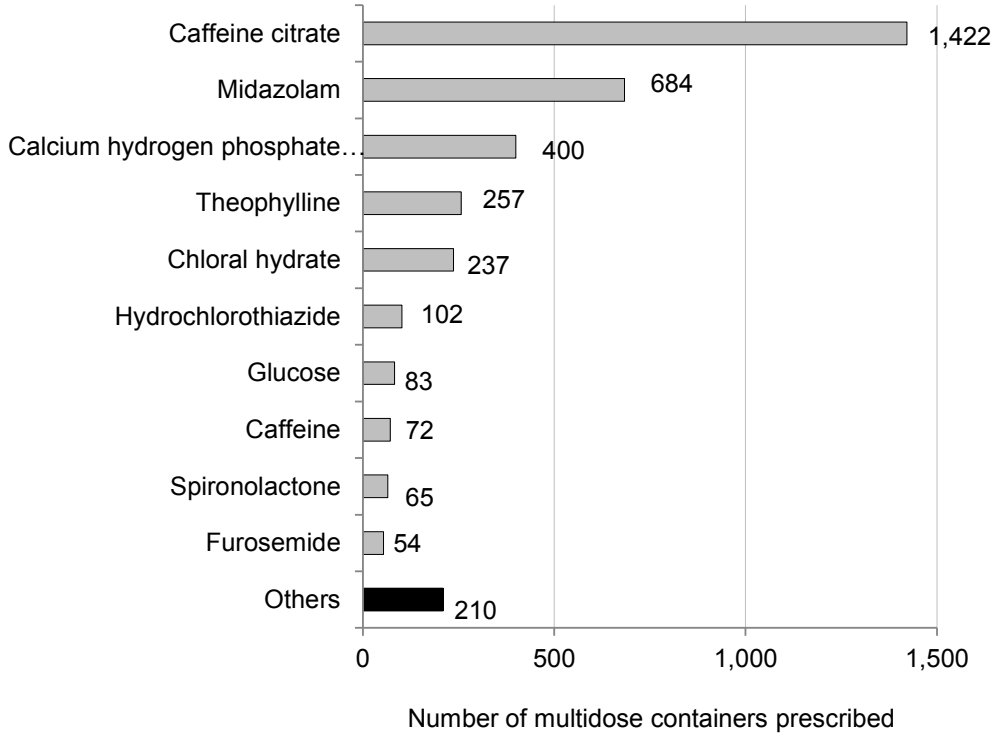


Figure 13.7 Top 10 active substances prescribed as oral liquids and ranked by number of multidose containers.

The top 3 active substances represented almost 70% of all active substances prescribed as oral liquids, which indicates that these are also part of the active substances most highly demanded as compounded medicines for paediatric use in Germany.

The top 5 therapeutic groups, ranked by number of multidose containers of the corresponding oral liquids, are listed below in Table 13.3. The most frequent therapeutic group was bronchodilators and anti-asthma drugs, which represented 50% of all active substances prescribed as oral liquids. All 5 groups included active substances that were part of the top 10 shown above (Figure 13.7).

Electrolytes and cardiovascular drugs were the only therapeutic groups common to the corresponding top 5 of oral solids (Table 13.2). In comparison, the top 5 therapeutic groups of oral solids included a larger number of active substances per group, which indicates that the prescription of oral liquids is likely to be reserved for a limited number of active substances, as opposed to oral solids that potentially permit more prescribing flexibility.

Table 13.3 Top 5 therapeutic groups ranked by number of multidose containers of oral liquids prescribed.

Therapeutic groups	Number of active substances	Active substances included in top 10	Number of containers
Bronchodilators and anti-asthma drugs	5	3	1,791
Anxiolytic, sedatives, hypnotics and antipsychotics	3	2	958
Electrolytes	3	1	401
Cardiovascular drugs	7	3	236
Nutritional agents and vitamins	5	1	91

The multidose oral liquids prescribed may be quantitatively compared to the oral solids prescribed in packs (and not in individual units). Considering that capsules corresponded to 92.4% of all oral solids prescribed, it is possible to estimate that oral solids were prescribed in packs of 50 units (Section 2.1.3) and, therefore, the 69,161 individual units of oral solids corresponded to 1,383 packs (of 50 units each). Consequently, when the 3,586 multidose oral liquids are compared to the 1,383 packs of oral solids, it is concluded that oral liquids were prescribed to paediatric patients in larger quantities than oral solid dosage forms. This finding clarifies the conclusion of Brion *et al.* (2003) that, in Germany, a “non-well defined combination of liquids, powders and capsules is dispensed”. Oral liquids allow dosing flexibility and are easy to administer (in particular to paediatric patients) (Section 2.1.3) and, hence, it was not surprising that these were the most frequently prescribed dosage forms to paediatric patients in Germany.

Solutions and suspensions were prescribed in 86% of the hospitals and the top 10 active substances corresponded to the top 10 prescribed as oral liquids, with the exception of glucose (Figure 13.7), which is consistent with the fact that solutions and suspensions were the most frequently prescribed oral liquid dosage forms. As previously stated, because only a few prescriptions were fully completed by paediatricians (Breitkreutz, 2009), the majority of data entries were incomplete and, therefore, the individual strengths and pack sizes of oral liquids will not be addressed in detail.

Oral drops were prescribed in 39% of the hospitals, in a total of 392 containers corresponding to just 12 different active substances. The top 3 active substances were theophylline, glucose and caffeine citrate, which are part of the top 10 active substances prescribed as oral liquids (Figure 13.7) and accounted for over 70% of all oral drops.

Syrups, on the other hand, were prescribed in only 19% of the hospitals, in a total of 37 containers corresponding to just 8 different active substances. The top 3 active substances were ketamine HCl, chloral hydrate and nystatin, which accounted for 70% of the syrups prescribed. Tinctures represented just 0.2% of all oral liquids and corresponded to opium tincture only, which was prescribed in 2 hospitals in a total of 7 multidose containers. Mixtures were the least prescribed oral liquids (less than 0.1%) and only 1 mixture of ipecacuanha and another mixture of thyme were prescribed in 1 hospital each.

13.4.3 **Oromucosal preparations**

Oromucosal preparations were prescribed in just 4 hospitals (11% of all participant hospitals), in a total of only 24 multidose containers. The active substances prescribed as oromucosal preparations were: acriflavinium chloride (5 mg/g, 10 g); miconazole (20 mg/g, 20 g); aluminium hydroxide (300 g); and procaine HCl (10 mg/g, 20 g). A combination of 3 active substances was also prescribed as an oromucosal preparation, namely: betamethasone, pheniramine maleate and nystatin (225 mL).

13.5 **Summary**

- Compounded medicines are commonly prepared in hospital and community pharmacies and the quality of compounded medicines is of major concern in Germany.
- The NRF is the German national formulary, a reference for the practice of pharmaceutical compounding developed in collaboration with several pharmaceutical institutions.
- Data collection was not undertaken in Germany since the prescriptions for paediatric compounded medicines in 40 German hospitals had been recently collected by the IPB (*Heinrich Heine* University in *Düsseldorf*). The appropriate data were shared for analysis and a total of 36 German hospitals were included in the research.
- According to the data shared, a total of 147 active substances (including 6 NTI drugs) were prescribed for oral (and oromucosal) paediatric compounded medicines, corresponding to 32 therapeutic groups.
- The therapeutic groups with the greatest number of different active substances were: cardiovascular drugs (n=26), supplementary drugs and other substances (n=14) and antiepileptics (n=11) / nutritional agents and vitamins (n=11).
- Oral solid dosage forms were prescribed in 97% of hospitals and included capsules, oral powders, pellets and tablets.
- Capsules were prescribed in a total of 63,878 units (92.4% of oral solids) and the top 5 active substances were: calcium gluconate, hydrochlorothiazide, spironolactone, colistin sulfate and hydrocortisone. Oral powders were prescribed in a total of 5,110 units (7.4% of oral solids) and the top 5 active substances were: spironolactone, caffeine citrate, hydrochlorothiazide, topiramate and furosemide. Pellets were prescribed in a total of 101 units (<0.2%) and tablets in a total of 72 units (0.1% of oral solids).
- Oral liquid dosage forms were prescribed in 89% of hospitals and included solutions and suspensions, oral drops, syrups, tinctures and mixtures (multidose).
- Solutions and suspensions were prescribed in a total of 3,148 multidose containers (87.8% of oral liquids) and the top 5 active substances were: caffeine citrate, midazolam, calcium hydrogen phosphate and dibasic sodium phosphate, theophylline and chloral hydrate. Oral drops were prescribed in a total of 392 multidose containers (10.9% of oral liquids) and the top 3 active substances were: theophylline, glucose and caffeine citrate. Syrups represented only 1% of oral liquids; the least prescribed were tinctures (0.2%) and mixtures (<0.1%).
- Oral liquids were prescribed in larger quantities than oral solids.
- Oromucosal preparations were prescribed in 0.1% of hospitals and included 7 different active substances, in a total of only 32 multidose containers.

14. Compounding in Europe: overview and discussion

Europe is a large and heterogeneous continent, with a population of over 800 million distributed in 49 (EU and non-EU) countries (Lanzieri, 2008; *Europa*, 2009). A total of 11 European countries were included in this research, corresponding to 10 EU countries (Portugal, UK, Poland, Netherlands, Denmark, Slovenia, Finland, Spain, France and Germany) and 1 non-EU country (Switzerland). These 11 countries have a total population of 293.7 million, more than half of the EU's population, and 10 official languages. When ranked by population, the top 3 countries included in the research were Germany, France and UK (Table 14.1), which are also the most populated countries in the EU (Figure 2.2).

The European countries included in the research with most hospitals per 100,000 population were Finland, France and Switzerland, all with more hospitals per 100,000 population than the European average of 3.73. The countries with most hospital beds per 100,000 population were Germany, France and Finland (Appendix 3), all exceeding the European average of 665.8. The European countries with most pharmacists per 100,000 population were Finland, France and Portugal (Appendix 4), also all over the European average of 52.27. Finland, although the second least populated country (after Slovenia), was the European country with the most hospitals (and also most pharmacists) per 100,000 population. Germany, the most populated country included in the research, was the European country with the most hospital beds per 100,000 population, as highlighted in Table 14.1 (WHO Regional Office for Europe, 2010).

According to the EAHP survey, the average number of pharmacists in European hospitals is 4.7 pharmacists per hospital (EAHP, 2005). Spain, Netherlands and Denmark were the only European countries included in the research with more pharmacists per hospital than the European average. Denmark was, by far, the European country with the highest proportion of pharmacists: 10.3 pharmacists per hospital (more than twice the European average) (Table 14.1).

Table 14.1 Demographics of the European countries included in the research (ranked by population and top 3 underlined; data sources in individual chapters).

European countries	Population (in millions)	Number of hospitals per 100,000 population	Number of hospital beds per 100,000 population	Number of pharmacists per 100,000 population	Average number of pharmacists per hospital
Germany	82.1	4.07	829.09	59.87	4.0
France	64.4	4.68	716.78	113.82	3.3
UK	61.6	3.79	370.00	78.66	4.4
Spain	45.8	1.72	337.03	91.98	5.0
Poland	38.1	2.08	516.17	58.85	3.4
Netherlands	16.5	1.16	480.8	17.53	5.2
Portugal	10.6	1.93	345.44	97.83	3.7
Switzerland	7.6	4.53	553.92	57.04	4.1
Denmark	5.5	1.09	349.48	68.51	10.3
Finland	5.3	6.45	682.49	155.11	3.1
Slovenia	2.0	1.44	466.18	47	2.7
Europe	822.4	3.73	665.8	52.27	4.7

14.1 **Legislation**

EU pharmaceutical legislation is compiled in 10 volumes, which constitute "The Rules Governing Medicinal Products in the EU". Volume 1 corresponds to the "EU pharmaceutical legislation for medicinal products for human use" and volume 4 corresponds to the "Guidelines for GMP for Medicinal Products for Human and Veterinary use" (European Commission, 2011).

In volume 1, the EU Directive 2004/27/EC (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use) excludes pharmaceutical compounding from the provisions of this directive and allows member states to supply compounded medicines in accordance with the legislation in force and to fulfil special needs. These medicines are to be supplied "in response to a *bona fide* unsolicited order, formulated in accordance with the specifications of an authorised health care professional and for use by an individual patient under his direct personal responsibility" (European Parliament and the Council, 2004).

Compounded medicines are officially classified as either magistral formula or officinal formula. A magistral formula is "any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient" (European Parliament and the Council, 2001). An officinal formula is "any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to patients served by the pharmacy in question" (European Parliament and the Council, 2004).

Member states have transposed the EU directive into their national legal frameworks and adapted the concept of compounded medicines to their compounding practices. As a result, the terminology and meaning of compounded medicines, which are addressed individually in the respective preceding chapters, may vary considerably within the EU countries. For instance, Portugal has adopted the EU directive without major adaptations, and compounded medicines in this country correspond to the magistral and officinal formulae outlined above. In the UK, on the other hand, compounded medicines correspond to unlicensed medicines, and those prepared in GMP

facilities are distinguished and classified as specials, whereas all others are classified as extemporaneous preparations. For some health care professionals, “unlicensed medicines” correlates with medicines that are not regulated, which is not the case for the “UK unlicensed medicines”. Further concepts for compounded medicines were acknowledged as, for example, standardised (batch) preparations and non-standardised (individual) preparations (e.g. Netherlands and Germany).

The variations in terminology and meaning of compounded medicines in the EU may contribute to a lack of understanding between health care professionals. For instance, the concept of specials is not applicable to the majority of the EU countries; extemporaneous preparations are not necessarily prepared extemporaneously; and batch preparation is not always allowed in the EU. Although compounding practices vary within EU countries, the terminology and concept of compounded medicines should ideally be harmonised so that consensus is achieved and practices become more standardised across Europe.

The inclusion of an official definition for compounded medicines in the PhEur is under discussion (Keitel, 2011) and this will be an important step towards the harmonisation of terminology and standardisation of compounding practices in Europe.

a. **PIC/S PE 010-3**

In 2008, the Pharmaceutical Inspection Convention (PIC) published a guidance document for the preparation of compounded medicines, namely: Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (PE 010-3) (PIC, 2008). This guidance document was based on the PIC/S GMP Guide (PE 009-9) for industry (PIC, 2009), which is equivalent to the EU GMP guidelines (Volume 4) (European Commission, 2011). The PIC/S is an informal co-operative arrangement (with no legal status) between health authorities in the field of GMP and aims to harmonise the inspection procedures worldwide by developing common GMP standards (PIC, 2010). Whilst the guidance document PIC/S PE 009-9 was developed

for the preparation of proprietary medicines, the PIC/S PE 010-3 was developed for the preparation of compounded medicines.

However, PIC/S PE 010-3 did not take into account country-specific compounding practices across Europe and, therefore, its application is not straightforward Europe-wide. For instance, this guidance document states that: “for products prepared extemporaneously on a frequent basis, a product file should be kept including specifications, instructions and records (based on a pharmaceutical assessment of therapeutic rationale, safety data, toxicity, biopharmaceutical aspects, stability and product design); and also a product review (QC testing data and validation data)” (PIC, 2008). For those countries with limited resources, such a wide requirement is not practicable without highly specific guidance and support. For instance, in Poland, it is not currently required to keep detailed documentation of the compounded medicines prepared and Polish legislation does not specify any QA/QC requirements for pharmaceutical compounding. As a result, the development of product files in this country would not be straightforward.

The PIC/S PE 010-3 also includes statements that are too general to add any value to the practice of pharmaceutical compounding. For instance: “Personnel should be qualified and trained in accordance with their function”; “Premises and equipment should be suitable for their intended purpose”; “All areas should be clean, orderly and well lit” (PIC, 2008). According to Torniainen (2007), this guidance document responds to a need for authoritative European level guidance in pharmaceutical compounding, but more attention should be paid to terminology as English expressions vary throughout the document.

In conclusion, this guidance document is not immediately applicable in all EU countries and does not constitute a valuable reference for those engaged in pharmaceutical compounding across Europe. Nevertheless, in an EDQM expert workshop on “Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients”, held in September 2009, it was suggested that the PIC/S PE 010-3 would become the enforceable EU guidelines for pharmaceutical compounding. However, it is important to realise that the aim of enforceable

EU guidelines is to improve the quality of patient care and not to prohibit care at all (Kirchdorfer, 2011) and the PIC/S PE 010-3, because of its inadequacy, should not be regarded as standard setting for the practice of compounding Europe-wide.

b. **Resolution CM/ResAP(2011)1**

In January 2011, the Council of Europe recognised the need for European guidelines on pharmaceutical compounding with the publication of the "Resolution CM/ResAP(2011)1 on Quality and Safety Assurance Requirements for Medicinal Products Prepared in Pharmacies for the Special Needs of Patients". This resolution acknowledges the importance and need for compounded medicines and aims to ensure patient safety in Europe by harmonising compounding practices within the countries that are signatories to the Convention on the Elaboration of a PhEur[55] (Council of Europe, 2011), which include all the countries in the present research.

This resolution was adopted considering both the EDQM expert workshop and the PIC/S PE 010-3 document and consists of 11 principles, including the preparation process, product dossier and labeling of compounded medicines. In order to implement this resolution, European countries have to adopt additional guidance considering their national compounding frameworks (Council of Europe, 2011). For instance, a product dossier is required for stock preparations, but not all countries permit the preparation of compounded medicines as stock preparations (e.g. Portugal and Poland). Furthermore, it is suggested that a special authorisation for the practice of compounding should be required which, again, is not applicable to all European countries under their current legislations (e.g. Portugal and Poland).

The implementation of this resolution will not be straightforward as it lacks a clear definition of pharmaceutical compounding and compounded medicines (to be adopted Europe-wide). Consequently, the principles set in this

[55]The member states concerned are: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia", Turkey and UK.

resolution may be regarded as ambiguous, and even confusing, considering the different terminology, concepts and compounding practices across Europe. According to Bouwman-Boer (2011), this resolution appeared “out of the blue” and was not well received by European pharmacists who fear inappropriate interference in their practices. The principles set out should have considered the expertise of compounding pharmacists Europe-wide in order to avoid the “splashdown” of inadequate standards. One of the important deficiencies highlighted by Bouwman-Boer (2011) was the fact that this resolution facilitates the preparation of compounded medicines on a large scale by the pharmaceutical industry, which may reduce the drive for licensing and, consequently, the drive to produce licensed proprietary medicines instead of preparing compounded medicines. According to Vulto (2011), this resolution looks like “a remedy that is far worse than the disease” and it may have far-reaching effects on the compounding activities in Europe (Clark, 2011).

c. **Compounding settings**

For the majority of European countries, compounded medicines are mostly prepared in community and hospital pharmacies. In the UK, however, compounded medicines are mainly prepared by specials manufacturers which guarantee that these medicines are manufactured under GMP certified facilities and, for this reason, specials (compounded medicines manufactured under GMP) are regarded as a quality assured alternative to extemporaneous preparations (compounded medicines not manufactured under GMP). Nevertheless, “industrial” GMP was originally developed for the manufacture of licensed medicines and, therefore, it does not consider important aspects of the preparation of compounded medicines as, for instance, the development of a customised formula and the small scale method of preparation. Therefore, it is not just because specials are manufactured under GMP-certified facilities that these should be regarded as a quality assured alternative to extemporaneous preparations. Actually, extemporaneous preparations may be a better alternative if the respective formula and method of preparation were properly assessed, as opposed to the corresponding specials.

The concept of specials is unique to the UK but, in Portugal and Spain, although compounded medicines are mainly prepared in the community and hospital settings, these medicines may also be prepared by other entities previously authorised by the respective regulatory authorities. In Spain, in particular, selected regional boards of pharmacy have been given this authorisation and are currently competing with local pharmacies in relation to the preparation of compounded medicines. The ethics of having the regional boards of pharmacy as a competitor has been questioned in this country (Section 11.1).

In all other European countries included in the research, compounded medicines may only be prepared in community and hospital pharmacies, which is in accordance with the triad relationship doctor-patient-pharmacist that has traditionally characterised pharmaceutical compounding.

d. **Third-party compounding**

When compounded medicines are prepared and dispensed at the same place, the triad relationship is kept. However, for the benefit of patients, if community and hospital pharmacies are not able to provide quality assured compounded medicines, their preparation should be allowed outside those 2 settings.

Third-party compounding within community and hospital pharmacies is allowed for the majority of European countries but, once again, this practice varies throughout Europe. For instance, third-party compounding is not permitted in Poland, and Polish pharmacies have to prepare all compounded medicines dispensed. Third-party compounding is allowed in Portugal, and all Portuguese pharmacies may dispense compounded medicines prepared by others. Third-party compounding is also allowed in Spain (for most autonomous communities) and France, but pharmacies have to be previously authorised by the respective regulatory authorities in order to compound for other pharmacies. It is important that in the future the same criteria apply to all European countries so that third-party compounding outside community and hospital pharmacies is harmonised in Europe and patients have the same access to compounded medicines Europe-wide.

14.2 **Professional organisations and information sources**

14.2.1 **International professional organisations**

- The European Association of Hospital Pharmacists (EAHP): is a working community of national associations of hospital pharmacists that represents the interests of over 21,000 hospital pharmacists in 31 European countries. The mission of the EAHP is to support European hospital pharmacists in improving health care through science, practice and collaborative actions. The goals of the EAHP are: “to develop hospital pharmacy and to establish a common pharmaceutical policy in Europe; to work for the advancement of the position and role of pharmacists in hospitals; to uphold the interests of hospital pharmacists in EU member states with the corresponding authorities; and to promote cooperation with other professional bodies” (EAHP, 2010b). The EAHP is responsible for publishing two official journals (6 times per year) that contain peer-reviewed articles. These are the European Journal of Hospital Pharmacy Practice (EJHP Practice) and the European Journal of Hospital Pharmacy Science (EJHP Science). Among other topics, pharmaceutical compounding is currently discussed in both journals (EAHP, 2010c). Moreover, the EAHP holds an annual congress in a different European country each year. In 2010, the EAHP congress was held in Nice (France) and pharmaceutical compounding was one of the topics addressed (Seminar 11 / Paediatrics: handling of drugs in paediatric patients), as in most EAHP annual congresses (EAHP, 2010d). Every 5 years, the EAHP undertakes a survey on the current state and development of hospital pharmacy in Europe. In 2005 (latest available year), 22 European countries participated in this survey and data from 825 hospitals were collected (24% response rate), including information on sterile and non-sterile compounding practices (EAHP, 2005; 2010a).

Professional organisations specifically focused on pharmaceutical compounding Europe-wide are yet to develop. Nevertheless, there are 2 specialist international organisations that are available to European pharmacists, namely:

- International Society of Pharmaceutical Compounding (ISPhC): is a professional and scientific organisation that aims to promote pharmaceutical compounding worldwide. It was officially constituted in 2004 during the IX Scientific Congress of the Spanish Association of Compounding Pharmacists (AEFF), and the simultaneous 1st International Congress on Pharmaceutical Compounding, in *Ciudad Real*, Spain (ISPhC, no date). The ISPhC constitutes an open forum for pharmacists worldwide to collaborate and discuss the practice of pharmaceutical compounding (Marro, 2008).
- International Academy of Compounding Pharmacists (IACP): is an international association that focuses on the specialty practice of pharmacy compounding, mainly in the USA. The IACP is constituted by pharmacists, technicians, prescribers and patients interested in compounded medicines; and aims to promote and advance personalised medical solutions (IACP, 2010). European health care professionals may be part of IACP.

The European country included in the research with the greatest number of professional organisations specifically focused on pharmaceutical compounding is Spain. In this country, there are a total of 3 independent nation-wide organisations (AEFF, Aprofarm and AFA) and many more compounding departments in other institutions. Consequently, Spain is the country that has held more annual congresses and other compounding events within Europe.

14.2.2 **International information sources**

Pharmacopoeias

- The European Pharmacopoeia (PhEur): is the official reference that sets the standards for the quality of medicines in Europe by means of general and specific monographs legally enforceable in the countries which are signatories to the Convention on the Elaboration of a PhEur (EDQM, 2007). Pharmaceutical compounding is not specifically addressed in the PhEur but the inclusion of an official definition for compounded medicines is currently under discussion (Keitel, 2011).

National pharmacopoeias may complement the PhEur with additional standards, which allows a rapid and flexible inclusion of nation-specific

quality requirements (Swissmedic, 2009). The BP is an example of a national pharmacopoeia that complements the PhEur with a dedicated chapter and specific monographs for compounded medicines. According to Breckenridge[56], the BP works closely with the PhEur and plays a significant role in influencing the decisions of the PhEur Commission and in the standard setting process in Europe (BP Commission, 2008b). If the PhEur follows the example of the BP by including a dedicated chapter and specific monographs for compounded medicines, it would be a very important step towards the harmonisation of pharmaceutical compounding in Europe.

