International Nonproprietary Name prescribing: beyond national boundaries

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2015

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# TABLE OF CONTENT

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY</td>
<td>7</td>
</tr>
<tr>
<td>SAMENVATTING</td>
<td>8</td>
</tr>
<tr>
<td>ACRONYMS &amp; SYMBOLS</td>
<td>11</td>
</tr>
<tr>
<td>GENERAL INTRODUCTION</td>
<td>13</td>
</tr>
<tr>
<td>RESULTS</td>
<td>31</td>
</tr>
<tr>
<td>Chapter 1: Operational rules for the operationalization of electronic INN prescribing</td>
<td>33</td>
</tr>
<tr>
<td>Chapter 2: Attitudes of physicians and pharmacists towards INN prescribing in Belgium</td>
<td>53</td>
</tr>
<tr>
<td>Chapter 3: Attitudes of medicine and pharmacy students towards INN prescribing in Belgium</td>
<td>73</td>
</tr>
<tr>
<td>Chapter 4: INN prescribing: diversity in regulation across Europe</td>
<td>83</td>
</tr>
<tr>
<td>Chapter 5: The interchangeability of gabapentin 800 mg tablets: a randomized, controlled trial to establish individual bioequivalence</td>
<td>99</td>
</tr>
<tr>
<td>GENERAL DISCUSSION</td>
<td>117</td>
</tr>
<tr>
<td>LIST OF TABLES &amp; FIGURES</td>
<td>137</td>
</tr>
<tr>
<td>CURRICULUM VITAE</td>
<td>139</td>
</tr>
<tr>
<td>DANKWOORD</td>
<td>141</td>
</tr>
</tbody>
</table>

- *A detailed table of contents is given at the start of each chapter* -
SUMMARY

International Nonproprietary Name (INN) prescribing is defined as using the INN for prescribing. It was introduced as an alternative way of prescribing to contribute to rational drug utilization. It has a legal foundation in many European countries, next to brand name prescribing, generic prescribing and generic substitution. INN prescribing is implemented and operationalized in various ways and to different extent within Europe. Since the global financial crisis also affected Europe, it was turned into a cost-containment measure in many European countries, also in Belgium, similar to generic substitution. However, when these two popular cost-containment measures are not rationally operationalized, it can result in dispensing errors, patient confusion, medication non-adherence, and errors in self-administration. These consequences can abolish the savings made through INN prescribing and generic substitution.

In Chapter 1, we presented how the implementation of INN prescribing in electronic prescribing in Belgium was prepared. During the project, which lasted almost six years, detailed operational rules were established, along with a classification of the Belgian therapeutic arsenal according to these operational rules. This project also showed that involving all stakeholders is a crucial item of success.

In Chapter 2, the attitudes and opinions of Flemish general practitioners (GPs) and pharmacists towards INN prescribing were presented. Forcing INN prescribing into a cost-containment measure in spring 2012 in Belgium, resulted in negative reactions among primary health care professionals. The results of our questionnaire study showed that GPs and pharmacists prioritize patient safety and therefore they stressed the importance of continuity of treatment.

In Chapter 3, the attitudes of medicine students and pharmacy students towards INN prescribing were presented. The students confirmed the opinions of their peers and indicated that more prominently teaching INN prescribing can stimulate the use of it in daily practice.

Chapter 4 started with an overview of how INN prescribing and generic substitution are regulated and implemented in 16 European countries. The second goal of this study was to address the differences in (groups of) products exempted from INN prescribing and/or generic substitution. Part of these differences can be explained by the lack of a European definition and exhaustive list of narrow therapeutic index drugs. This study confirmed the need for a structured European guideline on these topics to harmonize the important differences in national regulation.

Chapter 5 presented the results of our clinical trial with 800 mg gabapentin tablets. The antiepileptic drug gabapentin is frequently exempted from INN prescribing and/or generic substitution for patient safety reasons. This study confirmed bioequivalence between the brand and generic product with 800 mg gabapentin, also on the individual level. In addition, no differences between different batches of each product could be detected. These results indicated that switching between these products should be possible in clinical practice without affecting patient safety, provided correct medication use and adherence.
SAMENVATTING


In Hoofdstuk 1 werd beschreven op welke manier in België de implementatie van VOS in elektronisch voorschrijven werd voorbereid. Tijdens dit project, dat meer dan vijf jaar duurde, werden er gedetailleerde operationele regels opgesteld en het Belgisch therapeutisch arsenaal werd volgens deze operationele regels ingedeeld. Dit project heeft ook aangetoond dat het vooraf consulteren van alle betrokken partijen een cruciale stap is om tot een succesvol einde te komen.

In Hoofdstuk 2 werden de meningen van Vlaamse huisartsen en apothekers over VOS beschreven. De introductie van VOS als besparingsmaatregel in het voorjaar van 2012 ging gepaard met veel verontwaardiging en ongerustheid bij huisartsen en apothekers. De resultaten van de enquête tonen aan dat huisartsen en apothekers het belang en de veiligheid van hun patiënten voorop stellen en dat continuïteit van de behandeling hierin een sleutelrol speelt.

In Hoofdstuk 3 bevestigden Vlaamse studenten geneeskunde en farmacie de mening van hun collega’s uit hoofdstuk 2. De studenten gaven ook aan dat als VOS meer aandacht zou krijgen tijdens de opleiding, dit de populariteit van VOS kan vergroten.

Hoofdstuk 4 bevat een overzicht van de reglementeringen en implementatie van VOS in 16 Europese landen. Hier werden ook de verschillen tussen deze landen betreffende de (groepen van) geneesmiddelen die voor VOS en/of generische substitutie niet geschikt worden geacht besproken. Deze verschillen kunnen deels verklaard worden doordat er in Europa geen officiële definitie en exhaustieve lijst van geneesmiddelen met nauwe therapeutisch-toxische marge bestaat. De resultaten van dit hoofdstuk tonen ook aan dat er nood is aan een Europese regelgeving inzake VOS en generische substitutie.

In Hoofdstuk 5 werden de resultaten van de klinische studie met gabapentine 800 mg tabletten weergegeven. Gabapentine is een antiepilepticum dat, omwille van patiëntveiligheid, vaak wordt aangeduid als een geneesmiddel waarbij frequent wisselen (‘switchen’) tussen de verschillende beschikbare merken wordt
afgeraden. In dit onderzoek werd individuele bio-equivalentie aangetoond tussen het originele merkproduct en het generisch product van gabapentine. Eveneens konden geen verschillen worden aangetoond wanneer er meerdere lotnummers van elk product werden gebruikt. Dit onderzoek toont aan dat switchen tussen deze producten in de praktijk mogelijk is, zonder dat de patiëntveiligheid in het gedrang komt, op voorwaarde dat deze producten correct worden gebruikt.
## ACRONYMS & SYMBOLS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABE</td>
<td>Average Bioequivalence</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-Converting Enzyme</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AED</td>
<td>Antiepileptic Drug</td>
</tr>
<tr>
<td>AUC(_{\text{0-inf}})</td>
<td>Area under the plasma concentration-time curve from time zero to infinity</td>
</tr>
<tr>
<td>AUC(_{\text{0-t}})</td>
<td>Area under the plasma concentration-time curve from time zero to time t</td>
</tr>
<tr>
<td>BA</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>BCFI/</td>
<td>Belgisch Centrum voor Farmacotherapeutische Informatie/</td>
</tr>
<tr>
<td>CBIP</td>
<td>Centre Belge d'Information Pharmacothérapeutique</td>
</tr>
<tr>
<td>BE</td>
<td>Bioequivalence</td>
</tr>
<tr>
<td>CDER</td>
<td>Centre for Drug Evaluation and Research</td>
</tr>
<tr>
<td>CDOE</td>
<td>Computerized Drug Order Entry</td>
</tr>
<tr>
<td>C(_{\text{max}})</td>
<td>Maximum (peak) plasma drug concentration</td>
</tr>
<tr>
<td>dm+d</td>
<td>Dictionary of Medicines + Devices</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ERMS FG</td>
<td>European Risk Management Strategy Facilitation Group</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European Clinical Trial database</td>
</tr>
<tr>
<td>FAGG/</td>
<td>Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten</td>
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<tr>
<td>AFMPS/</td>
<td>Agence Fédérale des Médicaments et des Produits de Santé</td>
</tr>
<tr>
<td>FAMHP</td>
<td>Federal Agency for Medicines and Health Products</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HMA</td>
<td>Heads of Medicines Agencies</td>
</tr>
<tr>
<td>IBE</td>
<td>Individual Bioequivalence</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonization</td>
</tr>
<tr>
<td>IMP</td>
<td>Individual Medication Packaging</td>
</tr>
<tr>
<td>INN</td>
<td>International Nonproprietary Name</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NTI</td>
<td>Narrow Therapeutic Index</td>
</tr>
<tr>
<td>NTID</td>
<td>Narrow Therapeutic Index Drug</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PIL</td>
<td>Patient Information Leaflet</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>PRN</td>
<td>Pro Re Nata</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>R1</td>
<td>Reference 1 = Neurontin® 800 mg batch ‘A’</td>
</tr>
<tr>
<td>R2</td>
<td>Reference 2 = Neurontin® 800 mg batch ‘B’</td>
</tr>
<tr>
<td>RIZIV/INAMI</td>
<td>RijksInstituut voor Ziekte- en InvaliditeitsVerzekering/Institut National d’Assurance Maladie-Invalidité</td>
</tr>
<tr>
<td>sABE</td>
<td>Scaled Average Bioequivalence</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>T1</td>
<td>Test 1 = Gabasandoz® 800 mg batch ‘A’</td>
</tr>
<tr>
<td>T2</td>
<td>Test 2 = Gabasandoz® 800 mg batch ‘B’</td>
</tr>
<tr>
<td>T_{1/2}</td>
<td>Elimination half-life</td>
</tr>
<tr>
<td>TIAFT</td>
<td>The International Association of Forensic Toxicologists</td>
</tr>
<tr>
<td>T_{max}</td>
<td>Time to reach maximum (peak) plasma concentration following drug administration</td>
</tr>
<tr>
<td>UCB</td>
<td>Upper Confidence Bound</td>
</tr>
<tr>
<td>UPLC-MS-MS</td>
<td>Ultra Performance Liquid Chromatography – tandem Mass Spectrometry</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WIPO</td>
<td>World Intellectual Property Organization</td>
</tr>
<tr>
<td>(\varepsilon_i)</td>
<td>Sum of the maximum allowed estimate of the subject-by-formulation interaction</td>
</tr>
<tr>
<td>(\eta)</td>
<td>Function of different variance terms to establish individual bioequivalence</td>
</tr>
<tr>
<td>(\theta_A)</td>
<td>The average bioequivalence limit, i.e. (\ln (1.25) = 0.223)</td>
</tr>
<tr>
<td>(\theta_I)</td>
<td>The individual bioequivalence limit, i.e. 2.5</td>
</tr>
<tr>
<td>(\mu_R)</td>
<td>Population average response of the log transformed measure (\text{AUC or } C_{\text{max}}) for the reference product</td>
</tr>
<tr>
<td>(\mu_T)</td>
<td>Population average response of the log transformed measure (\text{AUC or } C_{\text{max}}) for the test product</td>
</tr>
<tr>
<td>(\sigma_{\text{batch}})</td>
<td>Between-batch variability</td>
</tr>
<tr>
<td>(\sigma_D)</td>
<td>Subject-by-formulation interaction variability</td>
</tr>
<tr>
<td>(\sigma_{\text{wo}})</td>
<td>The specified constant within-subject variability</td>
</tr>
<tr>
<td>(\sigma_{WR})</td>
<td>Within-subject variability for the reference product</td>
</tr>
<tr>
<td>(\sigma_{WT})</td>
<td>Within-subject variability for the test product</td>
</tr>
</tbody>
</table>
GENERAL INTRODUCTION
GENERAL INTRODUCTION