- USP Pharmacists' Pharmacopeia: is the official reference that sets the standards for the quality of compounded medicines in the USA (US Pharmacopeial Convention, 2005). The 2008-2009 edition includes 129 official USP-NF (United States Pharmacopeia - National Formulary) monographs for compounded medicines and 73 USP general chapters covering compounding, packaging, labelling and storage of compounded medicines (*CompoundingToday*, 2011b). Although not enforceable in Europe, the USP Pharmacists' Pharmacopeia includes monographs and standards that are a valuable reference for the practice of compounding in Europe.

Formularies

- European formulary: an officially recognised European formulary for pharmaceutical compounding has not yet been published. There are official national formularies for pharmaceutical compounding (e.g. Netherlands and Germany) but no work has been done so far in terms of translating to English and adapting any of these formularies to the current compounding practices in Europe. Likewise, there are only non-official national formularies (e.g. the Spanish *Formulario Básico de Medicamentos Magistrales* and *Formulación en Farmacia Pediátrica*).
- European hospital formulary: it is common practice for European hospitals to have their own compounding formularies including monographs for the most frequently dispensed compounded medicines in their pharmacies.

[56]Sir Alasdair Breckenridge was the chairman of MHRA in 2008.

If these formularies were combined, monographs would no longer be available as “local-only” and, as a consequence, duplication of studies would be avoided across Europe.

- European paediatric formulary: the development of an officially recognised European formulary is currently under discussion by the EDQM and the respective European representatives. In November 2011, the “Workshop on the Elaboration of a European Formulary for Paediatric Formulations” was the first step of this EDQM initiative. Although not legally binding, the purpose of this compounding formulary is to become the Europe-wide reference for the preparation of compounded medicines for paediatric patients (Keitel, 2011).

An official or non-official European formulary, a European hospital formulary or a European paediatric formulary would be a very important step towards the harmonisation of pharmaceutical compounding in Europe.

Apart from pharmacopoeias and formularies, European pharmacists also use other international information sources as a reference for the practice of pharmaceutical compounding, namely:

- International textbooks, such as the “The Art and Science of Pharmaceutical Compounding” (Allen, 2008) and the “Trissel’s Stability of Compounded Formulations” (Trissel, 2009).
- International journals and databases, such as the International Journal of Pharmaceutical Compounding (IJPC) and the Compounding Today interactive website (*CompoundingToday*, 2011c).

14.3 **Methods**

To identify and characterise the oral compounded medicines most frequently dispensed in European hospital pharmacies, tailored methods were adopted across countries in order to gather comparable information. For the majority of European countries, a country-specific questionnaire was developed and data collection was undertaken by MC. For Switzerland and Poland, a country-specific questionnaire was also developed but an international collaboration was established and data collection was undertaken by local researchers. For France and Germany, data collection was not undertaken

but, rather, an international collaboration was established with local organisations which had recently collected the required data (Table 14.2). The first 2 countries included in the research were Portugal and the UK because of their proximity and easy access of MC to hospital pharmacies in both countries. When data collection was already in place in these countries, more European countries were included in the research, namely: Netherlands, Denmark, Slovenia, Finland and Spain, with at stages data collection undertaken simultaneously in several countries. The research period covered ranged from 2005 to 2009, depending on the year(s) of data collection and the year of the most recently available data at hospital pharmacies (Table 14.2).

Table 14.2 Data collection and research period by European country.

European countries	Data collection by	Research periods
Portugal	MC	2005-2008
UK	MC	2006
Switzerland	Bettina Gasser	2006
Poland	Aleksandra Neubauer-Vasquez	2007
Netherlands	MC	2007-2008
Denmark	MC	2008
Slovenia	MC	2008-2009
Finland	MC	2008
Spain	MC	2007-2009
France	AFSSAPS	2004-2008
Germany	IPB	2006-2007

Stakeholders for pharmaceutical compounding in each country were selected and contacted by MC in order to contribute their knowledge and experience to the research. For the majority of European countries, these stakeholders were particularly important in the initial stages of the research, for the design of the country-specific questionnaire (Section 14.3.1) and for identifying a purposive sample of hospitals (Section 14.3.2).

14.3.1 **Country-specific questionnaires**

Tailored questionnaires were developed for Portugal, UK, Switzerland, Netherlands, Denmark, Slovenia, Finland and Spain (Table 14.3). The first questionnaire was developed for Portugal and was piloted in selected Portuguese hospital pharmacies. The final version of this questionnaire was used as template for the subsequent country-specific questionnaires. Although all questionnaires sought to collect equivalent data across Europe, the contents and layout of each questionnaire varied slightly between countries. For instance, the UK questionnaire included 1 table for oral extemporaneous preparations and another for oral specials, rather than a single table for oral compounded medicines. The Dutch and Finnish questionnaires included an extra column - Manufacturer - so that the compounded medicines prepared in other hospital/community pharmacies would be identified.

Table 14.3 Country-specific questionnaires, languages and other data formats by country.

European countries	Country-specific questionnaires	Languages	Other data formats
Portugal	✓	Portuguese	44%
UK	✓	English	33%
Switzerland	✓	English	20%
Poland	x	x	100%
Netherlands	✓	English	58%
Denmark	✓	English	29%
Slovenia	✓	Slovenian	11%
Finland	✓	English	29%
Spain	✓	Spanish	57%
France	x	x	x
Germany	x	x	x

As the research progressed, layout and content improvements were also undertaken in order to simplify the request for information and to enhance response rates. A flow chart highlighting the systematic approach to the

research instrument is shown in Figure 14.1. Country-specific questionnaires were developed in the official national languages for Portugal, Spain, UK and Slovenia; and in English for Switzerland, Netherlands, Denmark and Finland (Table 14.3). Hospital pharmacies were invited to input data directly in the country-specific questionnaire provided or, alternatively, in any other convenient format (in order to encourage participation and enhance response rates). The majority of European hospitals provided data directly in the questionnaire provided. An average of 35% of hospitals provided data in their own formats, which varied from simple lists to complex and detailed tables. Hospital pharmacies in Europe keep records of the compounded medicines prepared and/or dispensed, although to very different extents and in differing formats. Information is documented in different ways as a result of nation-specific legal requirements (e.g. in Poland, only 3 dates are required; Section 6.1) as well as pharmacy organisation-specific requirements. In the Netherlands and Spain, more than 50% of the hospitals shared data in their own formats, particularly because the majority of these extracted data directly from their own software applications (Table 14.3). In general, data processing and analysis was more complicated and took much longer for those hospitals presenting data in their own formats. However, using data in this format was necessary in order to encourage participation and enhance response rates. Almost all hospitals provided the required data by email, as an attached document. In total, only 4 hospitals (Portugal and Spain) shared data with MC by telephone; 2 (Portugal and Denmark) by post; and 1 (Portugal) by fax. Furthermore, all hospitals provided data electronically, with the exception of 3 (Portugal and Denmark) that provided handwritten data. A country-specific questionnaire was not developed for Poland because of the arduous and time-consuming process necessary for retrieving information from manual records. Therefore, Polish pharmacists were requested to provide data in the most convenient format. Country-specific questionnaires were not developed for France and Germany, as data collection was previously undertaken by other bodies (Table 14.3).

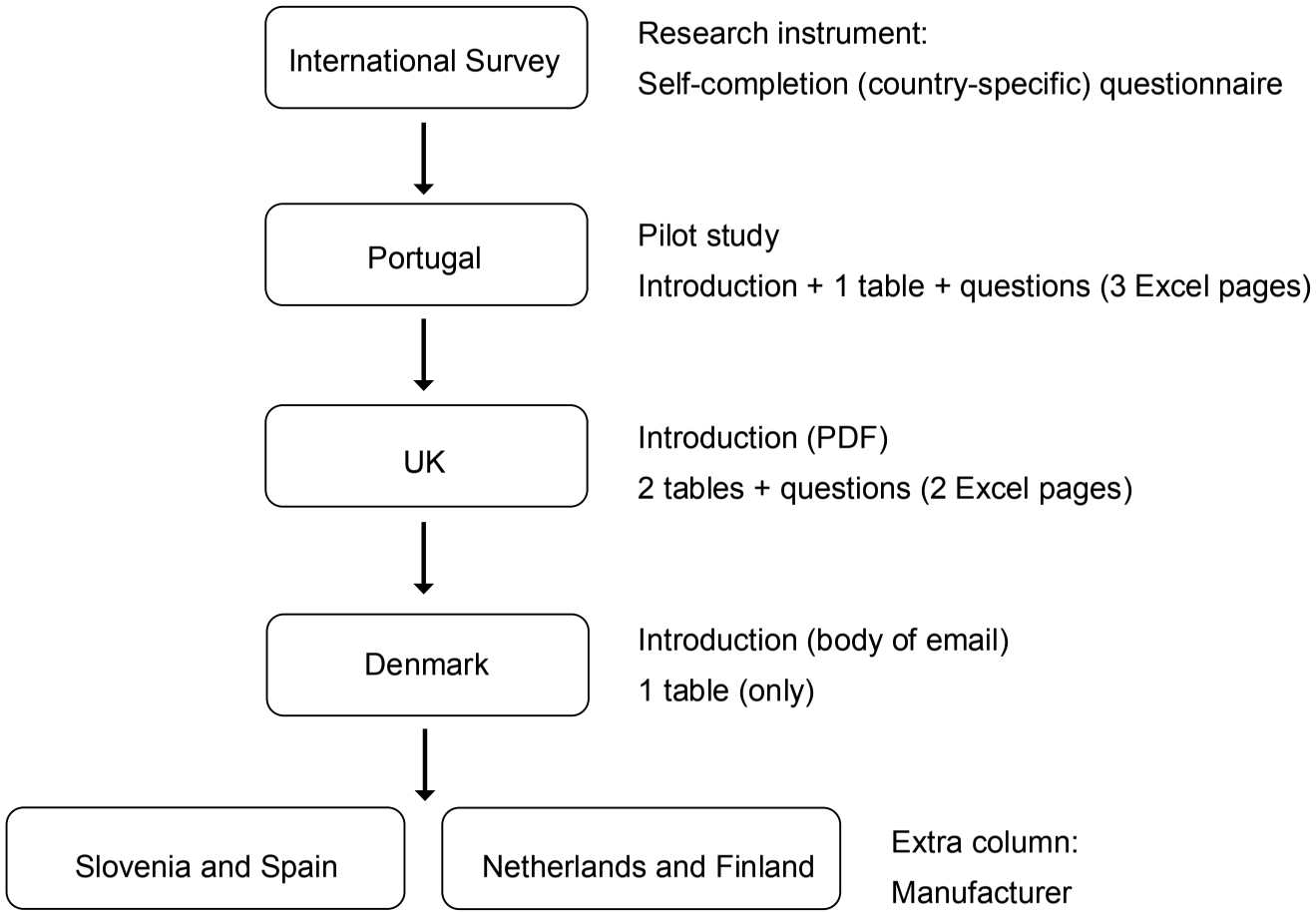


Figure 14.1 Flow chart highlighting the systematic approach to the research instrument.

14.3.2 **Purposive sample of hospitals**

The purposive sample for each European country was chosen to include the hospital pharmacies that most frequently dispense oral compounded medicines in that country. Thus, the data are not representative of all hospital pharmacies in a particular country; but the sample was designed to capture the greatest compounding activity per country, and to identify the most frequently dispensed compounded medicines. This sample was established by consulting key experts in the area of pharmaceutical compounding in each country and this was later confirmed with selected participant hospitals during data collection. Sample sizes varied from 7 pharmacies (Denmark) to 60 hospital pharmacies (Portugal and France), with an average of 31 hospitals per country (Table 14.4).

Table 14.4 Purposive samples and respective remarks per European country.

European countries	Purposive samples	Remarks
Portugal	60	Included selected hospitals nation-wide
UK	36	Included licensed hospital manufacturing units and paediatric hospitals
Switzerland	33	Included paediatric hospitals only
Poland	13	Included northern and central hospitals only
Netherlands	17	Included selected hospitals nation-wide
Denmark	7	Included 2 additional community pharmacies
Slovenia	29	Included all Slovenian hospitals
Finland	8	Included all university hospitals
Spain	40	Included selected hospitals nation-wide
France	60	Included all hospitals surveyed by AFSSAPS
Germany	36	Included all hospitals surveyed by IPB

A total of 339 European hospitals were included in the research, plus 2 additional community pharmacies from Denmark, which frequently prepared compounded medicines for Danish hospitals. The purposive samples for Portugal, Netherlands, Denmark, Finland and Spain included hospitals

nation-wide. For Slovenia, all hospitals were included in the project. For the UK, Switzerland and Poland, specific criteria determined the respective purposive samples. For France and Germany, the purposive samples corresponded to the hospitals whose data were provided by the AFSSAPS and the IPB, respectively (Table 14.4).

14.3.3 **Data collection**

For the majority of European countries, hospital pharmacies were contacted by email/telephone directly by MC. For Switzerland and Poland, none of the hospitals was contacted directly by MC but, instead, these were contacted by email/telephone by local researchers. For France and Germany, none of the hospitals was contacted directly by MC since the required data were provided by the AFSSAPS and the IPB, respectively.

Because email is the most accessible and efficient means of contacting a large and widespread sample of European hospitals, the majority of pharmacies were initially contacted by email, with the exception of Portugal. All Portuguese hospitals were initially contacted by telephone because the email addresses of the chief pharmacists for each hospital pharmacy were not available, which considerably lengthened the stage of data collection. All European hospitals that did not respond to the initial email/telephone contact were sent email reminders. In total, over 500 personalised email requests for collaboration were sent by MC to hospital pharmacies across Europe. The majority of non-respondents were followed up by telephone in order to increase response rates. The number of hospitals contacted by telephone in each country varied from 1 hospital (Finland) to 60 hospitals (Portugal) (Table 14.5). A total of almost 300 telephone calls were made by MC to hospital pharmacies across Europe. For Portugal, UK and Spain, email and telephone contacts were established in the respective official national languages. For Slovenia, the initial email and telephone contacts were made in English and, for this language reason, the majority of the contacts established by MC with Slovenian hospitals were unsuccessful.

In general, the disclosure of compounding information by the hospital pharmacies did not require authorisation from the management board of the

hospitals. Indeed, a few hospital pharmacies in Portugal and Spain mentioned the need for such authorisation, prior to sharing the required data. None of these hospital pharmacies though were refused authorisation. The fact that the required compounding data did not include any patients' details may have contributed to the ready disclosure of information.

Fieldwork was undertaken by MC in a total of 7 European countries. For each country, fieldwork was carefully planned with the respective stakeholders and, for most countries (with the exception of Germany), it included visits to key hospital pharmacies. The number of hospitals visited by MC in each country varied from 1 hospital (Switzerland) to 8 hospitals (Portugal), with an average of 4 hospital visits per country. Data were collected by MC during fieldwork in 6 hospital pharmacies (Portugal and Netherlands). For the Netherlands and Denmark, fieldwork also included visits to key community pharmacies. In total, 22 European hospitals and 4 community pharmacies were visited between 2006 and 2009 (Table 14.5).

Table 14.5 Fieldwork, number of hospitals visited and contacted by telephone per country.

European countries	Hospitals contacted by telephone	Fieldwork	Hospitals visited
Portugal	60	✓	8
UK	3	✓	5
Switzerland	X	✓	1
Poland	X	✓	2 + 1*
Netherlands	13	✓	4 + 2*
Denmark	3	✓	2 + 1*
Slovenia	12	X	X
Finland	1	X	X
Spain	27	X	X
France	X	X	X
Germany	X	✓	X

*Community pharmacies visited

14.3.4 **Limitations of the research**

The limitations that had the greatest potential impact on the research were acknowledged during the pilot study and were considered from the beginning to the end of the research. These limitations may be summarised as follows:

- Incomplete purposive sample of hospitals

It is possible that not all hospitals that most frequently dispense oral compounded medicines in each country were included in the research.

- Incomplete records at the hospital pharmacy

There is a chance that not all compounded medicines dispensed in the hospital were recorded at the hospital pharmacy. The limitation of a retrospective study is that it is restricted to existing data.

- Inaccurate records at the hospital pharmacy

It is possible that not all compounded medicines dispensed were accurately recorded at the hospital pharmacy. For instance, inaccuracy in relation to active substances and respective salts (morphine HCl reported as morphine or morphine sulfate); dosage strengths (e.g. grams reported as milligrams); dosage forms (e.g. solutions reported as suspensions); and quantities (packs reported as individual units).

- Transcribing errors at the hospital pharmacy

There is a chance that not all compounded medicines reported were accurately transcribed from the records at the hospital pharmacy. It is also possible that selected compounded medicines were mistakenly omitted from the records; mistakenly considered as “for oral administration”; or mistakenly considered as “compounded medicines”.

- Transcribing errors at data processing and analysis

It is possible that not all compounded medicines processed and analysed were accurately transcribed from the data reported; different languages are often a strong limitation to clear and effective communication. There is also a chance that selected compounded medicines were mistakenly omitted from the data reported; or mistakenly considered as “for non-oral administration”.

Despite the acknowledged limitations, this research offers the most comprehensive study to date that identifies and characterises the oral

compounded medicines most frequently dispensed in European hospital pharmacies.

14.4 **Results and discussion**

The overall response rate of the international (European) survey was 76%, which is much higher than the 24% achieved by EAHP (2005). The highest response rates were achieved in Denmark (100%) and Portugal (93%). Response rates were greater than 50% in all countries, with the exception of Switzerland, as shown in Table 14.6. In total, 242 European hospitals participated in the research. The majority of hospitals provided complete datasets and only a few hospital pharmacies, in 5 European countries, provided partial data, as follows: Portugal and Spain (quantitative but incomplete; semi-quantitative and qualitative data); Poland (semi-quantitative and qualitative data); Slovenia (qualitative data) and Finland (semi-quantitative data).

Table 14.6 Purposive samples, hospitals (participant, non-participant and non-respondent) and response rates per European country.

European countries	Purposive samples	Participant hospitals	Non-participant hospitals	Non-respondent hospitals	Response rates
Portugal	60	39	17	4	93%
UK	36	15	5	16	56%
Switzerland	33	15	18	18	45%
Poland	13	12	0	1	92%
Netherlands	17	12	1	4	76%
Denmark	7	7	0	0	100%
Slovenia	29	9	8	12	59%
Finland	8	7	0	1	88%
Spain	40	30	1	9	78%
France	60	60	_____		
Germany	36	36	_____		

Hospital pharmacies in all European countries provided datasets including non-oral compounded medicines, mainly for cutaneous application but also ear, nasal, rectal and vaginal preparations; as well as parenteral and eye preparations, which were excluded from the datasets (Section 2.4.1).

There were non-participant hospitals in all European countries, with the exception of Poland, Denmark and Finland (Table 14.6). The highest percentage of non-participants was in Portugal and Slovenia (28%), in which the majority of the reasons given by hospital pharmacies for not collaborating with data provision was that they had not dispensed any oral compounded medicines (only non-orals, in most cases) during the times indicated.

The most common reason stated for non-participation across Europe was that data were not readily accessible and, in most cases, the pharmacy staff was not able to commit the necessary time and effort to collecting the requested data. This reason was anticipated from the beginning of the research, in particular for those hospital pharmacies that kept manual records of the compounded medicines dispensed per day. For these hospitals, listing the most frequently dispensed compounded medicines for one year would be highly time-consuming.

The fact that compounding data was considered confidential was a reason stated by non-participant hospitals exclusively in Portugal and the UK.

14.4.1 **Active substances**

The active substances most frequently dispensed as oral compounded medicines in the European participant hospitals were all included in *Martindale 35* (2007), with the exception of only 13 active substances that were dispensed, mainly as capsules, in a total of 7 countries (Appendix 26). Since Martindale is based on published information (Section 2.4), this fact indicates that the majority of active substances used in pharmaceutical compounding are well known and referenced in the literature. Martindale was the reference of choice to determine the therapeutic category of the corresponding compounded medicines because it includes active substances, currently in use throughout the world, in one therapeutic group

(only) that reflects the uses of the substances being described (*Martindale 35*, 2007).

For each individual country, the active substances included in Martindale were grouped according to their therapeutic classification and NTI drugs were identified. The top 5 European countries ranked by number of active substances were: Spain, Netherlands, France, Portugal and UK. These were also the top 5 countries in relation to the number of NTI drugs and the number of therapeutic groups (Table 14.7).

Table 14.7 Number of active substances, NTI drugs and therapeutic groups per country.

European countries	Participant hospitals	Active substances	NTI drugs	Therapeutic groups
Spain	30	281	9	35
Netherlands	12	226	9	38
France	60	197	7	34
Portugal	39	175	8	33
UK	15	159	7	36
Germany	36	147	6	32
Poland	12	149	6	31
Switzerland	15	142	3	31
Denmark	7	87	3	23
Finland	7	85	4	25
Slovenia	9	68	3	19

For these countries, the number of active substances reported varied from 159 to 281; the number of NTI drugs ranged from 7 to 10; and the number of therapeutic groups from 33 to 38. These findings show that Spain, Netherlands, France, Portugal and UK are the European countries in which the highest diversity of oral compounded medicines was dispensed. Consequently, it may be concluded that there is a higher lack of active substances commercially available in appropriate forms in these countries in particular. The purposive samples included more hospitals than the majority

of other countries, which may have impacted the diversity of oral compounded medicines dispensed.

The top 5 countries dispensed active substances included in over 70% of all therapeutic groups (Appendix 27), which shows the diversity of pharmaceutical compounding in Europe and reinforces the importance of this practice in current therapeutics.

The top 3 active substances dispensed by most European hospitals were:

1. Spironolactone: reported in all European countries, by a total of 123 hospital pharmacies (51%), in both solid and liquid dosage forms. It was reported alone and also in combination with the following active substances: hydrochlorothiazide (most of the time) and altizide.
2. Captopril: reported in all European countries, by a total of 97 hospital pharmacies (40%), in both solid and liquid dosage forms. It was not reported in combination with any other active substances.
3. Hydrochlorothiazide: reported in all European countries with the exception of UK, Denmark and Slovenia, by a total of 96 hospital pharmacies (40%), in both solid and liquid dosage forms. It was reported alone and in combination with: spironolactone (most of the time), amiloride HCl and triamterene. Hydrochlorothiazide was not frequently dispensed as an oral compounded medicine in UK, Denmark and Slovenia, suggesting that it is commercially available in appropriate forms in these countries in particular.

The top 3 active substances were reported by 40 to 51% of all participant hospitals, indicating that there is a Europe-wide need for compounded medicines including spironolactone, captopril and hydrochlorothiazide.

Although these active substances were not exclusively dispensed to paediatric patients, this population has a special need for compounded medicines and, therefore, age-appropriate formulations including spironolactone, captopril and hydrochlorothiazide should be prioritised for studies. However, only spironolactone is currently considered in the EMA (2012b) “Revised priority list for studies into off-patent paediatric medicinal products”, regarding data on pharmacokinetics, efficacy and safety; and also age-appropriate formulations. It is recommended that captopril and

hydrochlorothiazide should be added to the EMA (2012b) priority list for studies.

Monographs for compounded medicines including spironolactone, captopril and hydrochlorothiazide may be found in national information sources across Europe but the respective formulas and methods of preparation are usually country-specific. Therefore, oral compounded medicines including these 3 active substances should be considered for licensing or prioritised for standardisation in official (European) monographs.

a. **NTI drugs**

NTI drugs were dispensed in all European countries, from 3 to 9 per country (Table 14.7). The top 5 ranked by number of NTI drugs were: Netherlands and Spain (n=9); Portugal (n=8); UK and France (n=7). These countries correspond to the top 5 ranked by number of active substances (Table 14.7), i.e. the countries that dispensed more active substances also dispensed more NTI drugs. In relation to the number of active substances, an average of 4% of NTI drugs were dispensed per country, ranging from 2.1% (Switzerland) to 4.7% (Finland).

A total of 19 different NTI drugs were dispensed by the participant hospitals, which represent 86% of all active substances included in the official list provided by ANVISA (2007) (Appendix 1). Only 3 NTI drugs from this list were not reported, namely: digitoxin, procainamide (both cardiovascular drugs) and ciclosporin (immunosuppressants). Thus, the participant hospitals dispensed the majority of the NTI drugs currently available. However, there is a chance that hospitals were not aware of this fact since an official list of NTI drugs has not yet been published in Europe and there are no official guidelines for compounding these potentially toxic active substances. These findings reinforce the need for official Europe-wide guidance on NTI drugs.

The most common NTI drugs were phenytoin, clonidine, warfarin sodium and clindamycin, which were reported by 9, 8, 7 and 6 European countries, respectively. Consequently, these are the NTI drugs that would best be prioritised for Europe-wide guidance regarding pharmaceutical compounding.

All 4 active substances were dispensed in variable dosage forms and strengths, as follows:

- Phenytoin was reported as cachets (Poland), oral powders (Portugal, Finland and Spain), capsules (Portugal, Switzerland, Netherlands, Spain, France and Germany), tablets (France) and oral liquids (Netherlands, Denmark and Spain). It was the most common NTI drug dispensed in Europe, which may be explained by the fact that, in order to control epilepsy, the dose of phenytoin should be adjusted to the individual needs of patients (*Martindale 35*, 2007). The solid dosage forms were reported in the strengths of 1-100 mg and the liquid dosage forms in the strengths of 5-15 mg/mL. The suggested initial dose of phenytoin in epilepsy is 3 to 4 mg/kg per day (in single or divided doses), up to a maximum of 300 mg daily in children (*Martindale 35*, 2007), which is in accordance with the strengths reported.
- Clonidine was reported as oral powders (Portugal) and capsules (Switzerland, France and Germany) in strengths of 2-100 µg; and also in Germany (1 hospital) in the strength of 50 mg (likely to be 50 µg). Clonidine was also reported as oral drops (Germany) and oral liquids (UK, Netherlands, Slovenia, Spain and Germany) in strengths of 5-100 µg/mL; and also in the UK (2 hospitals) in strengths of 12.5 mg/5mL and 50 mg/5mL, which are considerably higher than the usual maintenance dose of clonidine in hypertension (300 to 1200 µg per day up to a maximum of 1800 µg) (*Martindale 35*, 2007). Therefore, there is a good chance that µg/mcg were mistakenly reported as mg in the German and UK hospitals. A very similar compounding error was reported in the literature - 50 mg of clonidine being administered to a child instead of 50 µg - and represented, at that time, the largest reported ingestion of clonidine on a mg per kg basis (Romano and Dinh, 2001). Compounding errors with NTI drugs are potentially very dangerous and consequently close attention should be given to the use of these particular active substances in pharmaceutical compounding.
- Warfarin sodium was reported as oral solids (Portugal, Netherlands, Finland, Spain, France and Germany) in strengths of 0.1-3.8 mg; and as an oral liquid (UK) in the strength of 1 mg/mL. Warfarin sodium is an anticoagulant that should be adjusted to the individual needs of patients and

the strengths reported are in accordance with the doses of less than 5 mg per day used in elderly patients and those at increased risk of bleeding (*Martindale 35*, 2007).

- Clindamycin was reported as cachets (Poland), oral powders (Portugal), capsules (Netherlands, Spain and France) and oral liquids (UK) from 20 mg to 300 mg per dose, which is less than the maximum recommended dose of 450 mg in severe infections (*Martindale 35*, 2007).

Of these 4 most common NTI drugs, clonidine and clindamycin are currently considered in the EMA (2012b) "Revised priority list for studies into off-patent paediatric medicinal products". Therefore, it is recommended that phenytoin and warfarin sodium be added to this list as well, considering the potential toxicity of NTI drugs, in particular in paediatrics that have an increased sensibility to medicines (Section 1.1.5.1).

b. **Placebo**

Compounded placebo medicines were reported by a total of 5 European countries (Table 14.8), which correspond to the top 5 ranked by number of active substances (Table 14.7). Switzerland, Poland, Denmark, Slovenia and Finland did not report placebos as part of their most frequently dispensed oral compounded medicines; placebo was not part of the German database either, though it could have been prescribed but excluded from the research as a non-active substance. Thus, only the countries that dispensed the largest quantities of compounded medicines also dispensed compounded placebos. Placebos are indicated when a placebo effect is particularly beneficial for the therapeutic outcome as, for instance, in protocols for the withdrawal of opioids and in clinical trials.

Placebo compounded medicines were reported as solid dosage forms only, namely: capsules (all 5 countries), tablets (Netherlands) and oral powders (UK). The largest quantities of placebo were dispensed in the Netherlands (3 hospitals only), followed by France (8 hospitals) and Spain (14 hospitals). This finding suggests that placebo is prepared and dispensed on a large scale in the Netherlands by just a few hospitals, which is likely to include outsourcing since the majority of Dutch hospitals prepare compounded medicines for other hospitals and community pharmacies. In France and

Spain, placebo is dispensed on a smaller scale by a large number of hospitals, possibly for individual patients only. A monograph for placebo capsules is included in both the French National Formulary and the Spanish Reference Manual for Compounding in Hospital Pharmacy (Esteban, 2010), which may contribute for the wider use of placebo compounded medicines in these two countries.

Table 14.8 Placebo compounded medicines reported by the European countries and ranked by number of units.

European countries	**Dosage forms**	**Number of hospitals** (participant hospitals)	**Number of units**
Netherlands	Capsules Tablets	3 (12)	130,652
France	Capsules	8 (60)	53,460
Spain	Capsules	14 (30)	27,703
Portugal	Capsules	1 (39)	1,400
UK	Capsules Oral powders	2 (15)	392

c. **Combinations (of more than one active substance)**

The compounded medicines dispensed by the European hospitals were reported either by the active substance(s), their given titles or by the proprietary medicines used in their preparation. The majority of compounded medicines dispensed included just 1 active substance (single-drug). Nevertheless, combinations of more than 1 active substance per compounded medicine (multi-drug preparations) were also reported. These combinations varied from 2 up to 6 different active substances, in either solid or liquid dosage forms. The majority of combinations included just 2 active substances (all European countries); others included 3 active substances (Netherlands, France and Germany); 4 active substances (Switzerland, Finland and Spain); and 6 active substances (Poland). The rationale for combining more than 1 active substance per compounded medicine is usually either to achieve synergistic effects (e.g. spironolactone and hydrochlorothiazide) or to reduce dosing frequency (e.g. polypharmacy; Appendix 2). In any case, the combination of multiple active substances should be therapeutically coherent so that the safety and efficacy of the

compounded medicines can be assured. In addition, there is usually limited data regarding the stability and ADME of compounded medicines with multiple active substances and, therefore, these combinations should be avoided unless supported by adequate literature.

d. **Given titles**

The majority of compounded medicines were reported by the respective active substance(s). Some, however, were reported by the given titles that they are commonly known for. Given titles are designations attributed to specific formulae, which may be either official (e.g. included in the national pharmacopoeia or formulary) or non-official (e.g. included in hospital formularies). Given titles were reported by hospital pharmacies in all European countries, particularly in France and the UK. The given title reported by most countries was Lugol's Solution, dispensed by hospital pharmacies in all European countries, with the exception of UK, Denmark, Slovenia and Germany. A formulary for selected compounded medicines reported by given title is shown in Appendix 16. The prescription of compounded medicines by their given title is a common practice Europe-wide. Nevertheless, this practice might represent a problem when compounded medicines are prescribed in one country and prepared in another country.

For well-established given titles (e.g. Lugol's Solution and Shohl's Solution), the preparation of compounded medicines across Europe should be straightforward provided that pharmacists know the appropriate reference source for the formulae. Nevertheless, in order to avoid ambiguity, doctors should be recommended to provide the reference source (or the complete formula) of the compounded medicines prescribed since the same given title might correspond to different formulae depending on the reference source used. For instance, Joulie's Solution is described in the literature including dibasic sodium phosphate 13.6 g in the anhydrous, dihydrate and heptahydrate forms. A case report of the adverse effects resulting from different intake of phosphorous by a 4 year-old with Dent Disease has been discussed in Spain (Fernández and Rivas, 2011).

For well-established given titles that are country-specific (e.g. *Hoestdrank* in the Netherlands and *Mixture nervinae* in Poland), the preparation of the respective compounded medicines across Europe might be challenging since the corresponding formula may not be readily accessible across borders. Currently, there is a need for a Europe-wide compounding database for doctors and pharmacists including a complete description of the compounded medicines commonly prescribed by well-established given titles.

For non-official given titles, the preparation of the respective compounded medicines may be challenging not only across Europe but also within the same country. Hospital pharmacies in all countries prepare compounded medicines in accordance with local formulae as, for instance, cough syrup; electrolytes solution; and mouthwash for radiation therapy. These given titles should always be accompanied by the respective formulae so that patients and health care professionals know, at all times, the exact composition of the respective compounded medicines.

e. **Proprietary medicines**

Hospital pharmacies in all European countries reported proprietary medicines as part of the compounded medicines dispensed. The top 3 countries were: France (almost 80 proprietary medicines reported by a total of 16 hospitals); Spain (56 proprietary medicines reported by 9 hospitals); and Switzerland (41 proprietary medicines reported by 8 hospitals). In France, the electronic declaration of compounded medicines to the national authority included a specific section for the indication of the use of proprietary medicines. For this reason, it is likely that the majority of hospitals completed the respective section and, therefore, France is the European country where more proprietary medicines were reported as part of the compounded medicines dispensed. The country-specific questionnaires, on the other hand, did not include a dedicated section for reporting the use of proprietary medicines. Therefore, all proprietary medicines reported were indicated either as active substances or as supplementary information. In addition, hospital pharmacies do not systematically record the use of proprietary medicines in pharmaceutical compounding and, consequently, this information is not complete for most hospitals. For these reasons, it is likely that more

proprietary medicines were used in the preparation of the compounded medicines reported but detailed information was not shared.

The proprietary medicines used included solid and liquid dosage forms, but proprietary tablets were most frequently used, mainly to provide appropriate strengths and/or obtain an easy to swallow dosage form. Proprietary medicines are used in pharmaceutical compounding either because it is common practice at the hospital pharmacy or when the individual raw materials are not available. The availability of raw materials depends on the compounding suppliers, who do not always have the required raw materials and/or in reasonably small quantities. Compounding suppliers vary considerably throughout Europe and, therefore, the availability of raw materials is, most of the time, country-specific. Although the use of proprietary medicines in pharmaceutical compounding may be common practice for certain hospitals, in general, this practice is usually discouraged and it is actually forbidden in certain Spanish autonomous communities. In these regions, when the individual raw materials are not available, Spanish pharmacists are not allowed to prepare the compounded medicine. The variable practices and criteria throughout Europe suggest that there is a need for Europe-wide guidance on the use of proprietary medicines in pharmaceutical compounding.

The majority of professional information sources include formulae that imply the use of raw materials in bulk and, only rarely, the use of proprietary medicines is suggested. In fact, proprietary medicines not only include the required active substance(s) but also a miriad of excipients that may compromise the resulting compounded medicines. Actually, depending on the brand of the proprietary medicines used, the resulting compounded medicines may be considerably different. Therefore, if raw materials in bulk are available, pharmacists should not use proprietary medicines for the preparation of the respective compounded medicines, in particular if these are prepared on a large scale. For instance, the proprietary medicines reported in the UK were used in specials, which are usually prepared on a large scale and, therefore, should preferably include raw materials in bulk; likewise, in France, proprietary medicines were used in the preparation of

hospital preparations, which are also (usually) prepared on a large scale and, therefore, should preferably include raw materials in bulk as well. Europe-wide guidance on the use of proprietary medicines in pharmaceutical compounding should separately consider the individual and batch preparation of compounded medicines.

f. **Therapeutic groups**

A total of 46 therapeutic groups were identified from the research (Appendix 27), which represents 85% of all groups in *Martindale 35* (2007) and indicates that compounded medicines from the majority of current therapeutic areas were dispensed by European hospitals. This illustrated the diversity of pharmaceutical compounding in Europe and reinforces the importance of this practice in current therapeutics. Of these 46 therapeutic groups, 11 were common to all European countries (Table 14.9), which indicates that there is a Europe-wide need for compounded medicines from 20% of all current therapeutic areas. Although active substances were all reported as oral (and oromucosal) compounded medicines, the designation of 8 therapeutic groups suggested non-oral indications (Table 14.10) (Appendix 11-15 and 26).

Table 14.9 Therapeutic groups common to all European countries.

1. Analgesics, anti-inflammatory drugs and antipyretics
2. Antibacterials
3. Antiepileptics
4. Anxiolytic, sedatives, hypnotics and antipsychotics
5. Cardiovascular drugs
6. Electrolytes
7. GI drugs
8. Nutritional agents and vitamins
9. Supplementary drugs and other substances
10. Thyroid and antithyroid drugs
11. Urological drugs

Martindale classifies active substances according to their main therapeutic use and brings together active substances that have similar uses or actions. Nevertheless, active substances may be indicated in other additional

therapeutic uses. For this reason, the 8 groups that suggest non-oral therapeutic indications include active substances that were dispensed as oral compounded medicines in Europe.

Table 14.10 Therapeutic groups that suggest non-oral (therapeutic) indications.

1. Colouring agents
2. Dermatological drugs and sunscreens
3. Disinfectants and preservatives
4. Non-ionic surfactants
5. Organic solvents
6. Paraffins and similar bases
7. Stabilising and suspending agents
8. Supplementary drugs and other substances

The least common groups indicate the country-specific therapeutic areas and corresponded to the following:

- Exclusive to 1 country: non-ionic surfactants (Germany) and organic solvents (Netherlands) (Appendix 25).
- Exclusive to 2 countries: colouring agents (France and Germany) (Appendix 25).
- Exclusive to 3 countries: antidementia drugs (Poland, Spain and France); paraffins and similar bases (Portugal, UK and Switzerland) (Appendix 13); and stimulants and anorectics (UK, Netherlands and Denmark).

The top 3 therapeutic groups, per country, with the greatest number of different active substances were:

- Cardiovascular drugs (n=10-39): all countries but Denmark.
- Antibacterials (n=9-31): all countries but Finland and Germany.
- Nutritional agents and vitamins (n=9-34): all countries but UK, Switzerland and Slovenia.
- Electrolytes (n=7-14): UK, Switzerland, Denmark and Slovenia.
- Antiepileptics (n=8,11): Finland and Germany.

In conclusion, the greatest number of different active substances is associated with just 5 therapeutic groups, which represent only 11% of all therapeutic groups included in the research. The diversity of pharmaceutical compounding in Europe was shown before with the fact that the top 5 European countries dispensed active substances included in over 70% of all therapeutic groups. Therefore, the fact that the greatest number of different active substances is associated with just 11% of all therapeutic groups indicates that the largest diversity of pharmaceutical compounding in Europe is restricted to a few therapeutic groups only. Consequently, these 5 groups represent the therapeutic areas where there is a higher lack of active substances commercially available (i.e. proprietary medicines) in appropriate forms and, consequently, these are the therapeutic areas where more active substances are dispensed as compounded medicines.

Compounded medicines were reported as oral solid and oral liquid dosage forms, and also as oromucosal preparations, which are discussed separately below.

14.4.2 **Oral solids**

Oral solid dosage forms were dispensed in all European countries, as follows: cachets (Poland), oral powders (all countries but Poland), powders for oral liquids (Netherlands, Slovenia, Spain and France), capsules (all countries) and tablets (Switzerland, Netherlands, Denmark, France and Germany). The most frequently dispensed dosage forms varied within the countries, from traditional cachets to complex tablets. The top oral solids (the most frequently dispensed solid dosage forms by number of packs and/or by number of individual units) are shown in Table 14.11.

The Netherlands and France dispensed the highest variety of oral solid dosage forms, which suggests that these two countries are the ones that offer more flexibility in terms of meeting the individual patient needs.

Table 14.11 Oral solid dosage forms dispensed per country.

European countries	Most frequent oral solid dosage forms	Other solid dosage forms
Portugal	Oral powders	Capsules
UK	Oral powders	Capsules
Switzerland	Capsules	Oral powders Tablets
Poland	Cachets	Capsules
Netherlands	Tablets	Oral powders Powders for oral liquids Capsules
Denmark	Tablets	Oral powders Capsules
Slovenia	Capsules	Oral powders Powders for oral liquids
Finland	Oral powders	Capsules
Spain	Capsules	Oral powders Powders for oral liquids
France	Capsules	Oral powders Powders for oral liquids Tablets
Germany	Capsules	Oral powders Tablets

a. **Dosage forms**

Capsules were the only dosage form common to all countries, which shows that these are part of the current compounding practices Europe-wide. Gelatin capsules are an elegant, stable and flexible dosage form that may be rapidly prepared extemporaneously by means of inexpensive manual (or semi-automatic) capsule machines (usually in standardised quantities of 50, 100 or 300 units, depending on the equipment) and, therefore, these are widely dispensed in European hospitals. However, capsule calculations are not always straightforward as the active substance(s) determine the size of capsules, choice of excipients and the respective amounts (calculated per density). It is important that hospital pharmacies are fully familiar with these calculations so that the uniformity of capsules can be guaranteed. In most countries, uniformity of weight is not undertaken for capsules prepared extemporaneously, as required in Portugal (Section 3.1), but it would be recommended that a non-destructive quality control test be considered Europe-wide. When indicated for paediatrics patients, capsules are

commonly opened before administration and their contents added to liquids or food. Capsules were the most frequently dispensed oral solids in Switzerland (85%), Slovenia (76%), Spain (98%), France (99%) and Germany (92%).

Oral powders were also common to all countries, with the exception of Poland, and these were mainly dispensed as sachets (single-dose, individually weighed) (Figure 3.6). Oral powders are a traditional dosage form, stable and flexible, that may be prepared extemporaneously by means of basic compounding equipment. However, these are very time-consuming to prepare and, therefore, are only appropriate for the preparation of non-standardised (small) quantities. Oral powders are usually administered in or with water, or another suitable liquid, and may also by swallowed directly. Oral powders were the most frequently dispensed oral solids in Portugal (73%), UK (94%) and Finland (55%), which suggests that these have not been largely replaced by capsules and tablets, at least in all countries (Section 2.1.3). In these countries, capsules are less common probably due to the lack of capsule machines in the hospital setting and also the need for the preparation of non-standardised quantities of oral solids. In Poland, instead of oral powders, cachets were the most frequently dispensed oral solids. Cachets, one of the oldest dosage forms encountered in Europe, were the only dosage form exclusive to a single country, which shows that these have been substituted by other less traditional dosage forms across Europe.

Powders for oral liquids were only reported in the Netherlands, Slovenia, Spain and France but it is likely that other countries also dispensed this dosage form but classified it as oral powders. In fact, powders for oral liquids generally conform to the definition of oral powders (Section 2.1.3) (EDQM, 2007) and, therefore, their distinction is not always clear. Likewise, it is possible that some of the powders for oral liquids reported corresponded to oral powders (in particular those to be administered in or with water, or another suitable liquid). For these reasons, this dosage form was considered as part of the oral solids category. Examples of powders for oral liquids dispensed are glucose (nutritional agents and vitamins) and magnesium sulfate (electrolytes). A distinct difference between oral powders and

powders for oral liquids is most likely to be recorded in hospital pharmacies that have complete and detailed records of the compounded medicines dispensed. The Netherlands and Spain were the European countries that shared the most comprehensive records. In France, hospital pharmacies have to report the compounded medicines dispensed to the national authority and, consequently, it is expected that the exact dosage forms are reported. For these reasons, it is clear that the Netherlands, Spain and France specifically reported powders for oral liquids. In Slovenia, only one hospital reported one compounded medicine as a powder for oral liquid.

Tablets were the most frequently dispensed oral solids in the Netherlands (80%) and Denmark (84%) but these were also dispensed in Switzerland, France and Germany. Tablets are an elegant and stable dosage form but, unlike capsules, these are more complex to formulate and produce, plus they require expensive equipment for their preparation. Consequently, tablets are not usually prepared extemporaneously but instead, are produced in large quantities for stock preparation. Out of all European countries included in the research, UK, Netherlands and Denmark were the only ones in which compounded medicines were frequently prepared in large quantities for stock preparation. In the UK, special manufacturers do not commonly produce tablets and, hence, it is not surprising that tablets were not reported in this country. Therefore, the Netherlands and Denmark were the only European countries in which tablets corresponded to the top oral solids dispensed.

Pellets were also reported by hospital pharmacies in the UK and Germany and, although not considered an official dosage form in the PhEur (EDQM, 2007), these correspond to small cylinders (about 3.2 mm in diameter by 8 mm in length) of an active substance (Rudnic and Schwartz, 2005). In pharmaceutical compounding, pellets of an active substance are usually combined with “non-active” pellets, to obtain the required strength of the active substance, and are then divided in solid dosage forms (e.g. capsules). In the UK, pellets were dispensed as capsules and, in Germany, it is likely that the theophylline and topiramate pellets reported by hospital pharmacies were also dispensed as capsules. Because pellets are not an official PhEur dosage form, and may actually be considered as an “intermediate” product

(Nuez, 2009), this terminology should be discouraged so that there is no ambiguity in the classification of medicines Europe-wide.

b. **Quantities**

Oral solids were reported by all participant hospitals in Poland, Slovenia and Finland; and by over 90% of the hospitals in Switzerland, Netherlands, Spain, France and Germany, which indicates that the majority of European hospitals dispensed solid dosage forms as oral compounded medicines.

The quantities of oral solids were provided as the number of individual units dispensed and/or the number of packs dispensed. For selected European countries, data have been displayed in both formats so that all compounded medicines reported were included in the data analysis. Considering the number of individual units dispensed, the top 5 European countries that reported the largest quantities of oral solids were, in decreasing order: France, Denmark, Netherlands, Spain and Poland. However, the number of participant hospitals varied within countries and, therefore, the European countries that reported the largest quantities of oral solids per hospital were as follows: Denmark (522,588 units), Netherlands, France, Spain and Poland, as shown in Table 14.12.

In Denmark and the Netherlands, hospital pharmacies frequently prepare compounded medicines for their own patients, both extemporaneously and for stock, and also for other hospital and community pharmacies. Therefore, it is not unexpected that the largest quantities of oral solids (tablets), per hospital, were reported by these 2 countries.

France and Spain dispensed the largest quantities of capsules. In both countries, there was no evidence of capsules being prepared for stock, which suggests that the largest extemporaneous preparation of oral solids took place in France and Spain. Cachets correspond to a dosage form prepared extemporaneously and, therefore, Poland was the European country in which the next largest extemporaneous preparation of oral solids, (as cachets) took place.

Table 14.12 Top 5 European countries ranked by the total number of individual units of oral solids dispensed and the respective mean of individual units per hospital.

European countries	**Oral solids** (total units)	**Participant hospitals**	**Oral solids** (mean units per hospital)	**Ranking**
France	3,910,621	60	65,177	3
Denmark	3,658,118	7	522,588	1
Netherlands	3,281,601	12	273,467	2
Spain	1,052,518	30	35,084	4
Poland	213,021	12	17,752	5

c. **Active substances**

When the top 10 active substances (per solid dosage form) are considered for each European country, there is evidence of common active substances being frequently dispensed in hospital pharmacies across Europe. Table 14.13 displays the active substances common to most European countries.

Glucose (oral powders and capsules) and hydrocortisone (oral powders, capsules and tablets) were part of the top 10 active substances in a total of 6 countries and, therefore, these were the active substances most frequently dispensed as oral solids Europe-wide. The next most frequently dispensed active substances were calcium carbonate (oral powders, cachets and tablets), captopril (cachets and capsules), lactose and sodium bicarbonate (oral powders and capsules), which were part of the top 10 active substances dispensed in a total of 5 countries. Phenobarbital was the only NTI drug included in the top oral solids and was frequently dispensed, both as oral powders and capsules, in a total of 4 countries.

The majority of active substances were dispensed as 2 or 3 different dosage forms. These results show that although the same active substances are frequently dispensed, the solid dosage forms and the resulting oral compounded medicines may vary widely depending on the European country and the particular hospital pharmacy. Therefore, these top oral solids should be the ones considered for licensing or prioritised for standardisation in official (European) monographs.

Table 14.13 Active substances (per solid dosage form) dispensed by most European countries.

	Glucose	Hydrocortisone	Calcium carbonate	Captopril	Lactose	Sodium bicarbonate	Phenobarbital	Sodium chloride	Spironolactone	Total
Portugal	_____	Oral powders	Oral powders	_____	_____	Capsules	Oral powders	Oral powders Capsules	_____	5
UK	Oral powders	_____	_____	_____	Oral powders	Oral powders	_____	_____	_____	3
Switzerland	Oral powders	_____	Oral powders	Capsules	_____	Oral powders	_____	Oral powders Capsules	_____	5
Poland	_____	_____	Cachets	Cachets	_____	_____	_____	_____	_____	2
Netherlands	_____	Capsules	_____	Capsules	_____	_____	_____	_____	Oral powders Capsules	3
Denmark	Oral powders	Tablets	_____	_____	Oral powders	_____	_____	_____	_____	3
Slovenia	Capsules	_____	_____	_____	Capsules	Oral powders Capsules	Capsules	Oral powders	Capsules	6
Finland	_____	Oral powders Capsules	Oral powders	_____	_____	_____	Oral powders	_____	_____	3
Spain	Oral powders	_____	_____	_____	Oral powders	_____	_____	_____	_____	2
France	Oral powders	Capsules	Tablets	Capsules	Oral powders	Capsules	_____	Capsules Tablets	Capsules Tablets	8
Germany	_____	Capsules	_____	Capsules	_____	_____	Oral powders	_____	Oral powders Capsules Tablets	4
Total	6	6	5	5	5	5	4	4	4	

Although these active substances were not exclusively dispensed to paediatric patients, this population has a special need for compounded medicines and, therefore, age-appropriate formulations including these top active substances (dispensed by most European countries) should be considered for studies. However, only spironolactone is currently considered in the EMA (2012b) “Revised priority list for studies into off-patent paediatric medicinal products” and, therefore, it is recommended that all other top active substances be added to this list.