OVERVIEW ...................................................................................................................................... 15

1. PRESCRIBING REGULATION ........................................................................................................ 16

2. INTERNATIONAL NONPROPRIETARY NAME (INN) PRESCRIBING ............................................... 18

   2.1. International Nonproprietary Names ................................................................................................. 18

   2.2. INN prescribing ................................................................................................................................... 19

   2.3. INN prescribing in Europe ................................................................................................................... 19

   2.4. INN prescribing in Belgium ................................................................................................................. 19

   2.5. Controversy over medication switch .................................................................................................. 21

3. ELECTRONIC PRESCRIBING ......................................................................................................... 23

4. PROBLEM STATEMENT & SCOPE ................................................................................................ 24

5. OUTLINE ...................................................................................................................................... 25

REFERENCES.................................................................................................................................... 26
**OVERVIEW**

With this thesis, we will assess the regulation of International Nonproprietary Name (INN) prescribing in Belgium and Europe. INN prescribing is a concept and way of prescribing, introduced to contribute to rational drug prescribing and utilization. Despite the fact that it has a legal foundation in many European countries, it never really found foothold in continental Europe. That was until 2008, when the global financial crisis also affected Europe. From then, INN prescribing (and its related concept of generic substitution) was turned from an alternative, rational way of prescribing into a cost-containment measure.

The general introduction of this thesis starts with a background on prescribing regulation and defines the different types of medicinal products and different types of medicines prescribing. It also provides an insight in the general concept of INN prescribing and its regulation in Belgium and Europe.

The body of the thesis comprises five chapters, in which the results of the different studies, in line with the aims of this research, are presented.

Finally, in the general discussion, all results are integrated and different points of attention for further improvement of the concept of INN prescribing are addressed.
1. PRESCRIBING REGULATION

Within the European Union (EU) a medicinal product (syn. medicines, drugs) is defined as single or combined substances for prevention or treatment of diseases, or for making a medical diagnosis or to restore, correct or modify physiological functions by exerting pharmacological, immunological or metabolic action in humans [1].

Medicines have been used since ancient civilization with “Mithridatium” (120 BC), an antidote for poisoning, as one of the first examples of a named drug with a fixed combination of ingredients. The first example of medicines regulation is perhaps the supervision of the manufacturing of Mithridatium and other medicines in 1540 in England [2,3]. The basis for modern medicines regulation was established in the 19th century with the evolution of life sciences, including chemistry, physiology and pharmacology. Since then, different aspects of medicines regulation were further elaborated and established after disasters involving medicines (e.g. diethylene glycol poisoning in 1930, anaplastic anemia as adverse drug reaction (ADR) of chloramphenicol around 1950 and the unknown teratogenic properties of thalidomide in the early 60ies) [2,4–6].

Modern medicines regulation aims to promote and protect public health [2]. National medicines regulation differs in scope and implementation, as its characteristics are influenced by underlying attitudes of governments towards providing and financing healthcare and by their response to medical and financial crises [2,7].

Medicines regulation covers different pharmaceutical policies, such as policies on registration, pricing, reimbursement and medicines prescribing. Medicines prescribing policy, also referred to as ‘prescribing regulation’, describes the applicable rules and practical implementation of the allowed ways of prescribing. The allowed ways of prescribing can be “brand name prescribing”, “generic prescribing” and “International Nonproprietary Name (INN) prescribing”. The allowed ways of prescribing are influenced by the available types of medicinal products in each country, which can be classified as “brand products” or “generic products”.

Brand products include innovator products, licensed products and ‘well-established use’ products. All brand products have an invented name, i.e. the brand name, but differ in the type of submitted marketing authorization file. Innovators have to submit a complete marketing authorization file, containing results of pharmaceutical quality tests, pre-clinical tests (toxicological and pharmacological) and clinical trials [1,8]. Marketing authorization for licensed products and ‘well-established use’ products can be granted based upon an abridged file, without results of (pre-)clinical tests. These products are commonly referred to as ‘copies’. We prefer not to use this term as it comprises a container concept used to describe these two different types of medicinal products. Licensed products are products marketed by another company than the innovator company before patent expiry. The marketing authorization from the innovator company is then bought or duplicated for commercial reasons. The exact copy of the marketing authorization license is then referred to as a ‘piggy-back’ license [1,9]. ‘Well-established use’ products are products marketed based on a bibliographic file. Efficacy and safety of the active ingredient(s) can be demonstrated with scientific literature and they have to be used within the European Union for at least ten years [1].
In the EU, a generic product is defined as a medicinal product with the same qualitative and quantitative composition in active ingredient(s) and the same pharmaceutical form as its reference product (usually an innovator product), and for which bioequivalence with the reference product is established, using the appropriate bioequivalence studies [1]. Products can serve as reference products if their patent has expired and if these are marketed for at least ten years in the EU. Generic products are marketed with an abridged authorization file containing results of the pharmaceutical quality tests and the appropriate bioequivalence studies, and references to the results of pre-clinical and clinical tests of the reference product [1,8]. As there are fewer research and development costs for generic products, these are cheaper than brand products [10].

Generic products include ‘branded generics’ and ‘unbranded generics’. Both types of generics are marketed upon the same type of marketing authorization file, but differ in the way these are named. Branded generics can be named in two ways. Similar to brand products, the name of a branded generic can be (1) an invented name (e.g. Lipcut®, which is the Sandoz® generic of simvastatin, available in Finland) or it can be (2) the active ingredient name (the INN) accompanied by the marketing authorization holder’s name (e.g. Simvastatin Sandoz®). The name of unbranded generics only includes the active ingredient name (the INN) on the product package, e.g. simvastatin.

Possible ways to prescribe all these types of medicinal products are “brand name prescribing”, “generic prescribing” and “INN prescribing”. These ways of prescribing do not only differ in how medicines are prescribed, but also in the type of medicinal product that can be dispensed. Brand name prescribing refers to using the brand name for prescribing and having a brand product (innovator, licensed product or ‘well-established use’ product) dispensed.Generic prescribing covers the prescribing of a branded generic (referred to as branded generic name prescribing) and INN prescribing, provided this results in the dispensing of a generic product. INN prescribing involves the identification of the intended medicinal product by its active ingredient, and usually results in the dispensing of a generic product. It can however also result in the dispensing of a brand product, when the brand product has the same price as its generic counterpart or when there are no generic products available (yet).

Closely related to INN prescribing is generic substitution. In contrast to INN prescribing, generic substitution is a pharmaceutical policy performed at dispensing level. It was introduced to enhance the role of the pharmacist and to promote the use of generic products. Generic substitution refers to substituting the prescribed medicinal product (a brand or generic product) at the pharmacy by another medicinal product (usually a cheaper one) which is equivalent to the prescribed one [11]. Generic substitution can occur with or without informing and permission of the prescriber and patient. For practical and patient safety reasons, many European countries have determined (groups of) medicinal products or specific situations where generic substitution is not advised or not allowed. These ‘exemptions’ differ widely between European countries. Generic substitution is not allowed in Belgium.
2. INTERNATIONAL NONPROPRIETARY NAME (INN) PRESCRIBING

2.1. INTERNATIONAL NONPROPRIETARY NAMES

The International Nonproprietary Names (INNs) constitute an international nomenclature to identify active ingredients of medicinal products. Each INN is internationally recognized, unique and public property. The nomenclature was initiated in 1950 and is operated since 1953 after publishing the first list of INNs [12]. The INNs are mandated by the World Health Organization (WHO), in collaboration with the World Intellectual Property Organization (WIPO) [12–14]. Currently, there are about 7000 INNs registered [12].