The countries that shared most active substances were France (8 active substances) and Slovenia (6 active substances). The Netherlands and Germany were the European countries with more similarities in terms of active substances and the respective oral solid dosage forms dispensed. The fact that there is cooperation between the Dutch and German formularies in relation to formulations, procedures and guidelines is likely to contribute to the harmonisation of some compounding practices in both countries. This finding highlights the importance of international information sources and reinforces the desirability for a Europe-wide compounding formulary.

In comparison with the study by Brion *et al.* (2003), only 5 active substances were common to their top 20 of capsules and top 20 of oral powders, as follows (in decreasing order): spironolactone, captopril, phenobarbital, hydrocortisone and glucose. The few similarities between both studies may be explained with the fact that Brion *et al.* (2003) included only 21 hospitals (convenience sample; children's hospitals only) whereas the present study included 242 hospitals (purposive sample).

d. **Strengths**

The strengths of oral solids were not always provided by hospital pharmacies and, when provided, these were occasionally reported as an interval (e.g. aspirin 15-320 mg). Therefore, it was not always possible to determine the range and the exact number of strengths dispensed. Table 14.14 displays the range and number (approximate) of strengths for the top 5 active substances common to most European countries.

The active substances associated with the highest number of strengths (highlighted in bold) were hydrocortisone (up to 12 strengths) and captopril (up to 23 strengths). Very similar strengths were encountered: hydrocortisone 1 mg, 1.25 mg, 1.35 mg, 1.5 mg, 1.6 mg; and captopril 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg. On the other hand, a wide range of strengths was also encountered: hydrocortisone 0.1-80 mg and captopril 0.01-25 mg. The high number and wide range of strengths encountered reinforce the fact that individualised dosage strengths is one of the main reasons for pharmaceutical compounding, in particular for the paediatric population (Section 1.1.4).

Table 14.14 Top 5 active substances (per dosage form) dispensed by most European countries and indication of the respective range and number (approximate) of strengths (highest number of strengths highlighted in bold).

	Glucose	Hydrocortisone	Calcium carbonate	Captopril	Sodium bicarbonate
Portugal	———	1-80 mg **10 strengths**	100-250 mg 4 strengths	———	30 mg 500 mg 2 strengths
UK	14.6 g, 75 g 2 strengths	———	———	———	100 g 1 strength
Switzerland	68 g, 91 g 2 strengths	———	n/a	0.01-7.5 mg **19 strengths**	100 g 1 strength
Poland	———	———	50-2,000 mg 9 strengths	0.05-25 mg **23 strengths**	———
Netherlands	———	0.25-5 mg 6 strengths	———	0.5-6.25 mg 7 strengths	———
Denmark	75 g, 82.5 g 2 strengths	1 mg, 5 mg 2 strengths	———	———	———
Slovenia	15-100 g 5 strengths	———	———	———	500-2,000mg 5 strengths
Finland	———	0.1-2.5 mg **10 strengths**	50-500 mg 3 strengths	———	———
Spain	5-100 g 5 strengths	———	———	———	———
France	50 g, 75 g 2 strengths	0.5-9 mg **12 strengths**	500 mg 1 strength	0.5-25 mg **15 strengths**	125-1,000mg 4 strengths
Germany	———	0.1-7.5 mg **12 strengths**	———	0.1-8 mg **13 strengths**	———

Brion *et al.* (2003) also concluded that a large number of strengths, for the same active substance, were dispensed in European hospitals. In practice, the evidence-base for distinguishing certain dosage strengths might be arguable as, for instance, captopril 3.125 mg and captopril 3.2 mg. Nevertheless, if the dosage strengths are within the therapeutic window of the respective active substances, it is the pharmacists' duty to prepare the compounded medicines prescribed.

For compounded medicines prepared extemporaneously, it takes the same amount of time and effort to prepare, for instance, captopril 3.125 mg and captopril 3.2 mg. Provided that the pharmacy has a QA/QC system for the practice of compounding, the preparation of compounded medicines in variable strengths should not be more risky than the preparation of standardised strengths.

14.4.3 **Oral liquids**

Oral liquid dosage forms were dispensed in all European countries, as follows: solutions and suspensions (all countries), syrups (all countries but Denmark and Finland), mixtures (UK, Poland, Denmark and Germany), oral drops (Switzerland, Netherlands, Denmark, Spain, France and Germany), oral syringes (Netherlands, Finland, Spain and France) and others (Switzerland, Spain and Germany). Others included tinctures and elixirs. The dosage forms reported included both multidose and unidose oral liquids. Multidose oral liquids were dispensed in all European countries whereas unidose oral liquids were dispensed only in the UK, Switzerland, Netherlands, Finland, Spain and France.

Oral liquids may be rapidly prepared by pharmacists, both extemporaneously in small quantities and in advance for stock, by means of basic compounding equipment. They allow the administration of 1 or more active substances in flexible strengths (by variable volumes). In addition, oral liquids may be easily taken by patients (including paediatric and geriatric patients) and allow the adaptation of the vehicle to individual patient needs (e.g. sugar free) and preferences (e.g. flavour). Oral liquid dosage forms offer a myriad of advantages to both pharmacists and patients and, therefore, it was not

unexpected that these were dispensed in all European countries. However, the formulation and stability of oral liquids are usually complex (Section 2.1.3) and not all hospital pharmacies have sufficient resources to assure optimal formulations, in terms of choice of excipients (e.g. suspending agents, buffers and preservatives) and method of preparation. This reinforces the need for a Europe-wide compounding formulary including, in particular, monographs for oral liquid dosage forms. A national formulary based exclusively on oral liquids (for paediatrics) is already available in Portugal (LEF, 2007) but it is published in Portuguese only and, therefore, has limited use across Europe. Such locally developed professional information sources should be considered when compiling a Europe-wide compounding formulary in order to avoid duplication of potentially expensive and time-consuming studies.

a. **Dosage forms**

Solutions and suspensions were specifically reported in all countries and corresponded to the most frequently dispensed liquid dosage forms, which shows that these are part of the current compounding practices Europe-wide. In fact, solutions and suspensions corresponded to over 90% of all multidose oral liquids dispensed in the UK, Switzerland, Netherlands, Slovenia and Finland; and over 80% in all other European countries, with the exception of France (62%). The distinction between solutions and suspensions is not always straightforward as it is not always clear at hospital pharmacies if active substances are actually dissolved or suspended in a given vehicle. Therefore, it is likely that some interchange in terminology will have occurred and, for this reason, solutions and suspensions were considered altogether for the purposes of overall data comparison. However, it is important that hospital pharmacies acknowledge the differences between solutions and suspensions and label the compounded medicines accordingly. For instance, all suspensions should have the indication “Mix well before use”, in order to assure uniformity of dosage. In addition, it is likely that some interchange will have also occurred in relation to syrups, mixtures, oral drops, elixirs and tinctures reported and, therefore, some of these oral liquids may have corresponded to solutions/suspensions (and vice-versa). Despite the complexity of oral liquids, the formulation and stability of suspensions, in

particular, has been made easy by compounding suppliers that offer proprietary suspending vehicles and publish corresponding peer-reviewed stability studies. For instance, metronidazole benzoate in SyrSpend SF, a starch-based, sugar-free suspension system with low osmolality, which is considered a one-step suspension system (Vu *et al.*, 2008). In addition, there are non-proprietary suspending vehicles that have also been studied and are described in professional information sources. For instance, the "B.9. Vehicle for the preparation of oral suspensions, sugar-free", described in the Portuguese galenic formulary (CETMED, 2005). These proprietary and non-proprietary suspending vehicles are a valuable source for compounding settings that do not have sufficient resources to assure optimal formulations for oral liquids.

Unidose oral liquids were dispensed by 22 hospitals in 6 European countries, corresponding to only 0.1% of all participant hospitals, but not all hospital pharmacies distinguished unidose from multidose oral liquids. For the purposes of overall data comparison, quantities <10 mL have been considered to correspond to unidose; whereas quantities ≥10 mL have been taken as corresponding to multidose containers (unless otherwise indicated). As a result, the top 3 European countries were: Switzerland (228,689 units, 2 hospitals), Spain (59,147 units, 9 hospitals) and France (19,519 units, 2 hospitals). Only 3 active substances were frequently dispensed as unidose oral liquids in more than 1 European country, namely: midazolam, nystatin and methadone HCl (2 countries). Unidose oral liquids offer advantages when compared to multidose oral liquids, as follows: no administration errors in terms of volumes measured by patients or caregivers (unidoses are pre-packed at the pharmacy) and no contamination of subsequent doses (unidoses are individually packed). In the hospital setting, unidoses are particularly convenient as nurses are provided the exact dose for a patient. Unidose oral liquids are accurately measured and usually administered by means of oral syringes (Paediatric Formulary Committee, 2008), but these were specifically reported in 4 European countries only. However, it is likely that almost all unidose oral liquids were dispensed by means of oral syringes since these are the most popular unidose devices. Nevertheless, oral

syringes are not always well accepted by the paediatric population because of their resemblance to painful injectable products. An innovative alternative to oral syringes is blister packs constituted by small containers for unidose oral liquids.

Syrups were specifically reported in all European countries, with the exception of Denmark and Finland. However, as indicated, the distinction between solutions, suspensions and syrups is not always straightforward and it is likely that some interchange in terminology may have occurred. Hence, it is likely that syrups were also dispensed in Denmark and Finland but were reported as solutions/suspensions. Syrups are aqueous preparations characterised by a sweet taste and high viscosity and usually contain sucrose at a concentration of at least 45% (*w/w*). Therefore, syrups are generally regarded as a pleasant tasting dosage form, in particular, for the paediatric population. However, syrups containing sucrose should be avoided when compounded medicines are intended, for instance, to be used by diabetic patients or for long periods of treatment. For this reason, it is important that hospital pharmacies acknowledge the difference between syrups and other oral liquid dosage forms, and label the compounded medicines accordingly (e.g. contains sucrose). Syrups corresponded to less than 10% of oral liquids in all countries, from 0.2% in the UK to 9.3% in Portugal, and were dispensed both as multidose and unidose containers; unidose syrups were reported by only 1 Spanish hospital, whereas multidose syrups were reported by 81 European hospitals. A total of 10 active substances were frequently dispensed as syrups in more than 1 European country, as follows: chloral hydrate (5 countries); ipecacuanha and midazolam (4 countries); codeine, furosemide, ketamine HCl, phenobarbital, ranitidine, spironolactone and zinc acetate (2 countries). These active substances are described in professional information sources across Europe, which is likely to contribute to their widespread use in pharmaceutical compounding. However, there is ambiguity in the classification of the respective dosage forms. For instance, chloral hydrate is described as a mixture and as an elixir, both containing syrup, and also as an oral solution and as an oral liquid (Section 4.4.3). This reinforces the importance of

prioritising these top 10 syrups for standardisation in official (European) monographs.

Oral drops were specifically reported in 6 European countries, by a total of 30 hospital pharmacies, though the distinction between solutions, suspensions and oral drops is not always straightforward as it depends on the characteristics of the container/additional devices (i.e. dropper). However, it is important that hospital pharmacies acknowledge this distinction and dispense the compounded medicines accordingly. Oral drops are commonly prescribed taking into account the following:

1. The administration of the compounded medicine is facilitated by drops.
In this situation, if the dosage of the compounded medicine is per mL, the dropper should include a scale for measuring the required volume.
2. The dosage of the compounded medicine is indicated by number of drops.
In this situation, the dropper does not have to include a scale but attention should be paid at the hospital pharmacy in order to assure the dose per drop.
Oral drops were most frequently dispensed in France (31%), Germany (11%) and Denmark (10%); and least frequently dispensed in the Netherlands (6%), Switzerland and Spain (<0.1%). In France, hospital pharmacies have to report the compounded medicines dispensed to the national authority (AFSSAPS) and, consequently, it is expected that the exact dosage forms are reported. This fact is likely to have contributed to the highest % of oral drops being reported in France. Only 3 active substances were frequently dispensed as oral drops in more than 1 European country, as follows: morphine (2 countries); iodine and potassium iodide (2 countries), commonly dispensed as Lugol's Solution (Appendix 16).

Mixtures were specifically reported in 4 European countries, by a total of 11 hospital pharmacies. Mixtures are not an official PhEur dosage form but are subject of an individual monograph in the BP (Oral Liquids of the BP) and correspond to an oral liquid containing 1 or more active substances dissolved, suspended or dispersed in a suitable vehicle (BP Commission, 2008a). This definition also applies to the "liquid preparations for oral use" described in the PhEur, which adds ambiguity to the classification of oral liquids. Therefore, the need for mixtures as an additional BP official dosage

form should be questioned in the UK. Hence, it is likely that “mixtures” were also dispensed in other European countries but were reported as oral liquids. It is recommended that the countries which are signatories to the Convention on the Elaboration of a PhEur be consistent with the terminology used in the PhEur, so that there is no ambiguity in the classification of medicines Europe-wide. Mixtures were most frequently dispensed in Poland (10.6%) and corresponded to a minority dosage form in the UK (0.3%), Denmark (0.2%) and Germany (<0.1%). It is likely that these 4 European countries were the only ones that actually recognise mixtures as an additional official dosage form. Sodium benzoate was the only active substance frequently dispensed as mixtures in more than 1 European country (i.e. UK and Poland).

Tinctures were specifically reported in Spain and Germany, by a total of 3 hospitals; 1 additional Swiss hospital is likely to have dispensed a tincture (opium), but it was classified as an oral solution. Tinctures are extracts of liquid consistency, usually obtained using 1 part of herbal drug / animal matter and either 10 or 5 parts of extraction solvent. The extraction process can be time consuming and it is not always straightforward for hospital pharmacies. Therefore, it was not unexpected that tinctures corresponded to a minority dosage form in all countries (<0.5%) and only 2 active substances were dispensed, namely: belladonna and opium. Although these 2 tinctures are described in international information sources, which is expected to contribute to their widespread use in pharmaceutical compounding, it is likely that tinctures have been substituted by alternative oral liquid dosage forms in most countries.

Elixirs were only reported by 2 Spanish hospitals and represented <0.1% of all oral liquids; the only active substance reported was cyclophosphamide. Elixirs are not an official PhEur dosage form and, therefore, the use of this terminology should be discouraged so that there is no ambiguity in the classification of medicines Europe-wide.

b. **Quantities**

Oral liquids were reported by all participant hospitals in Portugal, UK, Netherlands, Denmark and Finland; and by 90% (or more) of hospitals in Switzerland, Poland and Spain, which suggests that almost all European hospitals dispensed liquid dosage forms as oral compounded medicines.

The quantities of oral liquids were provided as the number of multidose and unidose units dispensed. Considering the number of multidose units, the 5 European countries that reported the largest quantities of oral liquids were, in decreasing order: Netherlands, Spain, UK, France and Denmark. However, the number of participant hospitals varied within countries and, therefore, the European countries that reported the largest quantities of oral liquids per hospital were: Netherlands (6,842 units), Denmark, UK, Spain and France (Table 14.15).

In the Netherlands and Denmark, hospital pharmacies frequently prepare compounded medicines for their own patients, both extemporaneously and for stock, and also for other hospital and community pharmacies. Therefore, it is not unexpected that the largest quantities of oral liquids (per hospital) were reported by these 2 countries.

Table 14.15 Top 5 European countries ranked by the total number of multidose units of oral liquids dispensed and the respective mean of multidose units per hospital.

European countries	Oral liquids Total (multidose units)	Participant hospitals	Oral liquids Mean (multidose units per hospital)	Ranking
Netherlands	82,104	12	6,842	1
Spain	60,117	30	2,004	4
UK	50,200	15	3,347	3
France	47,474	60	791	5
Denmark	26,870	7	3,839	2

In the UK, hospital pharmacies with a manufacturing specials licence commonly prepare specials on a large scale, for their own patients and also for other hospital and community pharmacies. Therefore, it is not unexpected

either that the UK was the European country in which the next largest quantities of oral liquids were reported (per hospital).

c. **Active substances**

When the top 10 active substances (per liquid dosage form) are considered for each European country, there is evidence of common active substances being frequently dispensed in hospital pharmacies across Europe. Table 14.16 displays the top active substances common to most European countries.

Morphine (solutions/suspensions, syrups and oral drops) and phenobarbital (solutions/suspensions, syrups, mixtures and oral drops) were included in the top 10 active substances in a total of 7 countries, being the active substances most frequently dispensed as oral liquids Europe-wide. Phenobarbital was the only NTI drug included in the top oral liquids.

The next most frequently dispensed active substances were chloral hydrate (solutions/suspensions, syrups and mixtures), midazolam (solutions/ suspensions, syrups and oral drops) and spironolactone (solutions/ suspensions and syrups), which were part of the top 10 active substances dispensed in a total of 6 countries.

Although these active substances were not exclusively dispensed to paediatric patients, as mentioned above, this population has a special need for compounded medicines and, therefore, age-appropriate formulations including these top active substances (dispensed by most European countries) should be considered for studies. However, again, only spironolactone is currently considered in the EMA (2012b) “Revised priority list for studies into off-patent paediatric medicinal products” and, therefore, it is recommended that all other top active substances be added to this list.

The countries that shared most active substances were Switzerland and Germany (6 active substances). These 2 countries were the only ones included in the research in which data collection referred exclusively to paediatrics.

Table 14.16 Active substances (per liquid dosage form) dispensed by most European countries.

	Morphine	Phenobarbital	Chloral hydrate	Midazolam	Spironolactone	Caffeine citrate	Glucose	Total
Portugal	Sol/Susp	_____	Sol/Susp Syrups	_____	Syrups	Syrups	_____	4
UK	Sol/Susp	Sol/Susp	Sol/Susp Syrups Mixtures	Sol/Susp	_____	Mixtures	_____	5
Switzerland	Sol/Susp Oral drops	Syrups	_____	Sol/Susp Syrups	Sol/Susp	Sol/Susp	Sol/Susp	6
Poland	_____	Sol/Susp Syrups Mixtures	_____	Sol/Susp Syrups	Sol/Susp	_____	_____	3
Netherlands	_____	Sol/Susp	_____	_____	_____	_____	Sol/Susp	2
Denmark	Sol/Susp Oral drops	_____	_____	_____	_____	Sol/Susp	Sol/Susp	3
Slovenia	Sol/Susp	Sol/Susp	Sol/Susp	Sol/Susp	_____	_____	_____	4
Finland	Sol/Susp	Sol/Susp	_____	_____	Sol/Susp	_____	Sol/Susp	4
Spain	_____	_____	Syrups	Sol/Susp Syrups	_____	_____	_____	2
France	Syrups	_____	Syrups	_____	Sol/Susp	_____	_____	3
Germany	_____	Oral drops	Sol/Susp Syrups	Sol/Susp Syrups Oral drops	Sol/Susp	Sol/Susp Oral drops	Sol/Susp Oral drops	6
Total	7	7	6	6	6	5	5	

Therefore, the similarities encountered suggest that the need for oral liquid compounded medicines in the paediatric population is likely to be the same Europe-wide. This reinforces the importance of including these oral liquids in the EMA priority list for studies and also in European Paediatric Formulary (Section 14.2.2) in the format of standardised (official) monographs. Considering the study by Brion *et al.* (2003), the top 4 active substances (morphine, phenobarbital, chloral hydrate and midazolam) were included in their top 20 oral liquids. More similarities between both studies were unlikely since Brion *et al.* (2003) included only 21 hospitals (convenience sample) whereas the present study included 242 hospitals (purposive sample).

d. **Oral solids vs oral liquids**

Oral solids and oral liquids were dispensed in all European countries but the specific dosage forms varied within the countries. Capsules and solutions/suspensions were the only dosage forms dispensed in all countries, which indicates that these are the most common dosage forms in pharmaceutical compounding Europe-wide. However, capsule calculations and the formulation/stability of solutions and suspensions are not always straightforward. It is important that hospital pharmacies become fully familiar with the preparation of these dosage forms so that the quality and safety of compounded medicines can be guaranteed. This finding reinforces the importance of European guidelines on pharmaceutical compounding, particularly in relation to methods of preparation for the most frequently dispensed dosage forms. In addition, there is a continued need for compounding education in schools of pharmacy adapted to current practices. For instance, not all European schools of pharmacy have manual capsule machines and, therefore, not all pharmacy graduates actually know how to prepare such compounded medicines. Considering that capsules are extemporaneously prepared in all European countries, it is crucial that the academic curriculum is adapted to current compounding practices.

The multidose oral liquids were quantitatively compared to the oral solids dispensed (in packs), per European country. In conclusion, a total of 6 countries (55%) dispensed more oral liquids whereas 4 countries (36%)

dispensed more oral solids. In 1 country (Slovenia), oral liquids and oral solids were dispensed in comparable quantities, as displayed in Table 14.17.

Table 14.17 Top oral dosage forms (solid or liquid) per European country.

European countries	Oral solid dosage forms	Oral liquid dosage forms
Portugal	✓	_____
UK	_____	✓
Switzerland	_____	✓
Poland	✓	_____
Netherlands	_____	✓
Denmark	✓	_____
Slovenia	✓	✓
Finland	_____	✓
Spain	_____	✓
France	✓	_____
Germany	_____	✓

As stated, oral liquid dosage forms offer a myriad of advantages to both pharmacists and patients and, therefore, it was not unexpected that these were more frequently dispensed than oral solids across Europe. However, the formulation and stability of oral liquids can be complex and not all hospital pharmacies have sufficient resources to assure optimal formulations.

In Portugal and Poland, compounding practices may be considered “traditional” as sachets and cachets, respectively, are still popular dosage forms. In these 2 countries, it is not unexpected that oral liquids did not correspond to the most frequently dispensed dosage forms. In Denmark, practices are not traditional as pharmaceutical compounding is centralised in a few hospital and community pharmacies, which prepare compounded medicines in large quantities for stock. Tablets, an elegant and stable dosage form, may be rapidly prepared in large quantities provided that the pharmacy has the necessary equipment. Therefore, it is not unexpected that, in Denmark, oral liquids were not the most frequently dispensed dosage forms either. In France, considering the large quantities of capsules dispensed, it is

suggested that these are culturally preferable to other dosage forms. Hence, oral liquids were not more frequently dispensed than oral solids in this country.

Phenobarbital, spironolactone and glucose were the active substances common to both top oral solids and oral liquids dispensed by most countries. The fact that phenobarbital, an NTI drug, is included in both reinforces the need for Europe-wide guidance on NTI drugs. These active substances were part of the top 10 active substances (per solid or liquid dosage forms) in all countries, with exception of 3 countries for phenobarbital and spironolactone, and only 2 countries for glucose. Therefore, oral compounded medicines including these 3 active substances, in particular, should be the considered for licensing or prioritised for standardisation in official (European) monographs. This finding suggests that although there are active substances common to most European countries, dosage forms may vary remarkably between countries. As a result, the compounded medicines dispensed are deemed to be country-specific and, therefore, there is a high need for harmonisation of compounding practices across Europe.

14.4.4 **Oromucosal preparations**

Although the aim of the research was to identify and characterise the most frequently dispensed oral compounded medicines, some hospital pharmacies also shared data regarding oromucosal preparations. These medicines were either specifically classified by hospital pharmacies as oromucosal or, alternatively, the additional comments to their use clearly suggested that these were not oral compounded medicines, but rather oromucosal preparations. This finding suggests that the classification of oral liquids and oromucosal preparations is not always clear in hospital pharmacies and, therefore, it highlights the need for a better understanding of the compounded medicines dispensed to patients. The safety of raw materials in oral liquids and oromucosal preparations is not the same because different routes of administration are implied, and these issues have to be acknowledged when preparing compounded medicines.

Oromucosal preparations were reported in all European countries, with the exception of Poland, Slovenia and France (Table 14.18). The number of participant hospitals that reported oromucosal preparations varied from 7% (Switzerland) to 40% (UK). The European countries that reported the largest quantities of multidose units were: Portugal (>16,000 units), Spain and Denmark. The oromucosal preparations varied considerably within the European countries and only a few were reported in more than 1 country as, for instance, the mouthwash for CIOM (Portugal, Spain and Finland). The dosage forms reported included mouthwashes (mainly), oromucosal liquids (solutions and suspensions), semi-solid oromucosal preparations (gels, ointments and pastes) and gargles. There is evidence of oromucosal preparations being dispensed in large quantities (e.g. oral decontamination suspension; 2-6 L), which suggests that not all oromucosal preparations were prepared for individual patients but instead for the hospital wards. Since the request for data specifically referred to oral compounded medicines, the list included in Table 14.18 is not comprehensive as more European hospitals might have dispensed additional oromucosal preparations but excluded this information from the dataset.