Since the beginning, the aim was to contribute to the identification of medicinal products and to rational and safe medicines prescribing and dispensing, by providing a nomenclature with unique and universally available names for active ingredients. Additionally, using INNs can facilitate communication and information exchange (e.g. pharmacovigilance data) between scientists and health professionals [12].

All INNs are designed to avoid confusion (with brand names) by using distinctive sound and spelling. The common suffix (called ‘stem’ by the WHO) provide an additional advantage to the nomenclature as it indicates the connection between pharmacologically related active ingredients (e.g. all INNs for Angiotensin-Converting Enzyme (ACE) inhibitors have ‘-pril’ as common suffix) (Figure 1) [12].

Figure 1. All International Nonproprietary Names (INNs) for Angiotensin-Converting Enzyme (ACE) inhibitors, with their common suffix ‘-pril’

<table>
<thead>
<tr>
<th>Angiotensin-Converting Enzyme (ACE) inhibitors</th>
</tr>
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<tbody>
<tr>
<td>captopril</td>
</tr>
<tr>
<td>enalapril</td>
</tr>
<tr>
<td>lisinopril</td>
</tr>
<tr>
<td>perindopril</td>
</tr>
<tr>
<td>ramipril</td>
</tr>
<tr>
<td>quinapril</td>
</tr>
<tr>
<td>benazepril</td>
</tr>
<tr>
<td>cilazapril</td>
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<tr>
<td>fosinopril</td>
</tr>
<tr>
<td>trandolapril</td>
</tr>
<tr>
<td>spirapril</td>
</tr>
<tr>
<td>delapril</td>
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<tr>
<td>moexipril</td>
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<tr>
<td>temocapril</td>
</tr>
<tr>
<td>zofenopril</td>
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<tr>
<td>imidapril</td>
</tr>
</tbody>
</table>
2.2. INN PRESCRIBING

Using the INN for prescribing, i.e. INN prescribing, was introduced in the mid-eighties in France, by ‘La Revue Prescrire’, an independent journal on treatment and health strategies [15]. The main purpose was to contribute to rational and safe medicines prescribing and utilization, by adding the advantages of the INN nomenclature to the prescribing process. Although endorsed by the WHO, INN prescribing was only slowly accepted as a way of prescribing in continental Europe, next to brand name and branded generic name prescribing [12,16].

2.3. INN PRESCRIBING IN EUROPE

Twenty-six European countries provide a legal foundation for INN prescribing [17-20]. Since the global financial crisis also affected Europe, INN prescribing was one of the generic promotion measures, next to generic substitution and public awareness campaigns, implemented or elaborated to reduce pharmaceutical expenditures in many European countries [18]. The way and extent that INN prescribing is regulated and implemented varies widely between European countries.

Since June 2014, it is mandatory to prescribe by INN for prescriptions which will be dispensed in another country within the EU. The aim is to facilitate patient mobility within the EU [21,22].

Similar to generic substitution, the regulation of INN prescribing describes (groups of) medicinal products or specific situations where INN prescribing might not be appropriate, for patient safety and practical reasons. These ‘exemptions’ also differ widely.

2.4. INN PRESCRIBING IN BELGIUM

The legal foundation for INN prescribing in Belgium was laid in 2001 [23] and it became practically possible in 2005 (Figure 2) [24]. INN prescribing was defined as prescribing medicinal products using the active ingredient name, the corresponding strength and the method of administration (e.g. oral, injection, transdermal). The amount of units to be dispensed is determined by combination of the daily dose and the duration of treatment in weeks and/or days [24]. INN prescribing was introduced as an alternative way of prescribing to contribute to rational drug utilization. Related reimbursement policies obliged the pharmacist to dispense a generic product in response to an INN prescription. Therefore, INN prescribing could result in decreasing pharmaceutical expenditures for the government and the patient.

Next to INN prescribing, two other important pharmaceutical policies, involving prescribing and reimbursement regulation, were introduced to promote rational drug utilization and the use of generics. These policies were (1) the reference price system and (2) quota for prescribing ‘cheap medicines’ (Figure 2) [25–27].

The Belgian reference price system or nationally called the ‘reference reimbursement system’ started in June 2001, with the aim to reduce the pharmaceutical expenditures of the health insurance institute. The reference reimbursement system established a common reimbursement price for all medicinal products belonging to the same group of interchangeable medicinal products (usually the reference product and its available generic products). This means that the health insurance does not reimburse more than the reference price for all
medicinal products in each group. As a result, patients have to pay the difference when they are prescribed a medicinal product with its price above the reference price. This additional payment (added to the out-of-pocket fee) is called the ‘reference supplement’. Applying such a reference reimbursement system (1) decreases the demand for more expensive medicinal products and stimulates the use of cheaper ones (usually generic products) and (2) stimulates the price competition on the national pharmaceutical market [25,26].

At the end of 2005, quota for prescribing ‘cheap medicines’ were introduced, to further reduce the pharmaceutical expenditures of the health insurance, in order to make reimbursement of new, innovative medicinal products possible and to maintain low out-of-pocket expenditures for patients. These quota refer to a minimum percentage of ‘cheap medicines’ that have to be prescribed by physicians and dentists, on a yearly basis. ‘Cheap medicines’ are defined, in accordance with the reference reimbursement system, as (1) brand products with a reduced price, similar to the level of generic products, (2) generic products and (3) medicinal products dispensed with an INN prescription (regardless the type of medicinal product dispensed – a brand or generic product). The minimum percentage of ‘cheap medicines’ is determined based on the prescriber’s medical specialization [27–29].

Figure 2. Timeframe for the regulation of INN prescribing, the ‘reference reimbursement system’ and the quota for prescribing ‘cheap’ medicines in Belgium

Within the framework of the major rollout of electronic prescribing in Belgium, a project for the implementation of INN prescribing in electronic prescribing and the electronic medical file started in 2006 (Figure 2). The Ministry of Public Health requested the independent drug information center (Belgian Centre for Pharmacotherapeutic Information (BCFI/CBIP)) to coordinate the operationalization of electronic INN prescribing for outpatient care in daily medical practice.

From the introduction of INN prescribing until the end of 2011, the total percentage of INN prescriptions constantly increased, but remained very low. At the end of 2006, 2.8 % of all prescriptions were written by INN
General Introduction

(including those for which a brand product was dispensed). This percentage increased up to 3.3 % at the end of 2008, was 6.6 % the end of 2010 and 7.5 % in December 2011 [30].

In 2012, two new reimbursement policies involving INN prescribing were introduced (Figure 2). These policies were cost-containment measures, introduced in response to the global financial crisis, which started in 2008 and also affected Belgium [31].

The first policy obliges the pharmacist to respond to an INN prescription by dispensing one of the three ‘cheapest’ medicinal products available. When patients insist on having their regular medicinal product dispensed, they do not obtain reimbursement and have to pay the full price of the medicinal product package. This policy started in April 2012. For determining the three ‘cheapest’ medicinal products, all reimbursable medicinal products are grouped together based upon their (1) active ingredient(s), the INN(s), (2) corresponding strength, (3) package size and (4) method of administration (e.g. solid oral, liquids). For each group, the price per unit was calculated to determine the three cheapest products available within a margin of 5 %. The list of cheapest products is updated every month [32,33].

The second policy implies that all prescriptions for acute treatment with antibiotics or antifungal agents have to be considered as INN prescriptions. This means that the pharmacist is obliged to dispense one of the three cheapest medicinal products available, as described above. This policy is applicable to both brand name and branded generic name prescriptions. There are two situations where it is possible to deviate from this policy and have the prescribed medicinal product dispensed: (1) if the prescriber judges it is necessary for the sake and safety of the patient or (2) if the patient is allergic to an excipient with recognized action or effect [32,34]. These excipients with recognized action or effect are listed in a European guideline [35]. In both cases, the prescriber needs to indicate the reason for deviation on the prescription.

The introduction of these last two policies, where INN prescribing was forced from an indicative way of prescribing into a cost-containment measure, was associated with quite some national media attention. It caused commotion and dissatisfaction, mainly by primary care health professionals, who worried about patient safety.

2.5. CONTROVERSY OVER MEDICATION SWITCH

Since their introduction, generic products have been subject to discussion in terms of their quality, methods to establish bioequivalence (BE) and interchangeability with brand products [36–39]. With the availability of generic products, generic substitution became also possible. Supply-side and demand-side pharmaceutical policies involving generic products and generic substitution have been implemented in order to control the increasing pharmaceutical expenditures [40]. Generic substitution and its related policy of (mandatory) INN prescribing are related to controversy and are extensively discussed in literature by proponents and opponents.

Proponents can argue that BE is established using the appropriate methods described by regulatory authorities (e.g. European Medicines Agency (EMA), Food and Drug Administration (FDA) and Health Canada) [41–43] and that generic substitution can provide a more rational stock management in the pharmacy [44]. In some studies,
it was shown that patients are more likely to adhere to their treatment when their out-of-pocket fees are low [45] and that medication switch does not necessarily result in medication non-adherence [46]. However, it has also been shown that differences in medication appearance due to switching influence medication adherence negatively [47,48]. Some studies indicate that a proper explanation by primary care health professionals can avoid confusion and mistrust when initiating medication switch and that the more medication switches occur, the less patients are reluctant [49–51]. In contrast, many case reports are available in literature describing issues potentially related to medication switch [52–57].