Table 14.18 Oromucosal preparations dispensed per European country and the respective participant hospitals and quantities dispensed.

European countries	Participant hospitals	Oromucosal preparations	Quantities dispensed
Portugal	28%	1. Mouthwash for CIOM (50-560 mL) 2. Sodium fluoride gel (20 g) 3. Artificial saliva (100-1,000 mL)	> 16,000 units
UK	40%	1. Tranexamic acid 50 mg/mL (100-500 mL) 2. *Knox Mouthwash* (100-300 mL) 3. Folinic acid 3mg/10 mL (200 mL) 4. Tetracycline 5% (200 mL)	189 units
Switzerland	7%	1. Chlorhexidine 0.05% (250 mL)	80 units
Poland	0%	n/a	n/a
Netherlands	33%	1. Amphotericin B 2% paste (5 g) 2. Cetrimide 0.1% mouthwash (300 mL) 3. Chlorhexidine HCl 2% ointment 4. Colistin sulfate 1 mg/mL mouthwash (100 mL) 5. Povidone-iodine 1% mouthwash (100 mL) 6. Sodium fluoride 1% mouthwash and gel (100 mL) 7. Tacrolimus 1 mg/g paste (30 g)	1,838 units
Denmark	14%	1. Chlorhexidine mouthwash 0.12% (300 mL) 2. Lidocaine gel 20% (100 mL)	3,000 units
Slovenia	0%	n/a	n/a
Finland	29%	1. Miconazole and lidocaine gel (20 g) 2. Sodium hypochlorite solution 0.5%, 1% (100 mL) Mouthwashes for CIOM 3. Ergocalciferol solution (100 mL) 4. Ergocalciferol and vitamin A solution (200 g)	835 units
Spain	27%	1. Anaesthetic solution (500 mL) 2. Oral decontamination preparation (suspensions 2-6L and ointments 100-500 g) 3. Mouthwash for CIOM 4. Gargle solution 5. Others (12%)	4,531 units
France	0%	n/a	n/a
Germany	11%	1. Acriflavinium chloride 5 mg/g (10 g) 2. Miconazole 20 mg/g (20 g) 3. Aluminium hydroxide (300 g) 4. Procaine HCl 10 mg/g (20 g) 5. Betamethasone, pheniramine maleate and nystatin (225 mL)	24 units

14.5 **Conclusions and recommendations**

Pharmaceutical compounding, the preparation of customised medicines in order to meet the specific needs of patients, represents the origins of the pharmacy profession and, throughout the centuries, it has remained an integral part of this profession. Despite the changes in pharmacy practice, in particular the advent of industrialised medicine, compounding remains a relatively common practice worldwide. In Europe, compounded medicines are prepared and dispensed in all countries, but this study has shown that the practice varies considerably with regards to legislation, professional organisations, information sources and, ultimately, with regards to the oral compounded medicines dispensed to patients.

Legislation regarding pharmaceutical compounding is country-specific in relation to terminology and the concept of compounded medicines, which potentially contributes to a lack of understanding between health care professionals. The requirements for the preparation and QC of compounded medicines are also country-specific, which results in variable expectations depending on the European country considered. Third-party compounding and batch preparation (in advance) are not permitted in all European countries. Compounded medicines are mainly prepared in community and hospital pharmacies but, in a few countries, these may also be prepared in other authorised entities. The same criteria should ideally apply to all European countries so that the practice of compounding is harmonised in Europe. The PIC/S PE 010-3 and the Resolution CM/ResAP(2011)1 are European guidance on pharmaceutical compounding but there is still need for adequate (official) Europe-wide standards of practice.

Professional organisations for pharmaceutical compounding in Europe do not yet exist and even national organisations are very limited. Spain is the European country (sampled in this research) with the greatest number of professional organisations specifically focused on pharmaceutical compounding. The only two specialist international organisations available to European pharmacists are the ISPhC and the IACP.

Information sources on pharmaceutical compounding in Europe are also yet to be developed. There are official (and non-official) national formularies but no work has been done so far in terms of translating to English and adapting any of these formularies to current compounding practices in Europe. There are also national pharmacopoeias that address pharmaceutical compounding, but the PhEur does not yet consider this practice. There is a need for an officially recognised European formulary on pharmaceutical compounding and/or a dedicated chapter and specific monographs for compounded medicines in the PhEur.

The oral compounded medicines most frequently dispensed in hospital pharmacy varied considerably throughout Europe, from traditional cachets in Poland to complex tablets in the Netherlands and Denmark. Oral liquid dosage forms were more frequently dispensed than oral solids, which was not unexpected considering that oral liquids offer a myriad of advantages to both pharmacists and patients. The compounded medicines dispensed were reported either by the respective active substance(s), their given titles or by the proprietary medicines used in their preparation; placebo compounded medicines were also reported. Compounded medicines were prepared individually and also in batches of variable sizes, depending on the hospitals and the European countries considered. A wide range of active substances, including NTI drugs, and dosage strengths were dispensed, which showed the diversity of pharmaceutical compounding in Europe and reinforced the importance of this practice in current therapeutics. The active substances dispensed by most hospitals were spironolactone, captopril and hydrochlorothiazide. The active substances most frequently dispensed as oral solids and oral liquids Europe-wide were phenobarbital, spironolactone and glucose. Therefore, it was recommended that these oral compounded medicines, in particular, should be the ones considered for licensing or prioritised for standardisation in official (European) monographs.

This project corresponds to the largest and most complex research in pharmaceutical compounding across Europe and aims to contribute to the harmonisation of quality and safety of compounded medicines in Europe.

14.5.1 **Recommendations for further research**

Pharmaceutical compounding in Europe is a research subject that has rarely been addressed in the scientific literature. However, there has been an increasing interest in this subject by European health care professionals and authorities, which stimulated the 2 recent initiatives of EDQM (Sections 14.1 and 14.2.2).

This research project constitutes the first extensive and structured analysis of pharmaceutical compounding in Europe and it represents a major contribution to a better understanding of the current practices within the European countries. Further research is necessary to build on this project so that more Europe-wide initiatives are initiated and pharmaceutical compounding in Europe progresses, for the benefit of all.

The aim of this project was to identify and characterise the extemporaneously compounded oral medicines most frequently dispensed in European hospital pharmacies. A total of 11 European countries were included in the research, namely 10 members of the EU and 1 non-member of the EU. There is still need to identify and characterise the extemporaneously compounded oral medicines most frequently dispensed in hospital pharmacies in all 17 EU countries[57] and 21 non-EU countries[58].

The research project focused only on oral compounded medicines and there is still lack of knowledge regarding non-oral (both sterile and non-sterile) compounded medicines dispensed in European hospital pharmacies.

Considering oral compounded medicines, further research is necessary to identify the formulae, source of raw materials (i.e. proprietary medicines or bulk), method of preparation, QC and beyond-use-dates for the most frequently dispensed oral compounded medicines, per country and across Europe. A risk assessment should be undertaken and the oral compounded medicines identified at a higher risk (e.g. NTI drugs), should also be considered for further research.

[57]Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Romania, Slovakia and Sweden.
[58]Albania, Andorra, Armenia, Azerbaijan, Belarus, Bosnia-Herzegovina, Croatia, Former Yugoslav Republic of Macedonia, Georgia, Iceland, Liechtenstein, Moldova, Monaco, Montenegro, Norway, Russia, San Marino, Serbia, Turkey, Ukraine and Vatican City State.

The present research project consisted of a retrospective analysis of the compounding records and, almost always, no information was found regarding the patient and the evidence-base for the compounded medicines dispensed. There is a need for prospective studies on pharmaceutical compounding in Europe including data on patient information, clinical need and evidence-based analysis.

Compounded medicines are not always prepared extemporaneously as one-off preparations but, instead, these medicines are frequently prepared in advance in “small” batches: studies should be undertaken to clearly distinguish these 2 practices. Moreover, the facilities and equipment used in the preparation of compounded medicines vary within hospital pharmacies and also between countries. Country-specific compounding practices and issues should be explored in-depth by means of interviews with pharmacy staff.

Not all compounded medicines dispensed in the hospital setting are actually prepared at the respective hospital pharmacies and there is currently a lack of knowledge regarding the source of the medicines dispensed. For instance, further research is necessary to identify and characterise the specials prepared at specials manufacturers in the UK.

The research project did not include an analysis of the staff at hospital pharmacies and no information was collected regarding the size and level of education of the staff involved in pharmaceutical compounding. This information is important as it contributes to a better understanding of current compounding practices per country. In addition, pharmacists and pharmacy technicians are taught pharmaceutical compounding during graduate and/or at post-graduate courses. The information taught strongly influences current practices per country. Research should also be undertaken to distinguish teaching of pharmaceutical compounding throughout Europe.

Very little research has been undertaken regarding the community setting and there is a need to identify and characterise the oral and non-oral (both sterile and non-sterile) compounded medicines most frequently dispensed in European community pharmacies.

14.5.2 **Recommendations for further initiatives**

- Establishment of an official concept of compounded medicines, including types and definitions, common to all European countries. A clear distinguish should be made in relation to standardised (small and large scale) and non-standardised compounded medicines.
- Development of Europe-wide official and enforceable compounding legislation, based on standard operating procedures and not on industrial GMP (certified facilities). A clear distinguish should be made between SOP and individualised medicines: the way forward is the standardisation of practices and not the standardisation of medicines, which is incompatible with individualised therapy. Europe-wide legislation should include allowance of third-party compounding, batch preparation, use of all authorised active substances (no negative lists) and exceptional use of commercial medicines in compounding across Europe.
- Establishment of mandatory quality control tests (for all types of compounded medicines) and development of standardised legal requirements for labelling compounded medicines.
- Development of a Europe-wide professional organisation specifically focused on pharmaceutical compounding. Organisation of compounding educational events and courses for pharmacists, doctors and all health care professionals involved in this practice throughout Europe.
- Inclusion of a compounding dedicated chapter on the PhEur, addressing not only the official concept of compounded medicines Europe-wide but also reference formulas and SOP. Development of an official (or non-official) European formulary for pharmaceutical compounding, including the extensive work previously published in national formularies so that there is no duplication of time and efforts. Likewise, development of a Europe-wide textbook on pharmaceutical compounding based on national textbooks of reference.
- Development of an official list of NTI drugs and official guidelines for compounding these potentially toxic active substances. Development of an international reference list of compounded medicines commonly known by given titles (non-proprietary names).
- Licensing, or prioritised for standardisation in official (European) monographs, of the most frequently dispensed oral compounded medicines in hospital pharmacies across Europe.
- Development of an official register of compounding pharmacies (hospital, community and other settings), per European country, including the contact details of the responsible pharmacists. Development of an official template for registering all compounded medicines dispensed, preferably in a digital format to easy traceability. Establishment of mandatory periodical reports of large scale compounded medicines to national authorities (following the example of France).
- Teaching of modern pharmaceutical compounding at the university level by updating the academic curriculum to current Europe-wide practices. Establishment of mandatory compounding continuing education across Europe.
- Establishment of governmental or private compounding consulting companies to support and reinforce quality compounding Europe-wide.

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Appendix 1

NTI drugs

List of active substances with a narrow therapeutic index (NTI drugs) classified by therapeutic groups (adapted from ANVISA, 2007)

Therapeutic groups	Active substances
Antibacterials	Clindamycin
Antidepressants	Lithium
Antiepileptics	Carbamazepine Oxcarbazepine Phenytoin Primidone Valproic acid
Antigout drugs	Colchicine
Anxiolytic, sedatives, hypnotics and antipsychotics	Clozapine
Bronchodilators and anti-asthma drugs	Aminophylline Theophylline
Cardiovascular drugs	Clonidine Digitoxin Digoxin Disopyramide Minoxidil Prazosin Procainamide Quinidine Verapamil HCl Warfarin
Immunosuppressants	Ciclosporin

Appendix 2

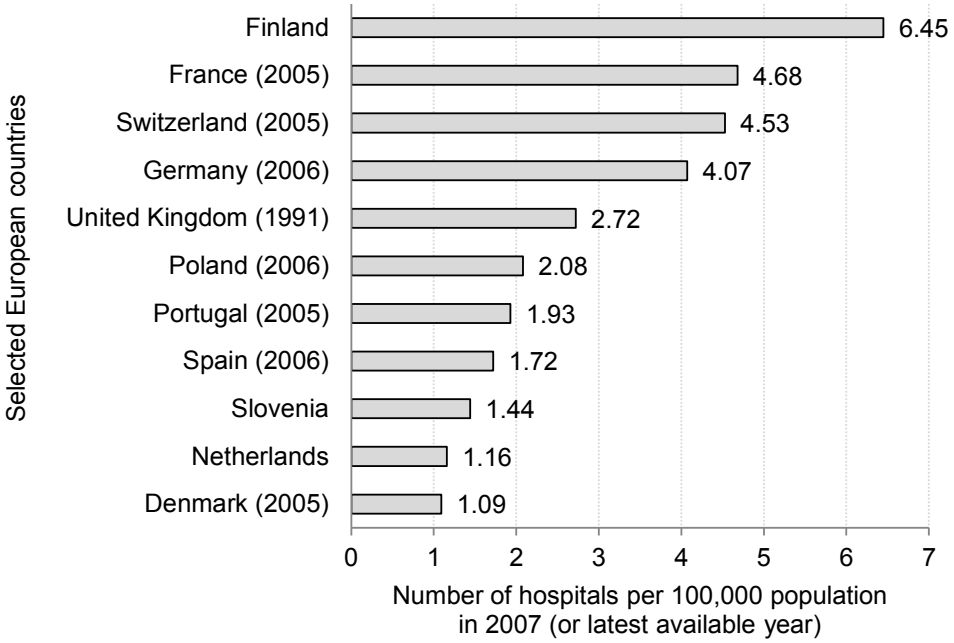
Compounding formulary

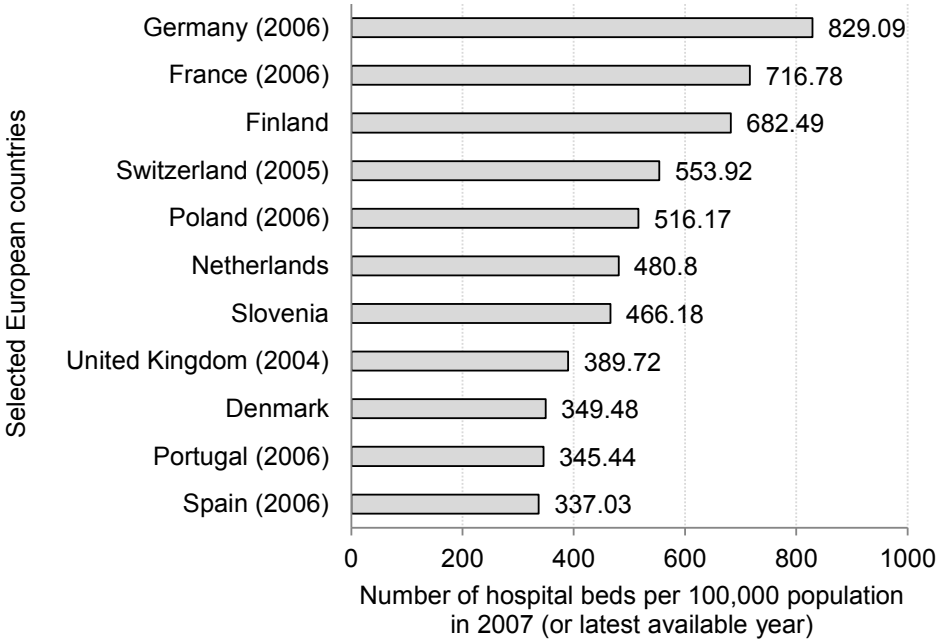
Compounded medicines	Formulas
Chloral hydrate 50 mg/mL oral liquid (Allen, 2006c)	Chloral hydrate 5 g Purified water 10 mL Syrup to 100 mL
Chloral Elixir, Paediatric BPC (Council of the Pharmaceutical Society of Great Britain, 1973)	Chloral hydrate 40 g Water 20 mL Black currant syrup 200 mL Syrup to 1,000 mL
Chloral Mixture BPC (Chloral Hydrate Mixture) (Council of the Pharmaceutical Society of Great Britain, 1973)	Chloral hydrate 100 g Syrup 200 mL Water to 1,000 mL
Golytely (powders for oral liquids) (Braintree Laboratories, 2001)	Macrogol 3350 236 g Sodium bicarbonate 6.74 g Sodium chloride 5.86 g Potassium chloride 2.97 g Sodium sulfate (anhydrous) 22.74 g (Purified water to 4,000 mL)
Methadone HCl 10 mg/mL Oral Solution (Swissmedic, 2006a)	Methadone HCl 5 g Methylparaben 0.335 g Propylparaben 0.144 g Propylene glycol 9.52 g Purified water to 500 mL
Polypharmacy (example) (Section 6.4.2)	Paracetamol 300 mg Diazepam 2 mg Codeine 15 mg Prednisone 5 mg Dipyrone 300 mg
Syrup BP (BP Commission, 2008a)	Sucrose 667 g Purified water to 1,000 g

Appendix 3

Number of hospitals and hospital beds

(adapted from WHO Regional Office for Europe, 2010)

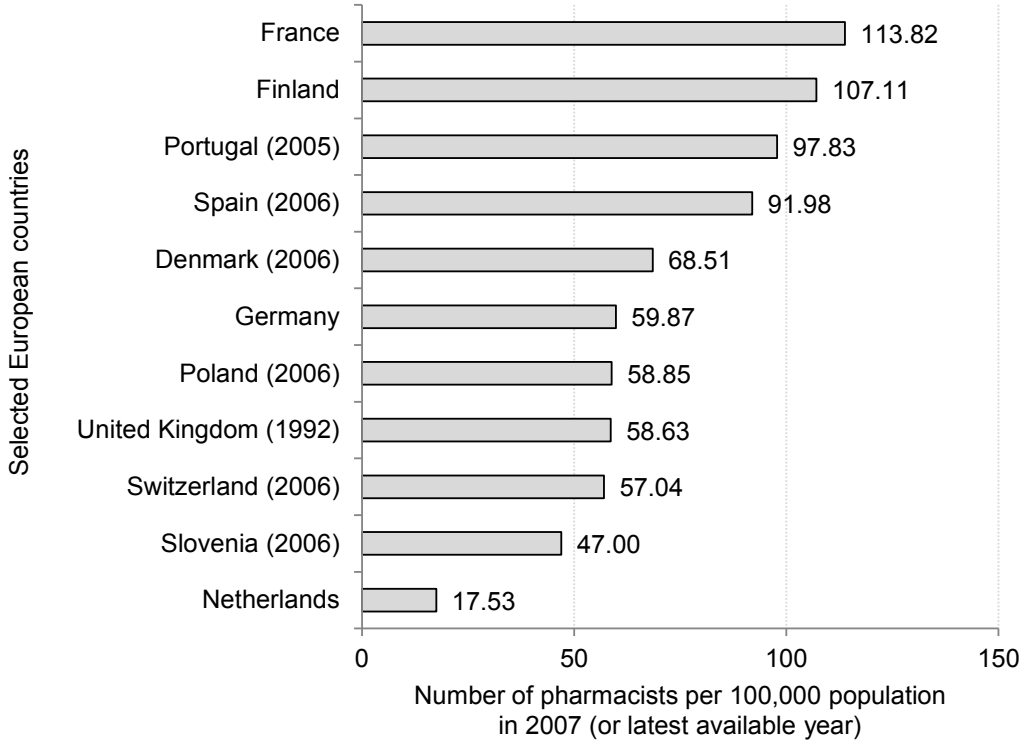




Appendix 4

Number of pharmacists

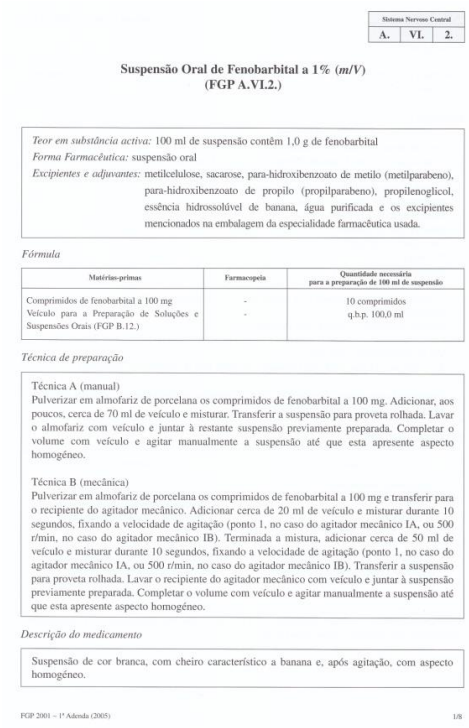
(adapted from WHO Regional Office for Europe, 2010; 2011)



Appendix 5

Phenobarbital 1% Oral Suspension (FGP 2005)

(adapted from CETMED, 2001)



Sistema Nervoso Central

A. VI. 2.

Suspensão Oral de Fenobarbital a 1% (*m/V*)
(FGP A.VI.2.)

Teor em substância activa: 100 ml de suspensão contêm 1,0 g de fenobarbital
Forma Farmacêutica: suspensão oral
Excipientes e adjuvantes: metilcelulose, sacarose, para-hidroxibenzoato de metilo (metilparabeno), para-hidroxibenzoato de propilo (propilparabeno), propilenoglicol, essência hidrossolúvel de banana, água purificada e os excipientes mencionados na embalagem da especialidade farmacêutica usada.

Fórmula

Matérias-primas	Farmacopeia	Quantidade necessária para a preparação de 100 ml de suspensão
Comprimidos de fenobarbital a 100 mg	-	10 comprimidos
Veículo para a Preparação de Soluções e Suspensões Orais (FGP B.12.)	-	q.b.p. 100,0 ml

Técnica de preparação

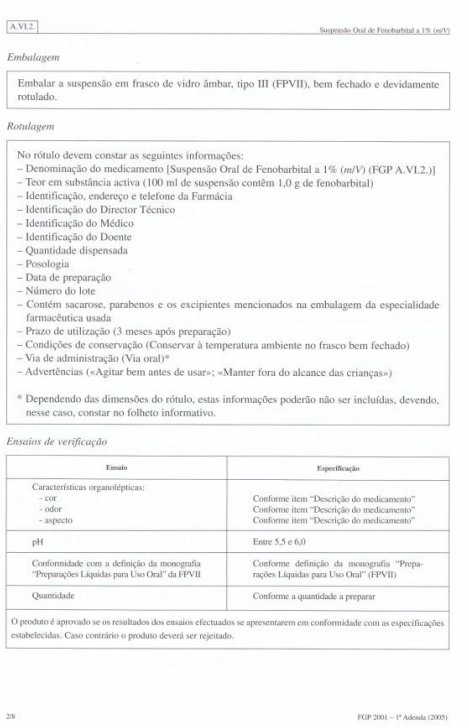
Técnica A (manual)
Pulverizar em almofariz de porcelana os comprimidos de fenobarbital a 100 mg. Adicionar, aos poucos, cerca de 70 ml de veículo e misturar. Transferir a suspensão para proveta rolhada. Lavar o almofariz com veículo e juntar à restante suspensão previamente preparada. Completar o volume com veículo e agitar manualmente a suspensão até que esta apresente aspecto homogéneo.

Técnica B (mecânica)
Pulverizar em almofariz de porcelana os comprimidos de fenobarbital a 100 mg e transferir para o recipiente do agitador mecânico. Adicionar cerca de 20 ml de veículo e misturar durante 10 segundos, fixando a velocidade de agitação (ponto 1, no caso do agitador mecânico IA, ou 500 r/min, no caso do agitador mecânico IB). Terminada a mistura, adicionar cerca de 50 ml de veículo e misturar durante 10 segundos, fixando a velocidade de agitação (ponto 1, no caso do agitador mecânico IA, ou 500 r/min, no caso do agitador mecânico IB). Transferir a suspensão para proveta rolhada. Lavar o recipiente do agitador mecânico com veículo e juntar à suspensão previamente preparada. Completar o volume com veículo e agitar manualmente a suspensão até que esta apresente aspecto homogéneo.

Descrição do medicamento

Suspensão de cor branca, com cheiro característico a banana e, após agitação, com aspecto homogéneo.