Opponents can use the available case reports for their argumentation, but should also take into account the studies which failed to show important differences in clinical outcomes due to switching [47,48]. Opponents claim that the applied limits for establishing BE (80 – 125 %) allow too much variation, in particular for narrow-therapeutic index drugs (NTIDs) [58–60]. However, an important review performed by the FDA demonstrated that in almost 98 % of the reviewed BE studies the difference between brand and generic product was only 10 % [61,62]. In anticipation of these concerns, some regulatory authorities (e.g. EMA) tightened the limits for BE establishment of NTIDs [41] and national authorities exempted different (groups of) products from generic substitution and/or INN prescribing (e.g. antiepileptic drugs (AEDs), immunosuppressive agents) [63–65]. Another common point of criticism is that BE studies have only been performed in a limited number of healthy volunteers and that their results cannot be extrapolated to patients [44,57,58]. Opponents report that there are currently no pharmaco-economic studies available to demonstrate the cost-benefit ratio for generic substitution [60]. In addition, it is frequently commented that extra costs related to ADRs and therapy failure due to medication switch can outweigh the benefits and cost-savings [38,66–69].

Finally, issues related to medication switch can have different origins. Differences in pharmacokinetic (PK) and pharmacodynamic (PD) parameters can result in altered clinical outcomes and serious consequences, which are more likely to appear with NTIDs. However, it is suggested that these differences are probably not the only reason for therapy failure after medication switch [11,44,49,57,60,70,71]. There is evidence that differences in medication appearance (e.g. change in color) contributes to patient confusion and uncertainty and result in medication non-adherence [72,73].

All these studies and arguments indicate that different elements should be taken into account when considering a medication switch, in order to contribute to cost-savings and assure patient safety and that finding a good balance between both is a big challenge.
3. ELECTRONIC PRESCRIBING

Electronic prescribing refers to making a prescription with a computerized tool and sending it to the pharmacy as a telematic message. In this way, it is possible to generate an accurate, error-free and understandable prescription [74]. Electronic prescribing differs from making a paper prescription with a computerized tool.

Electronic prescribing plays an important role in the strategy to improve health care and facilitate patient mobility across Europe [22,74]. Currently, electronic prescribing is widely used in Denmark, Sweden and the Netherlands and it is being progressively implemented in other European countries such as England, Estonia, Iceland and Scotland [74].

For Belgium, the first initiative towards electronic prescribing in outpatient care was taken in 2001, with an explorative study. Additional studies and working group meetings were performed until the ‘Recip-e’ project started in 2007. The main objectives for the ‘Recip-e’ project were (1) to allow free choice of health care provider for the patient and (2) to create a generic system which can be used for prescribing medicinal products, physiotherapy, nursing care, clinical biology tests and medical imaging [75,76]. All data exchange is performed via the national eHealth platform [77]. Starting from 2013, the electronic prescription is being gradually implemented in Belgium and national roll-out of the electronic prescription for medicinal products was announced in March 2014 [75,76].
4. PROBLEM STATEMENT & SCOPE

International Nonproprietary Name (INN) prescribing is a way of prescribing with legal foundation in many European countries, also in Belgium. Despite its potential as rational way of prescribing, it did not really found foothold in continental Europe. However, in response to the global financial crisis, many countries forced INN prescribing into a cost-containment measure. Based upon and reflecting the countries’ traditional attitudes towards providing and financing health care, INN prescribing is implemented in various ways and extents in European countries. In Europe and Belgium, different aspects of INN prescribing contributing to rational drug utilization have been discovered, but not all of its potential is fully exploited.

Therefore, the aims of this thesis are to investigate:

1. How INN prescribing was operationalized in Belgium for the implementation in electronic prescribing and the electronic medical record (Chapter 1);
2. How the important policy changes involving INN prescribing in spring 2012 were received by Flemish general practitioners and pharmacists (Chapter 2);
3. How the important policy changes involving INN prescribing in spring 2012 were received by Flemish medicine students and pharmacy students (Chapter 3);
4. How and to which extent INN prescribing (and related generic substitution) is regulated and implemented in European countries; and to compare the exemptions applied to this regulation (Chapter 4);
5. Whether there is a pharmacokinetic reason for exempting certain medicinal products from INN prescribing and/or generic substitution, by performing a clinical trial and using the appropriate bioequivalence method (Chapter 5).
5. OUTLINE

In the next five chapters, we present the results of our research in line with the aims.

In Chapter 1, we present the process, principles and results of the operationalization project for the implementation of electronic INN prescribing in Belgium. We describe the resulting operational rules and reference database to be implemented in commercial software.

In Chapter 2, we present the results of our questionnaire study which aimed to explore the attitudes of general practitioners and pharmacists in Flanders, towards the current way of INN prescribing.

In Chapter 3, we present the same topic as in Chapter 2 for medicine students and pharmacy students.

In Chapter 4, we present an overview of the different ways and extent INN prescribing (and its related policy generic substitution) is applied in 16 European countries. Additionally, we describe and compare the main (groups of) medicinal products exempted from these concepts.

In Chapter 5, we present the results of our clinical trial performed in 30 healthy volunteers to investigate individual bioequivalence of gabapentin 800 mg tablets, a medicinal product which is advised not to be switched in Belgium.

Finally, we integrate our results in the general discussion. We address some issues related to INN prescribing in Belgium and Europe and we make suggestions for improvements and changes in order to make INN prescribing a fully accepted way of prescribing.
REFERENCES


47. Kesselheim AS. The backlash against bioequivalence and the interchangeability of brand-name and generic drugs. CMAJ. 2011 Sep 6;183(12):1350–1.


58. Van Gelder T. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. Transpl Int. 2011 Dec;24(12):1135–41.


Results
OPERATIONAL RULES FOR THE IMPLEMENTATION OF INTERNATIONAL NONPROPRIETARY NAME PRESCRIBING

Published:
ABSTRACT

Objective. The aim is to describe the process, principles and results of the International Nonproprietary Name (INN) prescribing project in Belgium. The purpose of this project was to operationalize electronic INN prescribing for outpatient care in daily medical practice and to develop a factual database which can be used in electronic INN prescribing applications.

Methods. The operationalization process consisted of three phases: (1) expert consultation, (2) review by regulatory authorities and (3) test phase with stakeholders and end-users.

Results. The INN prescribing project resulted in (1) operational rules for electronic INN prescribing, and (2) a reference database to be implemented in commercial medical software. The operational rules for electronic INN prescribing define valid INN groups as sets of equivalent medicinal products, described by three elements: the therapeutic moiety (the active part of the therapeutic ingredient) or combination of therapeutic moieties, the strength (with standardized denominators), and the method of administration (with simplified but standardized options). The operational rules also define two categories of exemptions for INN prescribing: INN groups where the first choice of treatment should be continued throughout the therapy period (NO SWITCH) and medicinal product groups not suitable for INN prescribing (NO INN). The reference database is the result of the virtual classification of the Belgian therapeutic arsenal into INN groups, according to the operational rules.

Conclusion. Defining the operational rules for INN prescribing for and with different stakeholders was a difficult yet feasible assignment. The INN prescribing project resulted in explicit operational rules and a reference database. The Belgian experience may provide important information for other countries planning to operationalize or refine electronic INN prescribing. It can also be used for a thorough evaluation of the impact of the new concept of INN prescribing on daily practice and on medical education.
1.1. INTRODUCTION

International Nonproprietary Names (INNs) were introduced by the World Health Organization (WHO) in 1950 as a global, internationally accepted nomenclature for active ingredients and pharmaceutical substances [1]. This nomenclature is an alternative to the management of proprietary brand names, supported by the World Intellectual Property Organisation (WIPO) [2]. It was developed to facilitate the identification of medicines, the exchange of information such as pharmacovigilance data, and the communication amongst health professionals [1]. The concept of “INN prescribing” is defined as using the INN instead of the brand name for prescribing [1,3,4]. INN prescribing is said to contribute to rational drug choice and drug utilization [4]. Using the INN for prescribing may also prevent prescribing and dispensing errors [1] by increasing prescribers’ and pharmacists’ awareness of the prescribed active ingredient and the corresponding strength. INN prescribing has recently been promoted as a strategy to reduce pharmaceutical expenditures [5]. It has been extensively adopted by different countries, with 22 of the 27 member states of the European Union providing a legal foundation for INN prescribing [5].

The concept of INN prescribing is operationalized in different ways and various degrees in several countries. This variation in operationalization may be explained by the broad definition of INN prescribing, by differences in health care systems and in legal formats of prescriptions. Differences in drug policies, such as reference price systems, reimbursement and generic substitution policies, and therapeutic arsenals (i.e. all medicinal products marketed in a country) may also contribute to this variation. All this makes cross-national comparison complex.

In Belgium, the legal foundation for INN prescribing was laid in 2001 but it lasted until 2005 before INN prescribing was officially allowed in clinical practice [6]. By the end of 2007, INN prescribing was poorly adopted in Belgium with only 5.1 % INN prescriptions [7]. Given the low uptake and the upcoming major rollout of electronic prescribing, the Ministry of Public Health requested the Belgian Centre for Pharmacotherapeutic Information (BCFI/CBIP, the independent drug information centre in Belgium) at the end of 2006, to coordinate “the INN prescribing project”. The purpose of this project was to operationalize electronic INN prescribing for outpatient care in daily medical practice and to develop a factual database which can be used in electronic INN prescribing applications. The objectives were (1) to convert the legislation into operational rules for electronic INN prescribing and (2) to develop a reference database for INN prescribing to be implemented in commercial medical software.

The aim of this paper is to describe the process, principles and results of the INN prescribing project in Belgium.

1.2. METHODS

The development process of the INN prescribing project consisted of three phases (Figure 1.1): (1) expert consultation, (2) review by regulatory authorities, and (3) test phase with stakeholders and end-users.

In the first phase a group of external experts engaged in a series of five structured meetings with the goal to formulate a first draft of the operational rules. The group met at monthly intervals, for two-hour meetings. Members were experts from the independent drug information centre (BCFI/CBIP); the medicines agency, i.e.
the regulatory authority for medicines (the Federal Agency for Medicines and Health Products (FAMHP) including the Medicines Commission for Medicines for human use which is responsible for the marketing authorization of medicines for human use); public health (Federal Public Service for Health, Food Chain Safety and Environment); the health insurance institute (National Institute for Health and Disability Insurance (RIZIV/INAMI)); scientific associations of general practitioners and pharmacists, and experts in medical informatics from the software vendors. The experts started with reviewing literature on INN prescribing, analysing the legislation, and making an inventory of existing initiatives in Belgium concerning INN prescribing. Important findings were structured into different issues, which were discussed. The results of these discussions formed the basis of the draft document for the operational rules. At the same time, the group of external experts elaborated a classification of the Belgian therapeutic arsenal based on the draft operational rules. This virtual classification was the preliminary work for the development of the reference database.

The goal of the second phase was obtaining the approval for the draft operational rules from the Medicines Commission, which is the decision-making body within the medicines agency. The approval process was prepared by executives from the medicines agency, and the Medicines Commission, while experts from the independent drug information centre were only attending to coordinate the approval process. The executives and experts gathered five times, at monthly intervals, to discuss the draft operational rules and the classification of the therapeutic arsenal. After they had reached an agreement, representatives from the health insurance institute were asked to comment the operational rules. The final version of the operational rules was approved by the Medicines Commission [8].

In the third phase, the operational rules and the reference database were made accessible via an internet application for stakeholders and end-users, such as physicians, pharmacists and, ethical pharmaceutical industry (pharmaceutical companies developing new molecules) and generic pharmaceutical industry. During a one-year pilot phase, the reference database was tested and checked for applicability and inconsistencies. Comments were sent to the independent drug information centre. Relevant items were discussed and adjustments were made to the operational rules and the reference database. The adjustments were officially approved for the second time by the Medicines Commission for Medicines for human use.
Chapter 1

1.3. RESULTS

1.3.1. OPERATIONAL RULES

The group of external experts proposed to expand the concept of INN prescribing in order to implement it in electronic prescribing. They recommended the use of three key elements instead of one (the INN) to make a valid electronic INN prescription: (1) the therapeutic moiety or combination of therapeutic moieties, (2) the strength and, (3) the method of administration [8]. These three key elements are used to describe a set of equivalent medicinal products, called an ‘INN group’ (Figure 1.2). For example, all products marketed in Belgium containing alprazolam 2 mg tablets – Alprazolam Mylan® 2 mg, Alprazolam Teva® 2 mg, Alprazolam EG® 2 mg and Xanax® 2 mg – are classified in the same INN group ‘Alprazolam 2 mg (oral)’ (Figure 1.2a). Applying this way of classification to the 7319 medicinal product packages available on the Belgian market in July 2012, resulted in 6732 (92.0 %) medicinal product packages being suitable for INN prescribing, and being classified into 2765 INN groups. The remaining 587 (8.0 % of the Belgian therapeutic arsenal) medicinal product packages are exempted from INN prescribing (NO INN) (see 1.3.5. for further description). Each of the INN groups is identified by a standardized label and has a unique identification number.

Prescribers can make an unambiguous INN prescription by specifying and prescribing the label of the INN group. At the same time, the unique identification number is registered in the patient’s electronic medical record. Additional specifications can be indicated to the INN group to ensure the dispensing of products with specifically desired characteristics (e.g. divisible tablets) (Figure 1.2a). Finally, the Belgian legislation [6] states that the amount of product that has to be dispensed should be determined by combination of daily dose and duration of treatment (e.g. 1 tablet per day during 3 months), which is in contrast to prescribing by product name where the package size is indicated (e.g. 90 tablets). All this led to a more explicit definition of INN prescribing for Belgium: INN prescribing is using the INN, indicating the corresponding strength and the method of administration and, defining the amount of units to be dispensed by combination of daily dose and duration of treatment. In response to an INN prescription, the pharmacist will chose a medicinal product package which complies with the prescription specifications. The dispensed product is usually a generic, when available. If no generics are available or if the price of the brand is very low, the dispensed product might be a brand.

1.3.2. OPERATIONALIZATION OF THE THREE KEYS ELEMENTS

THERAPEUTIC MOIETY

To represent the active ingredient of the medicinal product, the INN nomenclature served as a basis to select the options for the first key element. This element is called ‘therapeutic moiety’ rather than INN, to indicate a more abstract representation of the active ingredient. ‘Therapeutic moiety’ can be defined as the therapeutic active part of a molecule. The basis for the operationalization of this element was also drawn from the ‘dictionary of medicines + devices’ (dm+d), developed by the National Health Service (NHS) in the United Kingdom [9] and,
Operational rules for the implementation of electronic INN prescribing

Figure 1.2. The INN group principle and the decision-support illustrated by (a) alprazolam divisible tablets, (b) Ceftazidime I.M. injection and (c) Gabapentin capsules.
from the Periodic Safety Update Report (PSUR) synchronization list, made by the Heads of Medicines Agencies (HMA) [10].

The INN nomenclature is a mix of names for bases, acids, alcohols, salts and esters [1]. Unless there was strong evidence for clinical relevance, it was decided to restrict the name of the first key element to the name of the base or acid. For example, it was shown by different studies that the two different salts of perindopril, tert-butylamine and arginine, are bioequivalent. Therefore the name of the therapeutic moiety was restricted to ‘perindopril’ [11,12]. The same applies to: amlodipine, metoprolol, diclofenac and piroxicam. In contrast, the full name of the active ingredient was kept for hydrocortisonacetate and hydrocortisonbutyrate when representing the first key element, because of major difference in potency between both [13].

A multilingual reference table was developed containing all therapeutic moieties needed to classify the Belgian therapeutic arsenal into INN groups. Basic information in English (INNs [14], dm+d [9], and the PSUR synchronisation list [10]) and in French (INNs [14]) was used to select the options for the therapeutic moieties in these languages. Because no basic information was available in Dutch, the independent drug information centre provided the official translation of the therapeutic moieties in Dutch.

The first key element can also be a combination of different therapeutic moieties, e.g. amoxicillin + clavulanic acid, provided this combination is instantiated by a medicinal combination product, which is mentioned on the PSUR synchronization list, and currently available on the Belgian market.

**STRENGTH**

The strength of the therapeutic moiety represents the second key element of the INN group and is defined by the one listed in the marketing authorization file of the corresponding medicinal products in the INN group. In case different strengths are registered for the same therapeutic moiety, because of differences in salts and esters, it was decided by consensus which strength was represented. For instance, the therapeutic moiety perindopril is registered as perindopril tert-butylamine 4 mg and perindopril arginine 5 mg, because of the difference in molecular weight. Perindopril tert-butylamine 4 mg and perindopril arginine 5 mg contain an equimolar amount of perindoprilat (the active metabolite of perindopril) [11]. Therefore, all medicinal product packages containing both doses were classified into the same INN group ‘Perindopril 4 mg (oral)’. Representing the strength as 4 mg, instead of 5 mg, was a consensus decision.

Pharmaceutical forms were grouped into ten categories (Table 1.1). For each category, a denominator was chosen to express the strength. The strength of all solid forms (e.g. tablets, capsules, suppositories) is expressed (in mg or g) per unit. The strength of single dose injection vials and vials for infusion is expressed per vial, and the strength for inhalers is expressed per dose. These denominators are implied, and therefore not mentioned, when representing the strength in the INN groups. In the other categories, the strength is expressed as a concentration per mL or per g, and the denominator is mentioned when representing the strength.
### Table 1.1. Denominators to express the strength of pharmaceutical forms

<table>
<thead>
<tr>
<th>Categories of pharmaceutical forms</th>
<th>Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid forms (e.g. tablets, capsules, suppositories)</td>
<td>Per unit</td>
</tr>
<tr>
<td>Syrups &amp; drinks</td>
<td>Per mL</td>
</tr>
<tr>
<td>Drops (for oral use)</td>
<td>Per mL</td>
</tr>
<tr>
<td>Vial for injection – single dose</td>
<td>Per vial</td>
</tr>
<tr>
<td>Vial for injection – multi dose</td>
<td>Per mL</td>
</tr>
<tr>
<td>Vial for infusion</td>
<td>Per vial</td>
</tr>
<tr>
<td>Topical preparations:</td>
<td></td>
</tr>
<tr>
<td>• Solid &amp; semi-solid</td>
<td>Per g</td>
</tr>
<tr>
<td>• Liquid</td>
<td>Per mL</td>
</tr>
<tr>
<td>Transdermal delivery systems</td>
<td>Per time unit (e.g. per hour, per 24 hours, ...)</td>
</tr>
<tr>
<td>Inhalers</td>
<td>Per dose</td>
</tr>
</tbody>
</table>

For injectable products, a distinction was made between single and multiple dose vials. For single dose vials, the total amount of therapeutic moiety was used to express the strength, regardless of the concentration, an approach similar as in solid forms (Figure 1.2b). The same applies to vials for infusion. By contrast, for multiple dose vials, the strength was expressed as the concentration of the therapeutic moiety (and the total volume of the vial indicates the package size).

### METHOD OF ADMINISTRATION

In 95 % of the cases, the combination of the therapeutic moiety and strength is sufficient to create unambiguous INN groups containing equivalent medicinal products. To handle the remaining 5 % of the medicinal products (e.g. diclofenac 100 mg tablets and diclofenac 100 mg suppositories), the ‘method of administration’ was introduced as the third key element. Using the list with standard terms for ‘routes and methods of administration’ [15] and ‘dosage forms’ [16] from the European Pharmacopeia, a list with 36 options for the third key element was created. Out of the 74 terms for human use on list of the European Pharmacopeia, 16 terms were selected. They were complemented with 7 new terms (Table 1.2).