FGP 2001 – 1ª Adenda (2005) 1/8



A.VI.2. Suspensão Oral de Fenobarbital a 1% (*m/V*)

Embalagem

Embalar a suspensão em frasco de vidro âmbar, tipo III (FPVII), bem fechado e devidamente rotulado.

Rotulagem

No rótulo devem constar as seguintes informações:
- Denominação do medicamento [Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.)]
- Teor em substância activa (100 ml de suspensão contêm 1,0 g de fenobarbital)
- Identificação, endereço e telefone da Farmácia
- Identificação do Director Técnico
- Identificação do Médico
- Identificação do Doente
- Quantidade dispensada
- Posologia
- Data de preparação
- Número do lote
- Contém sacarose, parabenos e os excipientes mencionados na embalagem da especialidade farmacêutica usada
- Prazo de utilização (3 meses após preparação)
- Condições de conservação (Conservar à temperatura ambiente no frasco bem fechado)
- Via de administração (Via oral)*
- Advertências («Agitar bem antes de usar»; «Manter fora do alcance das crianças»)

* Dependendo das dimensões do rótulo, estas informações poderão não ser incluídas, devendo, nesse caso, constar no folheto informativo.

Ensaios de verificação

Ensaio	Especificação
Características organolépticas:	
- cor	Conforme item "Descrição do medicamento"
- odor	Conforme item "Descrição do medicamento"
- aspecto	Conforme item "Descrição do medicamento"
pH	Entre 5,5 e 6,0
Conformidade com a definição da monografia "Preparações Líquidas para Uso Oral" da FPVII	Conforme definição da monografia "Preparações Líquidas para Uso Oral" (FPVII)
Quantidade	Conforme a quantidade a preparar

O produto é aprovado se os resultados dos ensaios efectuados se apresentarem em conformidade com as especificações estabelecidas. Caso contrário o produto deverá ser rejeitado.

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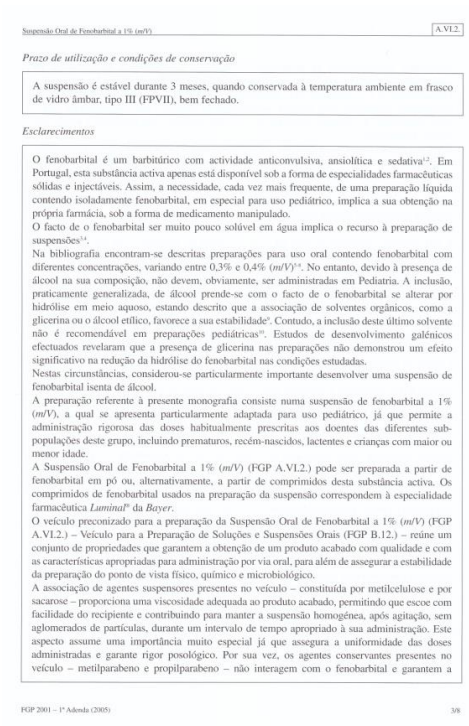

Suspensão Oral de Fenobarbital a 1% (*m/V*) A.VI.2.

Prazo de utilização e condições de conservação

A suspensão é estável durante 3 meses, quando conservada à temperatura ambiente em frasco de vidro âmbar, tipo III (FPVII), bem fechado.

Esclarecimentos

O fenobarbital é um barbitúrico com actividade anticonvulsiva, ansiolítica e sedativa[12]. Em Portugal, esta substância activa apenas está disponível sob a forma de especialidades farmacêuticas sólidas e injectáveis. Assim, a necessidade, cada vez mais frequente, de uma preparação líquida contendo isoladamente fenobarbital, em especial para uso pediátrico, implica a sua obtenção na própria farmácia, sob a forma de medicamento manipulado.
O facto de o fenobarbital ser muito pouco solúvel em água implica o recurso à preparação de suspensões[14].
Na bibliografia encontram-se descritas preparações para uso oral contendo fenobarbital com diferentes concentrações, variando entre 0,3% e 0,4% (*m/V*)[14]. No entanto, devido à presença de álcool na sua composição, não devem, obviamente, ser administradas em Pediatria. A inclusão, praticamente generalizada, de álcool prende-se com o facto de o fenobarbital se alterar por hidrólise em meio aquoso, estando descrito que a associação de solventes orgânicos, como a glicerina ou o álcool etílico, favorece a sua estabilidade[a]. Contudo, a inclusão deste último solvente não é recomendável em preparações pediátricas[10]. Estudos de desenvolvimento galénicos efectuados revelaram que a presença de glicerina nas preparações não demonstrou um efeito significativo na redução da hidrólise do fenobarbital nas condições estudadas.
Nestas circunstâncias, considerou-se particularmente importante desenvolver uma suspensão de fenobarbital isenta de álcool.
A preparação referente à presente monografia consiste numa suspensão de fenobarbital a 1% (*m/V*), a qual se apresenta particularmente adaptada para uso pediátrico, já que permite a administração rigorosa das doses habitualmente prescritas aos doentes das diferentes sub-populações deste grupo, incluindo prematuros, recém-nascidos, lactentes e crianças com maior ou menor idade.
A Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) pode ser preparada a partir de fenobarbital em pó ou, alternativamente, a partir de comprimidos desta substância activa. Os comprimidos de fenobarbital usados na preparação da suspensão correspondem à especialidade farmacêutica *Luminal*® da *Bayer*.
O veículo preconizado para a preparação da Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) – Veículo para a Preparação de Soluções e Suspensões Orais (FGP B.12.) – reúne um conjunto de propriedades que garantem a obtenção de um produto acabado com qualidade e com as características apropriadas para administração por via oral, para além de assegurar a estabilidade da preparação do ponto de vista físico, químico e microbiológico.
A associação de agentes suspensores presentes no veículo – constituída por metilcelulose e por sacarose – proporciona uma viscosidade adequada ao produto acabado, permitindo que escoe com facilidade do recipiente e contribuindo para manter a suspensão homogénea, após agitação, sem aglomerados de partículas, durante um intervalo de tempo apropriado à sua administração. Este aspecto assume uma importância muito especial já que assegura a uniformidade das doses administradas e garante rigor posológico. Por sua vez, os agentes conservantes presentes no veículo – metilparabeno e propilparabeno – não interagem com o fenobarbital e garantem a

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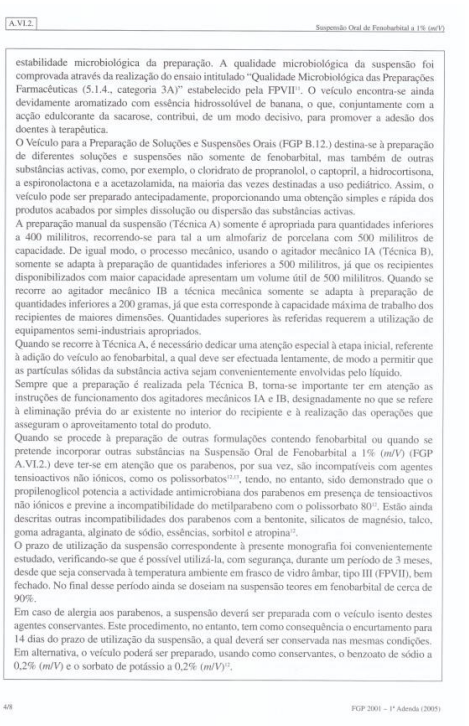

A.VI.2. Suspensão Oral de Fenobarbital a 1% (*m/V*)

estabilidade microbiológica da preparação. A qualidade microbiológica da suspensão foi comprovada através da realização do ensaio intitulado "Qualidade Microbiológica das Preparações Farmacêuticas (5.1.4., categoria 3A)" estabelecido pela FPVII[13]. O veículo encontra-se ainda devidamente aromatizado com essência hidrossolúvel de banana, o que, conjuntamente com a acção edulcorante da sacarose, contribui, de um modo decisivo, para promover a adesão dos doentes à terapêutica.
O Veículo para a Preparação de Soluções e Suspensões Orais (FGP B.12.) destina-se à preparação de diferentes soluções e suspensões não somente de fenobarbital, mas também de outras substâncias activas, como, por exemplo, o cloridrato de propranolol, o captopril, a hidrocortisona, a espironolactona e a acetazolamida, na maioria das vezes destinadas a uso pediátrico. Assim, o veículo pode ser preparado antecipadamente, proporcionando uma obtenção simples e rápida dos produtos acabados por simples dissolução ou dispersão das substâncias activas.
A preparação manual da suspensão (Técnica A) somente é apropriada para quantidades inferiores a 400 mililitros, recorrendo-se para tal a um almofariz de porcelana com 500 mililitros de capacidade. De igual modo, o processo mecânico, usando o agitador mecânico IA (Técnica B), somente se adapta à preparação de quantidades inferiores a 500 mililitros, já que os recipientes disponibilizados com maior capacidade apresentam um volume útil de 500 mililitros. Quando se recorre ao agitador mecânico IB a técnica mecânica somente se adapta à preparação de quantidades inferiores a 200 gramas, já que esta corresponde à capacidade máxima de trabalho dos recipientes de maiores dimensões. Quantidades superiores às referidas requerem a utilização de equipamentos semi-industriais apropriados.
Quando se recorre à Técnica A, é necessário dedicar uma atenção especial à etapa inicial, referente à adição do veículo ao fenobarbital, a qual deve ser efectuada lentamente, de modo a permitir que as partículas sólidas da substância activa sejam convenientemente envolvidas pelo líquido.
Sempre que a preparação é realizada pela Técnica B, torna-se importante ter em atenção as instruções de funcionamento dos agitadores mecânicos IA e IB, designadamente no que se refere à eliminação prévia do ar existente no interior do recipiente e à realização das operações que asseguram o aproveitamento total do produto.
Quando se procede à preparação de outras formulações contendo fenobarbital ou quando se pretende incorporar outras substâncias na Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) deve ter-se em atenção que os parabenos, por sua vez, são incompatíveis com agentes tensioactivos não iónicos, como os polissorbatos[12,15], tendo, no entanto, sido demonstrado que o propilenoglicol potencia a actividade antimicrobiana dos parabenos em presença de tensioactivos não iónicos e previne a incompatibilidade do metilparabeno com o polissorbato 80[12]. Estão ainda descritas outras incompatibilidades dos parabenos com a bentonite, silicatos de magnésio, talco, goma adraganta, alginato de sódio, essências, sorbitol e atropina[12].
O prazo de utilização da suspensão correspondente à presente monografia foi convenientemente estudado, verificando-se que é possível utilizá-la, com segurança, durante um período de 3 meses, desde que seja conservada à temperatura ambiente em frasco de vidro âmbar, tipo III (FPVII), bem fechado. No final desse período ainda se doseiam na suspensão teores em fenobarbital de cerca de 90%.
Em caso de alergia aos parabenos, a suspensão deverá ser preparada com o veículo isento destes agentes conservantes. Este procedimento, no entanto, tem como consequência o encurtamento para 14 dias do prazo de utilização da suspensão, a qual deverá ser conservada nas mesmas condições.
Em alternativa, o veículo poderá ser preparado, usando como conservantes, o benzoato de sódio a 0,2% (*m/V*) e o sorbato de potássio a 0,2% (*m/V*)[12].

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Uso(s) Terapêutico(s)

O fenobarbital é um barbitúrico com actividade anticonvulsiva, ansiolítica e sedativa[1,2]. Embora o seu mecanismo de acção não seja completamente conhecido, estima-se que a sua acção se deva ao efeito estabilizador da membrana, por modificação dos fluxos de Na^+ e de K^+ e por aumento da acção inibitória do ácido gama-aminobutírico (GABA), por provável acção a nível da membrana pós-sináptica[2,14].

O fenobarbital é usado no controlo de crises tónico-clónicas (grande mal), crises parciais e de convulsões febris. É ainda usado como hipnótico, sedativo e na sedação pré-operatória[1,2,4-14]. Esta substância é também útil na prevenção e no tratamento da hiperbilirrubinemia em recém-nascidos e na diminuição dos níveis de bilirrubina em situações de colestase crónica[1,15,16,19].

A Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) destina-se, especialmente, a uso pediátrico, já que em adultos se torna mais apropriada a administração de formas farmacêuticas sólidas, como os comprimidos. No entanto, pode também constituir uma alternativa apropriada às formas sólidas para outros grupos de doentes, nomeadamente em Geriatria e em indivíduos com dificuldade de deglutição. Está particularmente indicada no controlo da epilepsia, como hipnótico, sedativo, na sedação pré-operatória, na prevenção e no tratamento da hiperbilirrubinémia em recém-nascidos e na diminuição dos níveis de bilirrubina em situações de colestase crónica.

Modo de administração e posologia habitual

A Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) deve ser administrada com as refeições, de modo a diminuir os efeitos secundários a nível gastrointestinal[16]. De modo a obter-se rigor nas doses administradas, recomenda-se que a medição dos volumes seja efectuada com uma seringa graduada, como, por exemplo, as vulgarmente utilizadas pelos diabéticos para a administração subcutânea de insulina.

Na presente monografia somente se indicam regimes posológicos habitualmente usados em Pediatria, já que, como se referiu anteriormente, em adultos é mais comum a administração de formas farmacêuticas sólidas. As doses de fenobarbital a administrar variam em função da patologia em causa e de condições específicas do próprio doente e devem ser introduzidas de forma lenta, sendo ajustadas de acordo com as necessidades e a resposta do doente[1]. Todavia, estão descritos esquemas terapêuticos padrão[1,15], que correspondem aos seguintes:

Epilepsia	Sedativo	Hipnótico
Recém-nascido – 0,3-0,5 ml/kg peso, por dia; < 1 ano – 0,5-0,6 ml/kg peso, por dia; 1-5 anos – 0,6-0,8 ml/kg peso, por dia; 5-12 anos – 0,4-0,6 ml/kg peso, por dia; > 12 anos – 0,1-0,3 ml/kg peso, por dia. (a administração pode ser efectuada em 1 ou 2 tomas)	0,2 ml/kg peso/ 3 vezes por dia	0,3-0,5 ml/kg peso, ao deitar.

Sedação pré-operatória	Prevenção e Tratamento da Hiperbilirrubinemia em recém-nascidos
0,1-0,3 ml/kg peso, 60 a 90 minutos antes da cirurgia.	0,3-0,8 ml/kg peso, por dia, dividida em 2 ou 3 tomas, durante os primeiros dias de vida. A dose máxima corresponde a 1,2 ml/kg peso, por dia.

Nota: 1 ml de Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) contém 10 mg de fenobarbital.

Pode ser necessário observar um período de duas a três semanas para que se atinjam, na totalidade, os efeitos anti-convulsivos[1,2]. A interrupção do tratamento com fenobarbital deve ser efectuada de uma forma gradual ao longo de uma semana[1]. Quando existe a necessidade de substituir a suspensão de fenobarbital por outro medicamento, a sua introdução deve ser efectuada de forma gradual e em simultâneo com a descontinuação do fenobarbital[1]. A interrupção brusca do tratamento com fenobarbital após administração prolongada pode desencadear o estado de mal epilético[16].

Efeitos secundários

Em geral, os efeitos secundários associados ao fenobarbital estão relacionados com a dose administrada e com a sensibilidade individual[14].

Os efeitos secundários mais frequentes incluem sedação, tonturas, letargia e ressaca[1,2,14-16,19]. Nos idosos é também comum ocorrer excitação, confusão, depressão e hipotermia[1,2,15,16,19]. Outros efeitos secundários, embora menos frequentes, incluem excitação e hiperactividade paradoxal em crianças, sonolência, cefaleias, vertigens, polinevrite, bradicardia, hipotensão, náuseas, vómitos, anorexia, obstipação, exacerbação de porfiria, *rash*, urticária, deslipidémias, alterações de humor, dependência física e psicológica, ataxia, miose, midríase e nistagmo[1,2,14-19].

Os efeitos secundários mais sérios, embora ocorram raramente, manifestam-se por alucinações, choque, depressão respiratória, apneia, dermatite exfoliativa, eritema multiforme (ou síndrome de Stevens-Johnson), angioedema, hipocalcémia, anemia, agranulocitose, trombocitopenia, macrocitose, metahemoglobinémia, linfocitose, osteomalacia, pseudo-reumatismo barbitúrico, nefrotoxicidade, hepatite e perturbações hepáticas[1,2,14-16,18,19].

Precauções e contra-indicações

A suspensão de fenobarbital está contra-indicada em indivíduos com hipersensibilidade aos barbitúricos, história de porfiria, insuficiência hepática ou renal grave e doença respiratória com dispneia ou obstrução[2,15-19].

O fenobarbital deve ser usado com precaução em crianças, idosos, doentes debilitados e em indivíduos com dor (crónica ou aguda), depressão, tendências suicidas, história de abuso de medicamentos, insuficiência renal e/ou hepática moderada, alterações da pressão sanguínea, doença cardiovascular ou estado de choque[2,15,16,18]. A administração de fenobarbital deve ser efectuada com extrema precaução em pacientes com nefrite[1,2].

A administração da suspensão pode originar sonolência, pelo que se deverá redobrar a prudência no caso de se conduzir automóveis ou manejar máquinas[2,15-17].

A administração de fenobarbital está contra-indicada em grávidas e durante o período de aleitamento[2,3,16].

O fenobarbital pode originar falsos positivos no teste da fentolamina (utilizado no diagnóstico da distrofia simpática reflexa), reduzir a absorção da vitamina B12 marcada com ^{57}Co (utilizada no diagnóstico de anemias por deficiência em ferro), diminuir os níveis de bilirrubina e interferir com o teste de excreção de bromosulfaleína (utilizada na determinação de doença hepática)[2]. O uso de fenobarbital pode originar alterações no electrocardiograma, as quais se mantêm por algum tempo após a descontinuação do tratamento[2].

Devido à presença de sacarose na sua composição, a Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) não deve ser administrada em diabéticos, recomendando-se, nestes casos, o uso da Suspensão Oral de Fenobarbital a 1% (*m/V*), isenta de açúcar (FGP A.VI.3.).

Interacções

Devido ao facto de o fenobarbital ser um indutor de várias isoenzimas do citocromo P450, qualquer fármaco cujo metabolismo esteja envolvido neste sistema, constitui um potencial candidato à interacção com o fenobarbital[2,14,15]. Assim, o fenobarbital apresenta interacções medicamentosas com outros antiepiléticos (ácido valpróico, carbamazepina, beclamida, fenitoína, felbamato, lamotrigina, etosuximida), antidepressivos, anti-histamínicos, narcóticos, fenotiazinas, haloperidol, hipnóticos, sedativos, analgésicos opióides, metilfenidato, corticosteróides, digitoxina, anticoncepcionais e outros estrogéneos, xantinas, dissulfiram, metronidazol, cloranfenicol, doxiciclina, rifampicina, rifabutina, griseofulvina, itraconazol, voriconazol, mefloquina, antidiabéticos orais, anticoagulantes orais, sirolimus, tacrolimus, ciclosporina, quinidina, bloqueadores beta, disopiramida, clozapina, felodipina, nifedipina, verapamil, donepezil, losartan, nimodipina, indinavir, ritonavir, saquinavir, delavirdina, nelfinavir, amprenavir, tamoxifeno, ciclofosfamida, doxorrubicina, tenoposido, etoposido, vincristina, metotrexato, piridoxina, paracetamol, fenilbutazona, metadona, petidina, cimetidina, bexaroteno, relaxantes musculares de acção central, colestiramina, vacina anti-*Influenza*, leucovorin, teofilina, tretinoína, eucaliptol e álcool[2,14,19].

Sintomas de intoxicação e respectivo tratamento

Em caso de sobredosagem podem ocorrer efeitos tóxicos que se manifestam por descoordenação dos movimentos durante a marcha, disartria, nistagmo contínuo, sonolência, confusão, depressão respiratória, edema pulmonar, arreflexia e coma[2,16]. Pode ainda ocorrer sintomatologia típica de estado de choque com taquicardia e hipotensão, icterícia, oligúria e arrepios seguidos de acessos febris[2,16].

Em caso de intoxicação aguda, deve-se proceder à terapia de suporte e sintomática[15]. As funções respiratória, cardiovascular, renais e a manutenção do equilíbrio electrolítico devem merecer particular atenção[2,15]. Quando o doente está consciente e com o reflexo vagal intacto, deve-se induzir a emese por administração de xarope de ipecacuanha[2]. No caso de a emese estar contra-indicada, deve-se proceder a lavagem gástrica seguida de administração de carvão activado ou um catártico[2,15]. Deve-se ainda monitorizar os sinais vitais e os parâmetros laboratoriais, bem como manter a temperatura corporal[2]. A alcalinização da urina e a hemodiálise podem também revelar-se procedimentos com utilidade[2].

Caso surja algum dos sintomas descritos, a administração da suspensão de fenobarbital deverá ser imediatamente interrompida. O doente intoxicado deverá ser rapidamente encaminhado para o hospital mais próximo, fazendo-se acompanhar pela embalagem do medicamento.

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Anexos:
- Ficha de preparação
- Folheto informativo**

** No caso de a Suspensão Oral de Fenobarbital a 1% (*m/V*) (FGP A.VI.2.) ser preparada a partir de uma especialidade farmacêutica contendo esta substância activa, os excipientes mencionados na embalagem da especialidade farmacêutica usada deverão ser acrescentados no folheto informativo.

Appendix 6

Portuguese questionnaire / Table (version 1)

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

INDICAÇÕES Por favor preencha a seguinte tabela apenas com os Medicamentos Manipulados ORAIS LÍQUIDOS dispensados pelos Serviços Farmacêuticos no ano de 2006

Substância Activa	Dosagem unidades	Forma Farmacêutica Solução / Emulsão / Suspensão	Volume unidade	Número de vezes dispensado em 2006 Jan	Fev	Mar	Abr	Maio	Jun	Jul	Ago	Set	Out	Nov	Dez	TOTAL
EXEMPLO	Captopril	1mg/mL	Solução	100mL	0	2	5	1	3	5	2	1	2	2	0	1	24
																	0
																	0
																	0
																	0
																	0
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																	0
				+													0
					0	0	0	0	0	0	0	0	0	0	0	0	0

Appendix 7

Portuguese questionnaire / Questions (version 1)

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

1 - Qual a principal FORMA FARMACÊUTICA dispensada pelos Serviços Farmacêuticos no ano de 2006?

Papéis Medicamentosos | Cápsulas | Supositórios | Pomadas/Cremes | Soluções/Suspensões

2 - Considerando todas as formas farmacêuticas, qual o número médio TOTAL de Medicamentos Manipulados dispensados pelos Serviços Farmacêuticos no ano de 2006?

[< 100] | [100 - 500] | [500 - 1000] | [1000 - 2000] | [> 2000]

COMENTÁRIOS

The individual results are protected and will be directly available only to the participants.

The research project results will be reported anonymously in peer reviewed scientific journals, internal reports and conference presentations.

The research project is compliant with the Data Protection Act 1998. The Data Protection Registration Number of The School of Pharmacy University of London is xxxxxx.

Thank you very much for participating in this European wide research project on Extemporaneous Preparations in Hospital Pharmacy.

Appendix 8

Portuguese questionnaire / Introduction

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

INTRODUÇÃO MARÇO 2007

Os Medicamentos Manipulados são diariamente dispensados pela maioria dos Serviços Farmacêuticos dos Hospitais Europeus. No entanto, o tipo e número de medicamentos manipulados dispensados varia consideravelmente.
Neste projecto de Doutoramento, orientado pelo Professor Doutor Kevin Taylor e Prof. Doutora Catherine Tuleu, procuramos conhecer o *State-of-the-Art* dos medicamentos manipulados na Europa.

O xxxxxx é convidado a participar neste projecto de âmbito Europeu. O seu contributo é muito importante para conhecermos a realidade Portuguesa.

Agradecíamos o preenchimento de **1 Tabela** e a resposta a **2 Questões**.
Os dados fornecidos à *The School of Pharmacy - University of London* serão protegidos e permanecerão anónimos.
Quaisquer esclarecimentos por favor contactem-me por e-mail (xxxxxx) ou telefone (xxxxxx).

Muito obrigada,

Maria João Carvalho
Department of Pharmaceutics
The School of Pharmacy – University of London
29-39 Brunswick Square
London WC1N 1AX
United Kingdom

Appendix 9

Portuguese questionnaire / Table (version 2)

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

Por favor preencha a seguinte tabela considerando os MEDICAMENTOS MANIPULADOS ORAIS mais frequentemente dispensados pelos Serviços Farmacêuticos em 2006

	Substância Activa	Dosagem	Forma Farmacêutica	Quantidade	Número de vezes dispensado em 2006
Exemplos	Captopril	1 mg / mL	Solução	50 - 250 mL	75
	Nitrofurantoína	5 mg / mL	Suspensão	100 - 300 mL	67
	Bicarbonato de Sódio	500 mg	Cápsulas	30 - 300 caps	45
	Fenobarbital	7 mg	Papéis medicamentosos	20 - 40 pp	41
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					

Appendix 10

Portuguese questionnaire / Questions (version 2)

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PROJECTO DE DOUTORAMENTO

MEDICAMENTOS MANIPULADOS EM FARMÁCIA HOSPITALAR NA EUROPA

PORTUGAL

1 - Por favor estime o número TOTAL de MEDICAMENTOS MANIPULADOS ORAIS dispensados pelos Serviços Farmacêuticos em 2006:

MEDICAMENTOS MANIPULADOS ORAIS ☐

2 - Por favor indique o número de FARMACÊUTICOS e o número de TÉCNICOS nos Serviços Farmacêuticos em 2006:

Farmacêuticos: ☐ Técnicos: ☐

Comentários _____

The individual results are data protected and will be directly available only to the research team.

The research project results will be reported anonymously in peer reviewed scientific journals, internal reports and conference presentations.

The research project is compliant with the Data Protection Act 1998. The Data Protection Registration Number of The School of Pharmacy is xxxxxx.

Thank you very much for participating in this European wide research project on Extemporaneous Preparations in Hospital Pharmacy.

Appendix 11

Dermatological drugs and sunscreens

Active substances included in this therapeutic group were reported by only 4 European countries (Portugal, UK, Finland and Spain), as follows:

- Acitretin: is a retinoid that is given orally for the treatment of severe psoriasis resistant to other forms of therapy (*Martindale 35*, 2007). Acitretin was reported as an oral suspension (1 mg/mL) / special by 1 UK hospital and as capsules (8 mg) by 1 Spanish hospital.
- Salicylic acid: is applied topically for its keratolytic and caustic properties, depending on the concentrations used (*Martindale 35*, 2007). It was reported as 15 mg sachets by only 1 Portuguese hospital but, because of the similarities between salicylic acid and acetylsalicylic acid (aspirin), a frequently dispensed active substance in Portugal, it is likely that the hospital pharmacy dispensed aspirin instead.
- Tretinoin: is a retinoid (acid form of vitamin A) that is mainly applied topically for the treatment of acne vulgaris but it is also given orally (*Martindale 35*, 2007). Tretinoin was reported as capsules of variable strengths by only 1 hospital in Spain.
- Urea: is mainly applied topically in the treatment of ichthyosis and hyperkeratotic skin disorders. Nevertheless, urea has other therapeutic indications and may also be given intravenously and orally (*Martindale 35*, 2007). For instance, oral urea has been successfully used in the management of children with chronic syndrome of inappropriate antidiuretic hormone secretion (SIAD) (Huang *et al.*, 2006). Oral urea was reported in Finland as capsules (75 mg) by only 1 hospital and in Portugal as sachets (20-30 g) by another hospital.

Appendix 12

Disinfectants and preservatives

Active substances included in this therapeutic group were reported by all European countries, with the exception of Slovenia, as follows:

- Acriflavinium chloride: is an acridine derivative, a slow-acting antiseptic, which has been used in the treatment of oropharyngeal infections (*Martindale 35*, 2007). It was reported in Germany as an oromucosal preparation.
- Alcohol: was reported by 1 French hospital as an oral solution of alcohol and menthol, which is mainly used to relieve symptoms of bronchitis, sinusitis and other similar conditions (*Martindale 35*, 2007).
- Butylated hydroxyanisole and butylated hydroxytoluene: are antioxidants frequently used in combination (*Martindale 35*, 2007) and were reported as capsules of 5 mg and 25 mg (of each) by 1 French hospital.
- Cetrimide: is a quaternary ammonium antiseptic that is used as an aqueous solution in concentrations of 0.1 to 1% for cleansing skin, wounds and burns (*Martindale 35*, 2007). It was reported as an oromucosal preparation 0.1% (300 mL) by 1 Dutch hospital.
- Chlorhexidine: is an antiseptic and disinfectant that is used as oral gels, sprays and mouthwashes for the treatment of mouth infections and to reduce dental plaque accumulation (*Martindale 35*, 2007). It was reported as oral and oromucosal preparations in 5 European countries, namely: Portugal (alone and in combination), Switzerland, Netherlands (chlorhexidine HCl), Denmark and Spain (chlorhexidine and also chlorhexidine gluconate in combination), by a total of 8 European hospitals. Chlorhexidine was reported as oral and oromucosal solutions (0.05-1%, 4 strengths; 50-500 mL) and ointments (2%).
- Hexetidine: is a bactericidal and fungicidal antiseptic frequently used as a mouthwash 0.1% in the treatment of local infections and oral hygiene (*Martindale 35*, 2007). It was reported in Spain (1 hospital) as an oromucosal preparation (anaesthetic solution) including nystatin, mepivacaine HCl, sodium bicarbonate and hexetidine.
- Hydrogen peroxide: is an oxidising agent used as an antiseptic for the disinfection of mucous membranes (*Martindale 35*, 2007). It was used as a solution in mouthwashes for CIOM in Spain (2 hospitals).
- Potassium/sodium metabisulfite: sulphites are strong reducing agents and are used as antioxidants (*Martindale 35*, 2007). Metabisulfite was reported in Spain as capsules of 5 and 100 mg (1 hospital). Potassium metabisulfite, in particular, was reported as capsules of 10 and 20 mg by 1 French hospital. Sodium metabisulfite, on the other hand, was reported in the UK, Netherlands, France and Spain, both as capsules (1-200 mg; 7 strengths) and powders for oral liquids (25 mg), by a total of 5 European hospitals.

- Povidone-iodine: is an iodophore that is used as a disinfectant and antiseptic; it has been used as a 1% mouthwash for oral infections, including candidiasis (*Martindale 35*, 2007). It was reported by only 1 Dutch hospital as a 1% mouthwash (100 mL).
- Sodium benzoate: is used in the treatment of hyperammonaemia and in nonketotic hyperglycinaemia; it is also a common ingredient in cough preparations (*Martindale 35*, 2007). It was reported in 7 European countries, namely: Portugal, UK (both as specials and extemporaneous preparations), Switzerland, Poland (in combination with multiple active substances), Netherlands, Finland and Spain, by a total of 19 European hospitals. Sodium benzoate was reported as oral liquids (2-250 mg/mL, 5 strengths; 100-1,000 mL), capsules (100 and 500 mg), oral powders (0.85-3 g) and cachets.
- Sodium hypochlorite: is a disinfectant and antiseptic (with the brief and rapid actions of chlorine) that is used in dentistry as 0.5-5.25% solutions (*Martindale 35*, 2007). It was reported only in Finland (1 hospital) as 0.5 and 1% oromucosal preparations (dental solutions).

Appendix 13

Paraffins and similar bases

Active substances included in this therapeutic group were reported by only 3 European countries (Portugal, UK and Switzerland), as follows:

- Cholesterol: Oral cholesterol is included in compounding formularies as, for instance, 150 mg/mL suspension (Nationwide Children's Hospital, 2010) and 200 mg/mL suspension (IWK Health Centre, 2009). Cholesterol was reported as oral solids in Portugal (300 mg oral powders) and Switzerland (200 mg capsules), by a total of 2 hospitals; and also as an oral liquid (100 mg/mL solution) in the UK, by only 1 hospital.
- Liquid paraffin: oral liquid paraffin has been used as a lubricant and in the symptomatic treatment of constipation, in volumes up to 45 mL daily (*Martindale 35*, 2007). It was reported by 2 Swiss hospitals as an oral liquid of 200 mL and 500 mL, respectively.

Appendix 14

Stabilising and suspending agents

Active substances included in this therapeutic group were reported by only 4 European countries (Portugal, Netherlands, Finland and Spain), as follows:

- Carmellose: has a variety of uses in pharmaceutical manufacturing but it is also given orally in the treatment of constipation and management of obesity (*Martindale 35*, 2007). Carmellose was reported by 1 Portuguese hospital as an oral liquid (solution) 1%.
- Cellulose: although primarily used in pharmaceutical manufacturing, various forms of cellulose have been used in constipation and obesity (*Martindale 35*, 2007). Cellulose was reported as capsules in the Netherlands and also in Spain (capsules of microcrystalline cellulose 200 g), by a total of 2 hospitals.
- Ceratonia: is commonly used in combination with an osmotic carbohydrate sugar alcohol for small bowel distension for magnetic resonance imaging (Ajaj *et al.*, 2004). Ceratonia was reported in Portugal (1 hospital) as an oral suspension (2,000 mL) in combination with sorbitol and in Finland (1 hospital) as an oral solution (750 mL) in combination with mannitol.
- Methylcellulose: is widely used in pharmaceutical manufacturing as an emulsifying, suspending and thickening agent. However, oral methylcellulose is also used clinically as, for example, a bulk laxative in the treatment of constipation and the control of faecal consistency in ostomies (*Martindale 35*, 2007). Methylcellulose was reported in Portugal as an oral liquid (solution) 0.5% and 1% (2 hospitals); in the Netherlands as an oral liquid (300 mL - 1L) 0.5%, 1% and 2% (3 hospitals); in Finland as an oral liquid (solution) 1% (2 hospitals); and, finally, in Spain as an oral liquid (both solutions and suspensions) 1% and oral powders (sachets) 7.5 g, by a total of 3 hospitals. In Finland, it was reported that the methylcellulose solution was indicated for enterography. Nevertheless, because methylcellulose solutions (of variable strengths) are commonly used as vehicles in pharmaceutical compounding, it is likely that some of the oral liquids reported by the European hospitals corresponded, instead, to vehicles for the preparation of oral compounded medicines.

Appendix 15

Supplementary drugs and other substances

This therapeutic group includes monographs for drugs which are not easily classified, new drugs whose place in therapy is not yet clear and drugs no longer used clinically but still of interest; it also includes herbal medicines (*Martindale 35*, 2007). Active substances included in this group were reported by all European countries, as follows:

- Ammonia: oral solutions of ammonia (diluted) have been administered as reflex stimulants (*Martindale 35*, 2007). Ammonia aniseed (oral solution) was reported by 1 hospital in Switzerland and ammonia spirit aniseed (as part of an anti-cough preparation) was reported by 2 Dutch hospitals.
- Amylase: is commonly included in preparations of digestive enzymes and is given orally to reduce the respiratory-tract inflammation, local swelling and oedema (*Martindale 35*, 2007). It was reported as oral powders, in combination with protease and amylase (digestive enzymes, Appendix 26), by 1 Slovenian hospital.
- Belladonna: has been used for its antimuscarinic actions but is now considered an obsolete therapeutic option (*Martindale 35*, 2007). It was reported as belladonna tincture by 1 Spanish hospital.
- Betaine: is given orally in the treatment of patients with homocystinuria in usual doses of 3 g twice daily (*Martindale 35*, 2007). It was reported in Portugal (1 hospital) as oral powders (3 g).
- Bethanechol chloride: is a muscarinic parasympathomimetic that is used for its activity on the bladder and GI tract (*Martindale 35*, 2007). It was reported as capsules (0.3-20 mg) in Spain and France and as an oral solution (1 mg/mL) in France, by a total of 4 hospitals.
- Borax and boric acid: have similar uses and should not be used internally. Preparations of borax in glycerol or honey were formerly used as paints for the throat, tongue and mouth but should no longer be used because of toxicity risks (*Martindale 35,* 2007). Borax was reported by 1 Portuguese hospital as oral powders (30 g) and by 2 Spanish hospitals as a gargle solution (in combination with other substances). Boric acid was reported by 2 Portuguese hospital as oral powders (100 g).
- Bromides (ammonium, sodium and potassium): bromides depress the CNS; potassium and sodium bromide have been used as sedatives and anticonvulsants but are considered toxic and have been replaced by more effective and less toxic drugs (*Martindale 35,* 2007). Bromides were reported in Poland and mainly as part of the oral solutions: *sol. sal. erlenmayeri* and *mixture nervinae* (Appendix 16). Potassium bromide was also reported in Denmark (1 pharmacy) as an oral solution 6.5% (500 mL); and in Germany (1 hospital) as capsules (425, 848 and 850 mg).

- Calcium hydroxide: is a weak alkali frequently indicated for external use (*Martindale 35,* 2007) but was reported, in combination with barium sulfate, as (oral) capsules (14.6-176 mg) by 1 French hospital. Since the identification of the French hospitals was not disclosed by AFSSAPS (Section 12.3), it was not possible to check the (oral) therapeutic use of these compounded medicines.
- Cannabis: the major psychoactive constituent of cannabis is dronabinol, which is used as an antiemetic in patients receiving chemotherapy; it is also reported to have analgesic, muscle relaxant and appetite stimulant effects (*Martindale 35,* 2007). It was reported only in the Netherlands (4 hospitals) as oral powders (125 g), powders for oral liquids (0.5 and 1 g) and oral solutions (1 mg/mL, 100 mL).
- Cellulase: is used orally in minor digestive disorders, as dyspepsia and flatulence (*Martindale 35,* 2007) and was reported in Spain (1 hospital) as capsules (10 mg).
- Cinchona bark: is constituted by several alkaloids, including quinine and quinidine, and is indicated for malaria (*Martindale 35,* 2007). It was reported as capsules in France (1 hospital), as part of the proprietary medicine Quinimax (quinine, quinidine and cinchona bark).
- Citric acid: is used to dissolve renal calculi, alkalinise the urine and prevent encrustation of urinary catheters. It is also used for the management of dry mouth, treatment of coughs, GI disturbances and metabolic acidosis (*Martindale 35,* 2007). It was reported in 5 European countries, namely: UK (in combination with citrate salts and named tricitrates oral solution, specials only), Poland, Netherlands (in combination with glycerol), Denmark (in combination with glycerol and as monohydrate) and Slovenia (in combination with multiple active substances and named laxative salts) and by a total of 6 European hospitals. Citric acid was reported as oral solutions (5 and 10%), capsules, oral powders (100 g) and cachets (0.5 g). Citric acid is also part of the Shohl's Solution (Appendix 16), which was reported in Portugal and Spain, by a total of 4 hospitals.
- Cobalt chloride: although not commonly used in therapy because of safety concerns, it may be indicated in the treatment of certain types of anaemia as it produces reticulocytosis and a rise in the erythrocyte count (*Martindale 35,* 2007). It was reported only in France (1 hospital) as capsules of 4.75 mg.
- Crataegus: has flavonoid glycosides with cardiotonic properties (*Martindale 35,* 2007) and was reported in Poland (1 hospital) as an oral solution (in combination with multiple active substances).
- Creatine: is an endogenous substance used in cardiac and metabolic disorders, as well as a dietary supplement (*Martindale 35,* 2007). It was reported by 1 Portuguese hospital as oral powders of 3 g.
- Diphemanil metilsulfate: is usually indicated for external use but has been investigated orally for the treatment of symptomatic bradycardia in infants (*Martindale 35,* 2007). It was reported in France as capsules (1-50 mg; 9 strengths) and oral solutions (10 mg/mL), by a total of 5 hospitals.

- Disulfiram: inhibits aldehyde dehydrogenase, the enzyme responsible for the oxidation of acetaldehyde (a metabolite of alcohol), resulting in increased blood levels of acetaldehyde, which is responsible for unpleasant symptoms and, therefore, is used as an adjunct in the treatment of chronic alcoholism. Disulfiram was reported as an oral suspension (40 mg/mL, 500 mL) by only 1 Danish pharmacy.
- Drotaverine: is an antispasmodic used in the management of biliary and urinary-tract spasm and also GI spasm (*Martindale 35,* 2007). It was reported as cachets (10 mg) by 1 Polish hospital only.
- Fluorescein: the sodium salt has been given orally for angiography and the dilaurate salt for the assessment of exocrine pancreatic function (*Martindale 35,* 2007). It was reported in Portugal only (1 hospital) as oral powders of 5 g.
- Glycerol: is an osmotic dehydrating agent that is given orally for the short-term reduction of vitreous volume and intra-ocular pressure and as an adjunct in the management of acute glaucoma; it is also used to reduce intracranial pressure and as a demulcent in cough preparations (*Martindale 35,* 2007). Glycerol was reported in 5 European countries, namely: Portugal, UK, Netherlands (in combination with citric acid), Denmark and Spain, and by a total of 10 European hospitals. It was reported as oral solutions (50, 60 and 62.8%), syrups (20%) and as a gargle solution (in combination with other substances).
- Glycopyrronium bromide: is a quaternary ammonium antimuscarinic used orally as an adjunct in the treatment of peptic ulcer disease (*Martindale 35,* 2007). It was reported in the UK and the Netherlands as an oral liquid (0.5, 1 and 5 mg/5mL; 50-300 mL) by a total of 2 hospitals.
- Hydrochloric acid: is used diluted as an escharotic in the treatment of achlorhydria and in other GI disorders (*Martindale 35,* 2007). It was reported only in the Netherlands (1 hospital) as a syrup 1.1 mg/mL (300 mL).
- Indigo carmine: is usually administered by IV or intramuscular injection (*Martindale 35,* 2007) but it is also used orally in routine chromoendoscopy for GI diseases (Kida *et al.*, 2003). It was reported in Portugal and France as an oral liquid (0.3, 0.8 and 1%) and as capsules (300 mg), by a total of 4 hospitals.
- Lipase (see amylase and Appendix 26).
- Macrogols: are a group of substances that have different activities according to their molecular weight. These may be administered with electrolytes in bowel preparation before colonoscopy, radiological procedures and surgery; and may also be used in chronic constipation and faecal impaction (*Martindale 35,* 2007). Macrogols (and Macrogols 3000 and 4000, in particular) were reported in 5 European countries, namely: UK, Switzerland, Netherlands (in combination with electrolytes and indicated as a laxative), Slovenia (indicated for pre-colonoscopy bowel emptying; also in combination with other substances) and Germany, by a total of 7 European hospitals. Macrogols were reported as oral solutions (300-3,000 mL) and oral powders (0.5 g, 15 g, 100 g and 300 g).

- Manuka: has antimicrobial properties (*Martindale 35,* 2007) and it was dispensed as oral powders (80 g) by only 1 UK hospital (as a special).
- Melatonin: has been tried in several disorders and may be beneficial in malignant neoplasms, hyperlipidaemias, cluster headaches, tinnitus, alopecia in women and irritable bowel syndrome associated with sleep disturbances (*Martindale 35,* 2007). Melatonin was reported in 6 European countries, namely: Switzerland, Netherlands, Denmark, Spain, France and Germany, by a total of 22 European hospitals. It was reported as tablets (3 mg) and capsules (0.5-10 mg; 12 strengths).
- Menthol (see alcohol in Appendix 12).
- Methacholine chloride: is a quaternary ammonium parasympathomimetic with the muscarinic actions of acetylcholine (*Martindale 35,* 2007). It was reported in Portugal (1 hospital) as oral powders (75 mg).
- Miglustat: is an inhibitor of the glucosylceramide synthase and is indicated in the type 1 Gaucher disease and in the type C Niemann-Pick disease (*Martindale 35,* 2007). It was reported in Portugal (1 hospital) as oral powders (35 mg).
- Monosodium glutamate: is a sodium salt of the amino acid glutamic acid that is commonly used as a flavour enhancer agent (*Martindale 35,* 2007). Clinically, there is some preliminary evidence of the benefits of monosodium glutamate as, for example, in improving nutritional status and well being in elderly individuals (Yamamoto *et al.*, 2009). Monosodium glutamate was reported in the UK and the Netherlands as capsules (200 mg) and oral powders (100, 250, 500 and 1,000 mg), by a total of 2 hospitals.
- Nitisinone: is used in hereditary metabolic disorders, as the tyrosinaemia type 1 and alkaptonuria (*Martindale 35,* 2007). It was reported only in Spain (1 hospital) as oral powders 1.5 mg.
- Pancreatic enzymes (such as pancreatin or pancrelipase): are responsible for the hydrolyse of fats, break down of proteins and conversion of starch; these enzymes are given orally in conditions of pancreatic exocrine deficiency and the dose is usually adjusted according to the individual needs of patients (*Martindale 35,* 2007). Pancreatin was reported in 5 European countries, namely: Portugal, Poland, Netherlands, Spain and Germany, by a total of 10 hospitals. It was reported as oral solids (capsules, oral powders and cachets; 100-15,000 IU; 50-275 mg) and oral liquids (2,000 IU/mL).
- Papain: is used orally for its anti-inflammatory activity or to aid digestion (*Martindale 35,* 2007). It was reported as a syrup by only 1 French hospital.
- Patent blue V: is usually administered intravenously to colour the lymph vessels (*Martindale 35,* 2007) but was reported as (oral) capsules (2.5 mg) by 1 French hospital. Since the identification of the French hospitals was not disclosed by AFSSAPS (Section 12.3), it was not possible to check the (oral) therapeutic use of this compounded medicine.
- Phosphoric acid: is used well diluted in medicines intended for the management of nausea and vomiting (*Martindale 35,* 2007). It was reported as an oral solution in Finland

(500 mL) and France (10%); and as part of Joulie's Solution (Appendix 16) in Spain, by a total of 3 hospitals.

- Phosphorus: elemental phosphorus is no longer used in medicine but the inorganic phosphates have several oral indications (*Martindale 35,* 2007). Phosphorus was reported by 3 Spanish hospitals - as an oral solution (10 mg/mL) and capsules (25 and 50 mg) - but it is likely that the respective inorganic phosphates were used instead.
- Potassium bromide (see bromides).
- Protease (see amylase and Appendix 26).
- Quercetin: is a flavonoid and, therefore, may be used to relieve capillary impairment, venous insufficiency and haemorrhoids (*Martindale 35,* 2007). It was reported in Spain only (1 hospital) as capsules of 50 mg.
- Riluzole: is indicated in a motor neuron disease (amyotrophic lateral sclerosis) and the usual oral dose is 50 mg twice a day (*Martindale 35,* 2007). It was reported in France only (1 hospital) as capsules of 50 mg.
- Sodium carbonate: is used in antacid preparations (*Martindale 35,* 2007) and was reported as capsules (50 and 200 mg) in the Netherlands only (1 hospital).
- Sodium phenylbutyrate: is a prodrug for sodium phenylacetate and is used in patients with urea cycle disorders as an adjuvant treatment for hyperammonaemia (*Martindale 35,* 2007). It was reported as oral liquids (200, 250 mg/mL and 250 mg/5 mL; 100 mL) in the UK (specials only), Netherlands and Spain; and also as capsules (100 mg) in Finland and sachets in Spain, by a total of 6 European hospitals.
- Strychnine nitrate: has a central stimulant effect and has been used in multi-ingredient preparations for the treatment of ophthalmic and urinary-tract disorders; and also in the treatment of nonketotic hyperglycinaemia (*Martindale 35,* 2007). It was reported as oral solutions (1 and 4 mg/mL) in Portugal and Switzerland; and also as oral powders in Portugal, by a total of 2 hospitals.
- Taurine: is an aminoacid used as an essential nutrient; it is also included in preparations for cardiovascular and metabolic disorders (*Martindale 35,* 2007). It was reported only in Spain and Germany as capsules (30, 200 and 300 mg) by a total of 3 hospitals.
- Tetrabenazine: is used in the management of movement disorders (such as chorea, ballism, dystonias, tardive dyskinesia) and other similar symptoms of CNS dysfunction (*Martindale 35,* 2007). It was reported in the UK as an oral suspension (25 mg/5mL; 150, 200 and 300 mL) and in the Netherlands as capsules (1 mg), by a total of 3 hospitals.
- Thalidomide: is used for the treatment and prevention of type 2 lepra reactions; multiple myeloma refractory to standard therapies; primary brain malignancies; and several other conditions whose aetiology may involve the immune system (*Martindale 35,* 2007). It was reported as capsules (10, 50 and 100 mg) in Switzerland, Finland and Spain, by a total of 7 hospitals.
- Thyme: is mainly used in preparations for respiratory-tract disorders for its carminative, antiseptic, antitussive and expectorant activities (*Martindale 35,* 2007). It was reported in

Poland (1 hospital) as thyme syrup (in combination with multiple active substances) and 1 Germany (1 hospital) as a mixture (100 mL).