The first term added was ‘injection’ to summarize all products that can be administered by injection or by injection (e.g. intravenous, intramuscular) and by infusion. Secondly, the term ‘infusion’ was reserved for those products that can only be administered by infusion (e.g. Zinacef® 1.5 g powder for solution for infusion). The term ‘nebulization’ was added for inhalation products that have to be nebulized (e.g. Ventolin® Respirator solution 5 mg/mL).

The term ‘oral’ is used for oral medicinal products, and no distinction was made for products with a fast releasing profile (e.g. instant tablets). In contrast, for medicinal products with prolonged release two new terms were created: ‘oral, prolonged release 1x per day’ for those that have to be taken only once a day and ‘oral, prolonged release’ for those that have to be taken more than once a day. Similarly, the terms ‘injection, prolonged release’
for depot injections and ‘ophthalmological, prolonged release’ for eye products with prolonged release were introduced to guarantee homogeneous INN groups.

Finally, the list was completed with 13 combinations of single terms for INN groups containing medicinal products that can be administered via different methods (Table 1.2). For example, isosorbide dinitrate 5 mg tablets (Cedocard®) for angina pectoris can be administered orally or sublingually and therefore the third key element for this INN group is ‘oral/sublingual’.

Table 1.2. Single term options for the third key element ‘method of administration’ in English, Dutch & French and combination term options in English

<table>
<thead>
<tr>
<th><strong>English</strong></th>
<th><strong>Dutch</strong></th>
<th><strong>French</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Auricular</td>
<td>Auriculair</td>
<td>Auriculaire</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Cutaan</td>
<td>Cutané</td>
</tr>
<tr>
<td>Dental</td>
<td>Dentaal</td>
<td>Dentaire</td>
</tr>
<tr>
<td>Endocervical</td>
<td>Endocervicaal</td>
<td>Endocervical</td>
</tr>
<tr>
<td>Infusion*</td>
<td>Infuus*</td>
<td>Perfusion*</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Inhalatatie</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Injection*</td>
<td>Injectie*</td>
<td>Injection*</td>
</tr>
<tr>
<td>Injection, prolonged release*</td>
<td>Injectie, verlengde vrijstelling*</td>
<td>Injection, libération prolongée*</td>
</tr>
<tr>
<td>Intrauterine</td>
<td>Intra-uterien</td>
<td>Intra-utérine</td>
</tr>
<tr>
<td>Intravesical</td>
<td>Intravesicaal</td>
<td>Intravésicale</td>
</tr>
<tr>
<td>Oral</td>
<td>Oraal</td>
<td>Oral</td>
</tr>
<tr>
<td>Oral, prolonged release*</td>
<td>Oraal, verlengde vrijstelling*</td>
<td>Oral, libération prolongée*</td>
</tr>
<tr>
<td>Oral, prolonged release, 1x per day*</td>
<td>Oraal, verlengde vrijstelling, 1x per dag*</td>
<td>Oral, libération prolongée, 1x par jour*</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>Orofangyngaal</td>
<td>Bucco-phangyngée</td>
</tr>
<tr>
<td>Rectal</td>
<td>Rectaal</td>
<td>Rectal</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Sublinguaal</td>
<td>Sublingual</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Transdermaal</td>
<td>Transdermal</td>
</tr>
<tr>
<td>Urethral</td>
<td>Uretha</td>
<td>Uretra</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Vaginaal</td>
<td>Vaginal</td>
</tr>
</tbody>
</table>

**Combination terms:** Cutaneous/vaginal • Infusion*/intravesical • Injection*/infusion* • Injection*/inhalation • Injection*/intravesical • Injection*/oral • Injection*/rectal • Ophthalmological/auricular • Ophthalmological/auricular/nasal • Oral/oropharyngeal/cutaneous • Oral/rectal • Oral/sublingual • Oropharyngeal/nasal

*terms introduced to suit the Belgian therapeutic arsenal
1.3.3. ADDITIONAL SPECIFICATIONS AND INFORMATION

To have the most suitable product dispensed to the patient, the prescriber can add certain specifications, in addition to the INN group, to the prescription (Figure 1.2a, 1.2b). The following specifications were included on the level of the medicinal product package, in the reference database, if relevant:

1) specific route(s) of administration (e.g. intravenous, intramuscular, subcutaneous)
2) divisibility of solid forms
3) solubility of solid forms (e.g. effervescent tablets)
4) enteric coated solid forms
5) the vehicle for topical products (e.g. cream, ointment, paste)
6) excipients known to have a recognized action or effect (e.g. glucose, lactose) (the implementation of this specification is currently under construction)

When making an INN prescription for a topical product, the prescriber is obliged to choose one of the available vehicles, if relevant.

The European guideline “Excipients in the label and package leaflet of medicinal products for human use” provides a list of excipients known to have a recognized action or effect [17]. Only the excipients mentioned in the European guideline will be included in the reference database. Currently, this is only achieved for antibiotics and antifungal products available for outpatient care.

Finally, it was decided to include a link to information, on the medicinal product package level, regarding the therapeutic indication and the reimbursement of products. Indeed, within the same INN group, the official therapeutic indications (as mentioned in the Summary of Product Characteristics) as well as the reimbursement criteria may slightly differ between medicinal product packages within one INN group.

1.3.4. INN GROUPS WHICH REQUIRE SPECIAL ATTENTION (NO SWITCH)

To guarantee patient safety when prescribing by INN, the ‘NO SWITCH’ label for INN groups was created. This label means that medicinal products in these groups can be prescribed by INN, but once treatment is started with a product from a particular manufacturer, it is advised to continue treatment with exactly the same product (Figure 1.2c). However, switching between products during treatment is not impossible, but has to be done carefully and under the supervision of the prescriber.

The label was given to INN groups containing (1) medicinal products with a narrow therapeutic index (NTI) and/or (2) very toxic molecules (Table 1.3). Within the European Union, there is no official definition of a drug with a narrow therapeutic index. The European Medicine Agency (EMA) states in its ‘Guideline on the Investigation of Bioequivalence’ that “It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.” [18]. Therefore, the definitions of the Canadian and American authorities were also consulted. The Guidance for Industry concerning bioequivalence requirements on critical dose drugs from Health Canada
Chapter 1

defines critical dose drugs as “those drugs where comparatively small differences in dose or concentration lead to dose-and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious.”[19]. The Centre for Drug Evaluation and Research (CDER) from the Food and Drug Administration (FDA) gives the following definition of narrow therapeutic index: “there is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood and safe and effective use of the drug products require careful titration and patient monitoring.” [20].

Table 1.3. Pharmaceutical products and categories with the ‘NO SWITCH’ label

<table>
<thead>
<tr>
<th>NTIDs and/or very toxic molecules or antiepileptic drugs</th>
<th>Gabapentin**</th>
<th>Pregabalin**</th>
<th>Primidone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acenocoumarol</td>
<td>Lacosamide**</td>
<td>Propafenone</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Lamotrigine**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Levetiracetam**</td>
<td></td>
<td>Sotalol</td>
</tr>
<tr>
<td>Carbamazepine*</td>
<td>Levothyroxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>Lidoçaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Lithium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colchicine</td>
<td>Metildigoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Mycophenolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Oxcarbazepine**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Pheneturide*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eososuximide*</td>
<td>Phenobarbital*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>Phenprocoumon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate*</td>
<td>Phenytoin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecaïnide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other categories of pharmaceutical products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Mesalazine and sulphasalazine</td>
</tr>
<tr>
<td>Inhalation medication for pulmonary use</td>
</tr>
<tr>
<td>Medicines used in oncology</td>
</tr>
<tr>
<td>Transdermal delivery systems</td>
</tr>
<tr>
<td>Diagnostics and anesthetics</td>
</tr>
<tr>
<td>Pharmaceutical products for local use (e.g. dermatological products)</td>
</tr>
</tbody>
</table>

*Antiepileptics (NTID and/or very toxic)
**Antiepileptics (not NTID and/or very toxic)
The Belgian list of therapeutic moieties with NTI and/or very toxic was defined by the experts from the medicines agency, based on the preceding definitions, existing lists of products with NTI from Health Canada [19], the FDA [21] and the Danish Medicines Agency [22], reference books and websites such as Goodman & Gilman [23], Micromedex [24] and Medline Plus [25], information from The International Association of Forensic Toxicologists (TIAFT) [26] and expert opinions.

All antiepileptics on the Belgian market were considered as NO SWITCH. Most of them because they are drugs with a NTI and/or very toxic molecules (Table 1.3). However, also others (gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, stiripentol, tiagabine, topiramate and vigabatrine) are listed as NO SWITCH for precautionary reasons as in literature potential problems were reported, possibly related to switching between products of different manufacturers during treatment.

Other INN groups were also considered as NO SWITCH for various reasons (Table 1.3). For example, because of lack of evidence of bioequivalence between products (e.g. mesalazine and sulphasalazine), the complex pharmacotherapeutic profile (e.g. diagnostics and anesthetics), complex packaging (e.g. oral contraceptives) or because of precautionary measures with regard to toxicity (e.g. medicines used in oncology).

Out of all 2,765 INN groups, 794 groups were given the NO SWITCH label (28.7%), which corresponds to 1,528 medicinal product packages of the 7,319 packages (20.9%) available on the Belgian market.

1.3.5. PRODUCTS EXEMPT FROM INN PRESCRIBING (NO INN)

Finally, three categories of medicinal products were exempted from INN prescribing: (1) biologicals, including biosimilars, (2) medicinal products containing more than three therapeutic moieties, and (3) multiphasic contraceptive pills.

Biologicals, including biosimilars, were deemed not suitable for INN prescribing because of their molecular complexity [27] and the risks associated to their immunogenicity when switching [28]. The medicines agency provides, on its website, a list of all biologicals and biosimilars available on the Belgian market [29].

Medicinal products with more than three therapeutic moieties were exempted because of the complexity when prescribed by INN (e.g. complex polyvitamins). Similar for multiphasic contraceptive pills because of the complexity of packaging.

It is important to note that although these products are deemed not suitable for INN prescribing, it is still possible for the prescriber to start treatment with a generic medicine, when one is available, by prescribing the branded generic name.

Out of all 7,319 medicinal product packages available on the Belgian market, 587 of them are not suitable for INN prescribing (8.0% of the therapeutic arsenal).
1.3.6. REFERENCE DATABASE

The reference database (Figure 1.3) [30] includes all 7,319 medicinal product packages available on the Belgian market: 6,732 packages suitable for INN prescribing which are classified into 2,765 INN groups (including the 794 INN groups with the NO SWITCH label) and the remaining 587 packages exempted from INN prescribing (NO INN). For each medicinal product package it was determined (1) whether it can be prescribed by INN, (2) to which INN group it belongs, and (3) which additional specifications apply.

The reference database can be consulted at www.bcfi.be/inn, and contains all relevant information on the level of medicinal product packages, such as route of administration, divisibility, solubility, enteric coated, vehicles for topical products and excipients known to have a recognised action or effect (this latter aspect is currently under construction). Links to information on the therapeutic indications and reimbursement were added. For INN groups containing the NO SWITCH label, the main reason for having this label was indicated (e.g. medicines used in oncology).

All included information on the medicinal product packages allows the database to serve as a decision-support tool to foster safe and efficient medicines prescribing and dispensing. When prescribing by INN, the prescriber follows a step by step process, starting by choosing the therapeutic moiety (Figure 1.2). Next, all possible options for the strength and the method of administration are shown and the most suitable one has to be selected. When available, additional specifications (e.g. dispensed product needs to be divisible) can be added to have the desired product dispensed to the patient. Similarly, the pharmacist is guided to dispense the most suitable product. The drug choice process is complex [31,32], and literature has already shown the positive effect of decision-support and computerized drug order entry (CDOE) on preventing prescribing and dispensing errors [33–35]. For practical reasons, a search strategy was added by which the user can enter a specific product name to find the corresponding INN group.

The reference database is kept up to date by the independent drug information centre and will also be integrated in the authentic source of medicines on the eHealth platform [36,37]. The reference database is available for medical software vendors to integrate in their prescription and dispensing software.
Operational rules for the implementation of electronic INN prescribing

Figure 1.3. Screenshot from the reference database

1. Enter search term: by ingredient or by brand name
2. Select INN group: “Ibuprofen 600 mg (oral)”
3. Position of the selected INN group in the medication classification of the BCFI/CBIP
4. Unique identification number of the INN group
5. Unique identification number of the medicinal product package
6. Additional information on the level of the medicinal product package. For example route of administration, divisibility, ...
7. All available medicinal product packages for the INN group “Ibuprofen 600 mg (oral)” are displayed
8. All corresponding INN groups are displayed
9. NO SWITCH label
1.4. DISCUSSION

To our best knowledge, this study is the first to provide a transparent description of the operationalization process of INN prescribing, resulting in explicit operational rules and a publically available database.

INN prescribing is frequently used as a strategy to reduce pharmaceutical expenditures. However, in Belgium, several strategies such as the well-established reference price system [38,39] and the encouragement of prescribers to prescribe cheap products (either generics or originators in case they lowered their prices to the reference price) were already introduced as cost-saving measures before INN prescribing came into force. Therefore, the emphasis of the INN prescribing project was more on rational drug choice and operationalizing the concept for electronic prescribing, rather than on cost-savings. In retrospect, we believe that structuring the development process was essential to achieve consensus on this complex matter, with a variety of stakeholders with different interests.

The operationalization of INN prescribing in Belgium resulted in four important achievements.

The first achievement was the publication of explicit operational rules, accepted by the governing bodies and the stakeholders, making the approach transparent.

The second achievement was the development of a high level categorization of ‘method of administration’, based on dosage forms and route of administration.

Third was the agreement on an explicit list of therapeutic moieties with NTI and/or being very toxic.

Finally, the fourth achievement was the development of a publically available database, which classifies all medicinal product packages in the Belgian therapeutic arsenal, allowing correct registration of an INN prescription in the electronic medical record through a unique identification number, which was not possible before. In addition, this database provides reliable information for decision-support systems to foster efficient and rational drug choice in prescribing and dispensing.

Next to achievements, this project also has its limitations.

First, decisions to make homogeneous INN groups, to label some INN groups which require special attention (NO SWITCH), and to exempt certain products from INN prescribing (NO INN) were made in accordance to the best available evidence, which was sometimes limited. There was also an attempt to meet all the different interests from all the stakeholders, such as the ethical and generic pharmaceutical industry, the authorities and professional associations. Hence, the first limitation is that the reference database may be perceived in some aspects as country-specific and subjective.

Second, up to now, the project only focussed on INN prescribing for outpatient care. The developed operational rules need to be adjusted to fit the complex character of medicinal products for inpatient care and the classification of the therapeutic arsenal and the reference database need to be complemented with hospital drugs.
A few points need further attention.

First, there is the inconsistency between the Belgian laws on INN prescribing [6] and controlled drugs [40,41]. Controlled drugs can be prescribed by brand name or by INN, but the law on controlled drugs obliges the prescriber to specify the total amount of product that has to be dispensed and write it in full (e.g. thirty tablets, and not 30 tablets). This latter aspect is in contrast to how the amount of product has to be determined when prescribing by INN, being by combination of daily dose and duration of treatment. The consequence for prescribing controlled drugs by INN is that a package size (expressed in full writing) needs to be chosen.

Second, for pro re nata (PRN) use (if-needed use) it is difficult to determine the number of intakes and the duration of treatment. As result the amount of product that has to be dispensed cannot be determined in advance. Therefore, it might be appropriate to indicate a maximum amounts of units to be dispensed.

Third, it should be explored whether it is possible to provide feedback to the prescriber on the exact nature of the dispensed medicinal product package, in case of INN prescribing. This can prevent information gaps for the prescriber in situations where characteristics of the medicinal product package (e.g. colour, taste, package size) might be important (e.g. the identification of ingested drugs in voluntary or involuntary poisoning).

Fourth, it remains to be seen whether co-operation between stakeholders can be continued for the maintenance of the operational rules to ensure consistency with new policies influencing (electronic) INN prescribing.

Finally, the impact of this new concept should be rigorously tested, as well in the daily practice of prescribing and dispensing medicines, as in medical education for rational pharmacotherapy.

1.5. CONCLUSION

Defining the operational rules for INN prescribing for and with different stakeholders was a difficult yet feasible assignment. The INN prescribing project resulted in explicit operational rules and a reference database. The Belgian experience may provide important information for other countries planning to operationalize or refine electronic INN prescribing. It can also be used for a thorough evaluation of the impact of the new concept of INN prescribing on daily practice and on medical education.
REFERENCES


22. Danish Health and Medicines Authority. Bioequivalence and labelling of medicines with regard to generic substitution. 2012.


40. Koninklijk besluit houdende regeling van de slaapmiddelen en de verdovende middelen en betreffende risicobeperking en therapeutisch advies. 31 december 1930.

ATTITUDES OF PHYSICIANS AND PHARMACISTS TOWARDS INTERNATIONAL NONPROPRIETARY NAME PRESCRIBING IN BELGIUM

Published:
Elien Van Bever, Monique Elseviers, Marijke Plovie, Lieselot Vandeputte, Luc Van Bortel, Robert Vander Stichele.
ABSTRACT

Objective. International Nonproprietary Name (INN) prescribing is the use of the name of the active ingredient(s) instead of the brand name for prescribing. In Belgium, INN prescribing started in 2005 and a major policy change occurred in 2012. The aim was to explore the opinions of Dutch-speaking general practitioners (GPs) and pharmacists.

Methods. An electronic questionnaire with 39 5-point Likert scale statements and one open question was administered in 2013. Multivariate analysis was performed with multiple linear regression on a sum score for benefit statements and for drawback statements. Answers to the open question were qualitatively analyzed.

Results. We received 745 valid responses with a representable sample for both subgroups. Participants perceived the motives to introduce INN prescribing as purely economic (to reduce pharmaceutical expenditures for the government and the patient). Participants accepted the concept of INN prescribing, but 88 % stressed the importance of guaranteed treatment continuity, especially in older, chronic patients, to prevent patient confusion, medication nonadherence and erroneous drug use.

Conclusion. The current way INN prescribing is applied in Belgium leads to many concerns among primary health professionals about patient confusion and medication adherence. Slightly adapting the current concept of INN prescribing to these concerns can turn INN prescribing into one of the major policies in Belgium to reduce pharmaceutical expenditures and to stimulate rational drug prescribing.
2.1. INTRODUCTION

In an international setting, International Nonproprietary Name (INN) prescribing is defined as using the name of the active ingredient(s) instead of the brand name for prescribing [1–3]. International Nonproprietary Names (INNs) belong to an official nomenclature for active ingredients in the pharmaceutical domain. This is the result of a collaboration between the World Health Organization (WHO), which governs this public nomenclature, and the World Intellectual Property Institute (WIPO), which governs the brand names of pharmaceutical products [4–6]. INNs were developed to facilitate the identification of medicines, the exchange of pharmacovigilance data, and communication between health professionals [1].