- Tolonium chloride: may be used to stain oral and gastric neoplasms or to treat menstrual disorders and methaemoglobinaemia (*Martindale 35,* 2007). It was reported as an oral solution 1% by only 1 French hospital.
- Tormentil: is used for its astringent properties in preparations for diarrhoea and other indications (*Martindale 35,* 2007). It was reported only in Germany (1 hospital) as capsules of 5 and 10 mg.
- Trypsin: is a proteolytic enzyme that has been used orally, frequently associated with other substances, in the relief of oedema, inflammation and several GI disorders (*Martindale 35,* 2007). It was reported only in the Netherlands as powders for oral liquids (100 mL).
- Ubidecarenone: is given orally in conditions associated with coenzyme deficiency, as an adjunct in cardiovascular disorders and as dietary supplement (*Martindale 35,* 2007). It was reported in Portugal (1 hospital) as oral powders (7 mg) and in Spain (2 hospitals) as capsules (30, 50 and 150 mg).
- Ursodeoxycholic acid: is a naturally occurring bile acid that is used for dissolution of cholesterol-rich gallstones (in patients with functioning gallbladders) and in primary biliary cirrhosis (*Martindale 35,* 2007). Ursodeoxycholic acid was reported in 8 European countries, namely: Portugal, Switzerland, Poland, Netherlands, Finland, Spain, France and Germany, by a total of 67 European hospitals. It was reported as oral solids (capsules, oral powders and cachets; 5-1,600 mg; 41 strengths) and oral liquids (solutions, suspensions and syrups, both unidose and multidose; 15-60 mg/mL; 5 strengths; 1-300 mL).
- Valerian: has been used as a sedative and also as a carminative (*Martindale 35,* 2007) and was reported in Poland (2 hospitals) as oral liquids (in combination with multiple active substances).
- Vanillin: is used as a flavour (*Martindale 35,* 2007) but was as reported as an oral solution (10 mg/mL) by 1 German hospital. Since the identification of the German hospitals was not disclosed (Section 13.3), it was not possible to check the (oral) therapeutic use of this compounded medicine.
- Xylose: is given orally to test absorption from the GI tract, usually in a dose of 5 or 25 g with up to 700 mL of water (*Martindale 35,* 2007). It was reported as oral powders in Portugal (25 g), UK (5 g), Spain (25 g), France (25 g) and Germany (4.5-22g; 10 strengths), by a total of 7 hospitals.
- Zinc orotate: is a salt of orotic acid and has been used as a mineral source (*Martindale 35,* 2007). It was reported only in Germany (1 hospital) as capsules of 6.25 mg.

Appendix 16

Given titles[59] formulary

Compounded medicines ***Given titles***	**Formulas**
Albright's Solution (Shohl's Solution, modified) (Allen, 2005g)	Citric acid 6.68 g Sodium citrate 10 g Purified water to 100 mL
Gargle Solution (Comité del Formulario Nacional, 2007)	Glycerol 10 g Sodium bicarbonate 1 g Borax 1 g Spearmint oil 0.05 mL Purified water to 100 mL
Hoestdrank FNA (WINAp, 2004)	Ammonium chloride 2 g Liquorice 2 g Ammonia spirit aniseed 1 g Methyl hydroxybenzoate 150 mg Purified water 95.85 g
Joulie's Solution (Allen, 2005h)	Dibasic sodium phosphate, heptahydrate 13.6 g Phosphoric acid 3.5 mL Methylparaben 100 mg Propylparaben 50 mg Purified water to 100 mL
Knox Mouthwash * (Jackson and Lowey, 2010)	Triamcinolone acetonide 500 µg/mL Erythromycin ethyl succinate 47.5 mg/mL *Preferred formula
Lugol's Solution (5%) (Aqueous Iodine Oral Solution BP) (BP Commission, 2008a)	Iodine 50 g Potassium iodide 100 g Purified water* to 1,000 mL *freshly boiled and cooled
Lugol's Solution (Weak) (0.015%) (Comité del Formulario Nacional, 2007)	Iodine 0.15 g Potassium iodide 0.30 g Purified water to 1,000 mL
Mixture Nervinae (Janicki *et al*., 2003)	Ammonium bromide 4 g Potassium bromide 8 g Sodium bromide 4 g Purified water to 200 g

[59] For the purposes of this research, given titles are non-proprietary names attributed to specific compounded medicines.

Concentrated Peppermint Emulsion BP*/BPC (BP Commission, 2008a) *replaced Concentrated Peppermint Water BP (Marriot *et al.*, 2010) (Council of the Pharmaceutical Society of Great Britain, 1973)	Peppermint oil 20 mL Polysorbate 20 1 mL Double-strength chloroform water 500 mL Purified water* to 1,000 mL *freshly boiled and cooled When diluted with 39 times its volume of freshly boiled and cooled purified water, a preparation equivalent in strength to Peppermint Water BP is produced
Poção de Todd (*Potio Cinnamomi spirituosa*) (*Farmacopeia Portuguesa IV*, 1946)	Cinnamon tincture 5 g Alcohol 65º 30 g Simple syrup 20 g Purified water 45 g
Shohl's Solution (Allen, 2005g)	Sodium citrate 9 g Citric acid 14 g Purified water to 100 mL
Simple Linctus, Paediatric BPC/BP (Council of the Pharmaceutical Society of Great Britain, 1973) (BP Commission, 2008a)	Simple Linctus 250 mL Syrup to 1,000 mL Paediatric Simple Linctus is an oral solution containing 0.625% w/v of citric acid monohydrate in a suitable vehicle with an anise flavour
Sol. Sal. Erlenmayeri (Janicki *et al.*, 2003)	Ammonium bromide 2 g Potassium bromide 4 g Sodium bromide 4 g Purified water to 200 g
St Mark's Powders (Jackson and Lowey, 2010)	Glucose 20 g Sodium citrate 2.5 g Sodium chloride 3.5 g
Water Paste (Comité del Formulario Nacional, 2007)	Zinc oxide 25 g Talc 25 g Glycerol 25 g Purified water 25 g
WHO ORS (hypo-osmolar) (245 mOsm/L; 20.5 g) (WHO and UNICEF, 2006)	Sodium chloride 2.6 g Glucose, anhydrous 13.5 g Potassium chloride 1.5 g Trisodium citrate, dihydrate 2.9 g
WHO ORS (standard) (311 mOsm/L; 27.9 g) (Dutta *et al.*, 2001)	Sodium chloride 3.5 g Glucose 20 g Potassium chloride 1.5 g Trisodium citrate, dihydrate 2.9 g

Appendix 17

Top 20 active substances dispensed in 7 English paediatric hospitals (adapted from Yeung *et al.*, 2004)

1. Potassium chloride (n=435 units)
2. Midazolam (n=168)
3. Vancomycin (n=158)
4. Clonidine HCl (n=132)
5. Isoleucine (n=111)
6. Valine (n=106)
7. Potassium dihydrogen phosphate (n=101)
8. Mercaptopurine (n=101)
9. Co-careldopa (n=101)
10. Dichloroacetate sodium (n=93)
11. Cholesterol (n=89)
12. Sodium chloride (n=84)
13. Aspirin (n=75)
14. Didanosine (n=62)
15. Acetylcysteine (n=61)
16. Diazoxide (n=60)
17. Clobazam (n=59)
18. Sucralfate (n=57)
19. Cysteamine (n=57)
20. Warfarin (n=53)

Appendix 18

Top 50 extemporaneous preparations dispensed in selected UK NHS Trusts (adapted from Lowey and Jackson, 2008)

1. Levothyroxine (n=880 units)
2. Clobazam (n=743)
3. Clozapine (n=693)
4. Sodium chloride (n=621)
5. Morphine sulfate (n=475)
6. Ethambutol (n=371)
7. Lorazepam (n=353)
8. Pyrazinamide (n=330)
9. Vancomycin (n=320)
10. *Knox Mouthwash* (n=281)
11. Amiodarone (n=277)
12. Azathioprine (n=277)
13. Hydrocortisone (n=274)
14. Clonidine (n=266)
15. Sodium bicarbonate (n=261)
16. Captopril (n=246)
17. Acetazolamide (n=198)
18. Midazolam (n=185)
19. Tranexamic acid (mouthwash) (n=182)
20. Magnesium glycerophosphate (n=173)
21. Tacrolimus mouthwash (n=173)
22. Allopurinol (n=149)
23. Clonazepam (n=146)
24. Quinine sulfate (n=131)
25. Warfarin (n=131)
26. Pyridoxine (n=128)
27. Metformin (n=120)
28. Dinoprostone (n=113)
29. Sodium phenylbutyrate (n=112)
30. Ergocalciferol (n=110)
31. Omeprazole (n=108)
32. Dexamethasone (n=107)
33. Phenoxybenzamine (n=107)
34. Diazoxide (n=99)
35. Menadiol (n=95)
36. Ubiquinone (n=90)
37. Thiamine (n=84)
38. Potassium phosphate (n=77)
39. Indometacin (n=76)
40. *Joulie's Solution* (n=69)
41. Gliclazide (n=69)
42. Primidone (n=69)
43. Phenobarbital (n=64)
44. Isosorbide mononitrate (n=64)
45. Gabapentin (n=64)
46. Arginine (n=60)
47. *St Mark's Solution* (n=60)
48. Sildenafil (n=57)
49. Co-careldopa (n=53)
50. Bendroflumethiazide (n=53)

Appendix 19

Unlicensed formulations (BP 2008-2011)

BP 2008

(adapted from BP Commission, 2008b)

1. Caffeine citrate injection
2. Caffeine citrate oral solution
3. Dantrolene oral suspension
4. Levomenthol cream
5. Mercaptopurine oral suspension
6. Paediatric phenobarbital oral solution
7. Potassium chloride oral solution
8. Sodium bicarbonate oral solution
9. Sodium fluoride oral solution

BP 2009

(adapted from Lee, 2010)

1. Adrenaline and cocaine intranasal injection
2. Captopril oral solution
3. Cocaine paste
4. Compound glucose, sodium chloride and sodium citrate oral solution
5. Hydrocortisone sodium phosphate oral solution
6. Potassium dihydrogen phosphate oral solution
7. Vancomycin oral solution

BP 2010

(adapted from Lee, 2010)

1. Allopurinol oral suspension
2. Bupivacaine and fentanyl injection
3. Chloral hydrate oral solution
4. Magnesium glycerophosphate oral solution
5. Midazolam oral solution
6. Phosphate oral solution
7. Propylene glycol solution
8. Warfarin oral suspension

BP 2011

(adapted from Lee, 2010)

1. Bupivacaine and diamorphine injection
2. Clozapine oral suspension
3. Dinoprostone oral solution
4. Coal tar paste
5. Coal tar and salicylic acid ointment
6. Salicylic acid cream
7. Salicylic acid ointment
8. Silver nitrate solution
9. Sodium chloride nebulizer solution
10. Sodium carbonate oral solution
11. Cefuroxime eye drops
12. Disodium edetate eye drops

Appendix 20

Paediatric Phenobarbital Oral Solution (BP 2008)

(adapted from BP Commission, 2008b)

IDENTIFICATION
To 5 ml add 15 ml of *water*, make slightly acidic with 1M *sulphuric acid* and filter. The residue, after washing with *water* and drying at 105°, complies with the following tests.

A. The *infrared absorption spectrum*, Appendix II A, is concordant with the reference spectrum of phenobarbital (*RS 270*).

B. *Melting point*, about 175°, Appendix V A.

C. Dissolve 50 mg in 2 ml of a 0.2% w/v solution of *cobalt(II) acetate* in *methanol*, warm, add 50 mg of powdered *sodium tetraborate* and heat to boiling. A bluish violet colour is produced.

TESTS
Alkalinity
pH, 10.0 to 11.0, Appendix V L.

Weight per ml
1.090 to 1.100 g, Appendix V G.

ASSAY
To 2 g add 30 ml of *water* and 3 g of *sodium carbonate*, stir to dissolve and titrate with 0.1M *silver nitrate VS* until a distinct turbidity is observed when viewed against a black background, the solution being stirred vigorously throughout the titration. Each ml of 0.1M *silver nitrate VS* is equivalent to 25.42 mg of $C_{12}H_{11}N_2NaO_3$. Use the *weight per ml* of the injection to calculate the percentage w/v of phenobarbital sodium, $C_{12}H_{11}N_2NaO_3$.

Paediatric Phenobarbital Oral Solution

NOTE: There are currently no licensed formulations in the United Kingdom.

Action and use
Barbiturate.

DEFINITION
Paediatric Phenobarbital Oral Solution is an *oral solution* containing Phenobarbital Sodium in a suitable flavoured vehicle.

The oral solution complies with the requirements stated under Oral Liquids, the requirements stated under Unlicensed Medicines and with the following requirements.

Content of phenobarbital, $C_{12}H_{12}N_2O_3$
95.0 to 105.0% of the stated amount.

IDENTIFICATION
A. The *infrared absorption spectrum*, Appendix II A, of the residue obtained in the Assay is concordant with the *reference spectrum* of phenobarbital (*RS 270*).

B. The oral solution yields reaction A characteristic of *sodium salts*, Appendix VI.

TESTS
Alkalinity
pH, 7.5 to 9.0, Appendix V L.

ASSAY
Acidify 50 ml of the preparation being examined to *litmus paper* with 2M *hydrochloric acid* and extract with four 25-ml quantities of *ether*. Wash the combined ether extracts with two 2-ml quantities of *water* and wash the combined aqueous washings with 10 ml of *ether*. Add the ether washings to the combined ether extracts, evaporate the ether and dry the residue of phenobarbital, $C_{12}H_{12}N_2O_3$, to constant weight at 105°. Calculate the content of $C_{12}H_{12}N_2O_3$ in the oral solution as a percentage of the stated amount.

STORAGE
Paediatric Phenobarbital Oral Solution should be protected from light. It should not be refrigerated.

LABELLING
The quantity of active ingredient is stated in terms of the equivalent amount of phenobarbital.

Phenobarbital Tablets

Action and use
Barbiturate.

DEFINITION
Phenobarbital Tablets contain Phenobarbital.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of phenobarbital, $C_{12}H_{12}N_2O_3$
92.5 to 107.5% of the stated amount.

IDENTIFICATION
Heat 0.2 g of the residue obtained in the Assay on a water bath with 15 ml of *ethanol* (*25%*) until dissolved, filter while hot and allow the filtrate to cool. Filter, wash the crystals with a small quantity of *ethanol* (*25%*) and dry at 105°. The residue complies with the following tests.

A. *Melting point*, about 175°, Appendix V A.

B. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of phenobarbital (*RS 270*). If the spectra obtained are not concordant, heat the residue in a sealed tube at 105° for 1 hour and prepare a new spectrum of the residue.

C. Dissolve 50 mg in 2 ml of a 0.2% w/v solution of *cobalt(II) acetate* in *methanol*, warm, add 50 mg of powdered *sodium tetraborate* and heat to boiling. A bluish violet colour is produced.

TESTS
Disintegration
Maximum time, 30 minutes, Appendix XII A1.

ASSAY
Weigh and powder 20 tablets. Extract a quantity of the powder containing 0.3 g of Phenobarbital in a continuous extraction apparatus with *ether* until complete extraction is effected. Remove the ether and dry the residue of phenobarbital to constant weight at 105°. Calculate the content of $C_{12}H_{12}N_2O_3$ in the tablets as a percentage of the stated amount.

Appendix 21

UK questionnaire / Introduction

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

UNLICENSED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

UNITED KINGDOM

INTRODUCTION MAY 2007

The extemporaneous preparation of medicines is common practice in hospital pharmacy across Europe.
However, in each country the approach to extemporaneous preparation is surprisingly different and the type / amount of the most frequent formulae varies considerably.
The aim of this purely academic PhD project, conducted under the supervision of Professor Kevin Taylor and Dr Catherine Tuleu, is to characterise the state-of-the-art of extemporaneous preparations across Europe.

The xxxxxx is invited to participate in this European-wide project.
Your contribution is very important so that we can characterise the current situation in the United Kingdom.
We would be grateful if you would fill in **2 TABLES** and answer **2 QUESTIONS**.
The information given to The School of Pharmacy - University of London will be data protected and kept anonymous.
If you have any questions, please don't hesitate to contact me by e-mail (xxxxxx) or telephone (xxxxxx).

Thank you in anticipation,

Maria Joao Carvalho
Department of Pharmaceutics
The School of Pharmacy - University of London
29-39 Brunswick Square
London WC1N 1AX
United Kingdom

Appendix 22

UK questionnaire / Questions

UNIVERSITY OF LONDON
THE SCHOOL OF PHARMACY

PhD PROJECT

UNLICENSED MEDICINES IN HOSPITAL PHARMACY ACROSS EUROPE

UNITED KINGDOM

1 - Please estimate the OVERALL TOTAL number of the following unlicensed medicines DISPENSED by your Pharmacy in 2006:

ORAL EXTEMPORANEOUS PREPARATIONS ☐

ORAL SPECIALS ☐

2 - Please indicate the number of PHARMACISTS and the number of TECHNICIANS working in your Pharmacy in 2006:

Pharmacists: ☐ Technicians: ☐

Comments _____

The individual results are data protected and will be directly available only to the research team.

The research project results will be reported anonymously in peer reviewed scientific journals, internal reports and conference presentations.

The research project is compliant with the Data Protection Act 1998. The Data Protection Registration Number of The School of Pharmacy is xxxxxx.

Thank you very much for participating in this European wide research project on Extemporaneous Preparations in Hospital Pharmacy.

Appendix 23

List of special-order manufacturers / hospital manufacturing units (adapted from Joint Formulary Committee, 2006; Paediatric Formulary Committee, 2007)

England

1. Ipswich Hospital NHS Trust
2. Barts and the London NHS Trust, St. Bartholomew's Hospital
3. Guy's and St. Thomas' NHS Foundation Trust, St. Thomas' Hospital
4. St. George's Hospital
5. Moorfields Pharmaceuticals
6. Stockport Pharmaceuticals, Stepping Hill Hospital
7. Royal Victoria Infirmary
8. St. Peter's Hospital
9. Queen Alexandra Hospital
10. Torbay PMU, South Devon Healthcare
11. Royal Hallamshire Hospital
12. Queen Elizabeth Medical Centre
13. Queens Hospital, Burton Hospitals NHS Trust
14. Huddersfield Royal Infirmary
15. Northwick Park and St Mark's Hospital
16. Royal Free Hospital
17. Queens Medical Centre, Nottingham University Hospitals NHS Trust
18. University Hospital of North Staffordshire NHS Trust
19. Colchester General Hospital, Colchester Hospital University NHS Foundation Trust
20. Royal Preston Hospital
21. Eastbourne District General Hospital, East Sussex Hospitals NHS Trust

Northern Ireland

22. Victoria Pharmaceuticals, Royal Group of Hospitals

Scotland

23. Tayside Pharmaceuticals, Ninewells Hospital
24. Western Infirmary

Wales

25. Cardiff and Vale NHS Trust

Appendix 24

List of paediatric hospitals in England

(adapted from Yeung *et al.*, 2004)

1. Alder Hey Hospital (Liverpool)
2. Birmingham Children's Hospital (Birmingham)
3. Royal Alexandra Children's Hospital (Brighton)
4. Derbyshire Children's Hospital (Derby)
5. Great Ormond Street Hospital for Children (London)
6. Royal Manchester Children's Hospital (Manchester)
7. Sheffield Children's Hospital (Sheffield)

Appendix 25

Organic solvents, Colouring agents and Nonionic surfactants

Organic solvents

This therapeutic group was exclusive of the Netherlands and only 1 active substance was reported, namely:

- Dimethyl sulfoxide: a highly polar substance that has been administered orally for a wide range of indications. Nevertheless, according to *Martindale 35* (2007), the evidence of beneficial effects from the use of dimethyl sulfoxide is limited. This substance was reported as an oral liquid (100 mL) and by only 1 Dutch hospital pharmacy.

Colouring agents

This therapeutic group was exclusive of France and Germany (only) and almost all active substances reported are described in *Martindale 35* (2007) only as colouring agents in medicines, cosmetics and foodstuffs.

This is the case for carmoisine, erythrosine, ponceau 4R, sunset yellow FCF and tartrazine, which were all reported as capsules and in France only.

Carmine was the only colouring agent that is used in other indications, namely as a faecal marker since it passes through the GI tract unchanged (*Martindale 35*, 2007). Carmine was reported in France as capsules and oral powders of variable strengths (2.5-500 mg) and also in Germany as capsules 50 mg.

Nonionic surfactants

This therapeutic group was exclusive of Germany and only 1 active substance was reported, namely:

- Polysorbate 80: Polysorbates are hydrophilic nonionic surfactants and may be used in the management of upper respiratory-tract conditions (*Martindale 35*, 2007). Polysorbate 80 was reported as an oral liquid 1 mg/mL (100 mL) and by only 1 German hospital.

Appendix 26

Active substances not included in *Martindale 35* (2007)

dispensed by the participant European hospitals

Active substances	European countries	Dosage forms
Ambrisentan	Spain	Capsules
Ammonia spirit aniseed	Netherlands	Oral liquid
Cystamine dihydrochloride	Switzerland	Capsules
Darunavir	Spain	Capsules
Detrothyronine	Spain	Capsules
Heptobarbital	Netherlands	Capsules
Lipase	Slovenia	Oral powders
Lithium	Netherlands	Oral liquid
Maraviroc	Spain	Capsules
Nickel sulfate	UK	Capsules
	France	Capsules
Potassium dichromate	France	Capsules
Protease	Slovenia	Oral powders
Uracil	Denmark	Capsules

Appendix 27

Therapeutic groups (*Martindale 35*, 2007) included in the research

1. Analgesics, anti-inflammatory drugs and antipyretics
2. Anthelmintics
3. Antibacterials
4. Antidementia drugs
5. Antidepressants
6. Antidiabetics
7. Antiepileptics
8. Antifungals
9. Antigout drugs
10. Antihistamines
11. Antimalarials
12. Antimyasthenics
13. Antineoplastics
14. Antiparkinsonian drugs
15. Antiprotozoals
16. Antivirals
17. Anxiolytic, sedatives, hypnotics and antipsychotics
18. Blood products, plasma expanders and haemostatics
19. Bronchodilators and anti-asthma drugs
20. Cardiovascular drugs
21. Chelators, antidotes and antagonists
22. Colouring agents
23. Contrast media
24. Corticosteroids
25. Cough suppressants, expectorants, mucolytics and nasal decongestants
26. Dermatological drugs and sunscreens
27. Disinfectants and preservatives
28. Electrolytes
29. GI drugs
30. General anaesthetics
31. Hypothalamic and pituitary hormones
32. Immunosuppressants
33. Local anaesthetics
34. Miotics, mydriatics and antiglaucoma drugs
35. Muscle relaxants
36. Non-ionic surfactants
37. Nutritional agents and vitamins
38. Organic solvents
39. Paraffins and similar bases
40. Prostaglandins
41. Sex hormones
42. Stabilising and suspending agents
43. Stimulants and anorectics
44. Supplementary drugs and other substances
45. Thyroid and antithyroid drugs
46. Urological drugs

Presentations and publications

Oral presentations

Carvalho, M. (2008) 'Medicamentos manipulados na Europa', *31° Encontro Catarinense de Hospitais e Prestadores de Serviços de Saúde*. Santa Catarina, Brazil 15 October.

Carvalho, M. (2009) 'Extemporaneous preparations: Current practices in Europe', *1st Conference of the EuPFI: Formulating better medicines for children*. London, UK 2 March.

Carvalho, M. (2009) 'A realidade Europeia dos Medicamentos manipulados', *Simpósio UFP: Novos medicamentos manipulados e novos sistemas terapêuticos*. Porto, Portugal 24 April.

Carvalho, M. (2009) 'Extemporaneously compounded oral medicines in European hospital pharmacies', *ULLA Symposium: Crossing borders*. Copenhagen, Denmark 27 June.

Carvalho, M., Fenton-May, V. and Gosdschan, T. (2009) 'Common language – the basis for understanding and cooperation', *EDQM Expert Workshop: Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients*. Strasbourg, France 24 September.

Carvalho, M. (2010) 'Medicamentos manipulados: realidade Europeia', *Seminário UFP: Medicamentos manipulados*. Porto, Portugal 25 May.

Carvalho, M. (2011) 'Extemporaneous compounding in Europe', *3rd Conference of the EuPFI: Formulating better medicines for children*. Strasbourg, France 21 September.

Carvalho, M. (2011) 'Extemporaneous preparations: Compounding in Europe', *EDQM Workshop on the elaboration of a European Formulary for paediatric formulations.* Strasbourg, France 29 November.

Poster presentations

Carvalho, M. (2009) 'Extemporaneously compounded oral medicines in European hospital pharmacies', *9th ULLA Summer School*. Copenhagen, Denmark 26 June – 3 July.

Carvalho, M. (2012) 'Extemporaneously compounded oral medicines in European hospital pharmacies', *FIP Centennial Congress, Hospital Pharmacy Section*. Amsterdam, Netherlands 5-6 October.

Publications

Carvalho, M., Tuleu, C. and Taylor, K. (2008) 'Current compounding practices in Europe', *International Journal of Pharmaceutical Compounding*, 12, 8-13.

Carvalho, M., Taylor, K. and Tuleu, C. (2012) 'Why do we need hospital pharmacy preparation?', *European Journal of Hospital Pharmacy*, 19, 467-468.

Compounding Practices in Europe

Extemporaneously Compounded Oral Medicines in European Hospital Pharmacies

Maria Carvalho
PhD Thesis

UCL School of Pharmacy