INN prescribing supports prescribers and pharmacists in their choice of treatment and offers an opportunity for physicians to focus on diagnosis and therapy, and for pharmacists to focus on the best choice of medicinal product package, together with the patient. INN prescribing should take into account the type of treatment (acute or chronic), the medicinal product (e.g. narrow therapeutic index drugs) and the patient (e.g. age, disease, medication adherence) [2].

The concept of INN prescribing is widely adopted by European countries as an implemented health policy [7,8], which is sometimes used in combination with (generic) substitution to reduce pharmaceutical expenditures [7,9].

In Belgium, INN prescribing is prescribing medicinal products using the name of the active ingredient, the corresponding strength, method of administration (e.g. oral, injection, transdermal), the daily dose and duration of treatment in weeks and/or days. The duration of treatment is limited to 92 days (3 months) for reimbursable medicinal product packages [10].

INN prescribing was legally introduced in 2001 in Belgium and became practically possible in 2005 [10]. It was presented as an alternative way of prescribing, next to brand name and generic prescribing, to enhance rational prescribing. INN prescribing helps patients to minimize their out-of-pocket expenditures. INN prescribing and (generic) medication substitution are often related policies [7], but not in Belgium, where medication substitution is not allowed [11]. The Belgian medicines agency (the Federal Agency for Medicines and Health Products (FAMHP) [12]) established an exhaustive list of products for which treatment should be continued with the same product from the same manufacturer, once treatment has started. This list is called the ‘NO SWITCH’ list and includes narrow therapeutic index drugs (NTIDs). An additional smaller list was established with products exempted from INN prescribing [13].

Parallel to the introduction of INN prescribing in Belgium, two other important containment policies for pharmaceutical expenditures were introduced. First, there was the reference price system which implies that the reimbursement price is set at 69 % of the current originator reimbursement price, at the moment the patent of an original medicinal product expires and generics enter the market. Consequently, patients have to pay a ‘reference supplement’ when receiving an originator priced above the reference reimbursement price [14,15]. Second, a quota for ‘prescribing cheap medicines’ was introduced. The quota, applicable to physicians and dentists, refers to a minimum percentage of ‘cheap medicines’ that has to be prescribed each year. ‘Prescribing
cheap medicines’ is defined as (1) prescribing originator products with a reduced price, similar to the price of the generics, (2) prescribing generics (which, by definition, must be cheaper than the originator under patent) or (3) INN prescribing (regardless the type of medicinal product dispensed) [16].

When the global financial crisis affected Belgium, austerity measures were introduced to contain pharmaceutical expenditures. Two of these measures involved INN prescribing and came into force in April and May 2012 [11].

The first measure implies that the pharmacist is obliged to respond to an INN prescription by dispensing one of the three cheapest medicinal products available. The list of cheapest medicinal products available is updated each month.

The second austerity measure implies that all prescriptions for acute treatment with antibiotics or antifungal agents have to be considered as INN prescriptions. This means that the pharmacist is obliged to dispense a medicinal product package from the group of cheapest medicinal products, as described above. This is applicable to both brand name and generic prescriptions. A procedure of therapeutic objection from the prescriber towards medication switch is foreseen for exceptional cases [17,18].

The introduction of these new austerity measures required a change in the mindset and practices of prescribers, pharmacists and patients. It caused commotion and dissatisfaction and was associated with quite some media interest [19–25].

The aim of this study was to explore the attitude of general practitioners (GPs) and pharmacists in Flanders, the Dutch-speaking region of Belgium, regarding the current concept of INN prescribing introduced in response to the austerity measures of spring 2012.

2.2. METHODS

2.2.1. THE QUESTIONNAIRE

A questionnaire was designed to explore the attitudes of health care professionals and students with regard to INN prescribing, as no tool was available.

The target populations were Flemish general practitioners (GPs) and pharmacists working in public pharmacies.

Prior to drafting the questionnaire for GPs, a preliminary literature search was performed in PubMed with MeSH and search terms: “INN prescribing”; “Attitude of Health Personnel”[Mesh]; “generic prescribing”; “Drug Substitution”[Mesh]. Items to be surveyed were extracted from the four relevant articles [2,26–28], including a questionnaire performed in French health professionals from Biga et al. in 2005 [27]. An expert meeting, including GPs, pharmacists and clinical pharmacologists was organized to identify topics to be questioned. A draft questionnaire was developed and tested with the assistance of GPs and pharmacists. Based on the collected remarks, the draft questionnaire was adjusted and finalized.
In the first part of the questionnaire, demographic characteristics (gender, age, postal code, university affiliation) were asked. The questionnaires also assessed location (rural, urban or mixed rural-urban area), social class of neighborhood (deprived, residential or social-mixed) and type of general practice (solo, duo, group practice or district health centre) or pharmacy (retail pharmacy, cooperative pharmacy or health service pharmacy).

Next were 39 five-point Likert scale statements (strongly agree/agree/neutral/disagree/strongly disagree) classified in four themes: (1) motives for the introduction of policies concerning INN prescribing, (2) attitudes towards INN prescribing and the introduced policies, (3) benefits of INN prescribing and (4) drawbacks of INN prescribing. Some statements were negated to avoid leading bias.

The questionnaire ended with an open question where participants could write their own opinion concerning the (current) concept of INN prescribing in Belgium.

The questionnaire was first designed for GPs and then slightly adapted for the pharmacists. All questionnaires were made electronically accessible using an online survey tool (eSurvey Creator®) [29].

### 2.2.2. SELECTION OF THE SURVEY POPULATION

A different recruitment strategy for both population groups was applied in the period of February to July 2013.

For the GPs, the representatives of all local peer review groups (Lokale OnderzoeksKring (LOK)) in Flanders were contacted by the scientific association of Flemish GPs (Domus Medica) with the request to circulate the electronic link to the questionnaire via e-mail to the members of their review group. One week later, the representatives also received a letter by mail with the same request. An announcement was also made twice in the newsletter of the scientific association.

For pharmacists, the seven main professional associations in Flanders were contacted with the request to circulate the electronic link to the questionnaire. Most attached the link to their newsletter, one to three times.

### 2.2.3. STATISTICS

Descriptive statistics were performed on the demographic characteristics. Representativity of both subgroups was analyzed, based on population data for active GPs and pharmacists from the Health Insurance Institute (RijksInstituut voor Ziekte en InvaliditeitVerzekering (RIZIV/INAMI) [30]).

Further, to present the answers for all statements, the percentage of participants agreeing (i.e. those who answered ‘agree’ and ‘strongly agree’) with each statement, was calculated for the entire survey sample and per subgroup.

For each participant, the sum score for all statements pertaining to the third theme ‘benefits of INN prescribing’ (called ‘benefits’ hereafter; 13 statements; possible score range 13-65) and the sum score for all statements pertaining to the fourth theme ‘drawbacks of INN prescribing’ (called ‘drawbacks’ hereafter; 8 statements;
possible score range 8-40) was calculated. Some of the statements, formulated in the opposite direction, were recoded to align the values of the sum scores correctly.

The impact of demographic characteristics on the attitude towards INN prescribing was investigated with a multiple linear regression model with the sum score for ‘benefits’ and ‘drawbacks’ as a dependent variable.

All statistical analyses were performed using SPSS® (version 20) with the 0.05 significance level.

All answers to the open question were transcribed for qualitative analysis. After reading all the comments, a coding frame was constructed by two independent coders. Reoccurring topics in these comments were identified and categorized in themes. Each comment was applied to the appropriate topic. The results of both coders were collated in consensus.

2.2.4. ETHICAL CONSIDERATIONS

The survey was approved per sub group by the ethics committee of the Ghent University Hospital (registration numbers B670201316270 and B670201316272). For informed consent, the questionnaire started with an introduction stating the goal of the survey, explaining that all information received would be handled confidentially and that participants could withdraw from the survey at any time. Each participant had to give consent before starting the questionnaire by ticking an electronic box “I agree to participate in this study on a voluntarily basis”.

2.3. RESULTS

In total, 745 completed questionnaires were received (overall response 4.2 %). 522 of them were filled in by general practitioners (GPs) (response rate 5.2 %) and 223 by community pharmacists (response rate 2.9 %).

2.3.1. DEMOGRAPHIC CHARACTERISTICS AND REPRESENTATIVITY OF THE SURVEY SAMPLE

Details on the demographic characteristic are given in Table 2.1. GPs had a mean age of 48 years and almost 40 % of them were women. Most of the GPs worked in an urban general practice and the majority of the general practices was located in a social-mixed neighborhood. The largest part of the GPs had a solo practice, one-fifth worked in a duo-practice, and the others in a group practice, including district health centers. The mean age of the pharmacists was 43 years and over half of them were women. The pharmacists were almost equally divided over rural, urban and mixed rural-urban areas. The majority of the pharmacies was located in a social-mixed neighborhood and most pharmacists worked in a retail pharmacy.

Based on gender, the survey sample reflected the total population of the GPs, however GPs in the survey sample were younger than those in the total population. For pharmacists, the study population was representative for mean age, although male pharmacists were overrepresented (Table 2.1).
Table 2.1. Demographic characteristics and representativity (for mean age and gender) of the survey sample

<table>
<thead>
<tr>
<th></th>
<th>General practitioners N = 522</th>
<th>Pharmacists N = 223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>9.977</td>
<td>7.708</td>
</tr>
<tr>
<td>% of the total population</td>
<td>5.2 %</td>
<td>2.9 %</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>51 years</td>
<td>44 years</td>
</tr>
<tr>
<td>Survey sample</td>
<td>47.7 years (23 – 88)</td>
<td>43.0 years (23 – 77)</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population</td>
<td>40.6</td>
<td>73.6</td>
</tr>
<tr>
<td>Survey sample</td>
<td>39.5</td>
<td>56.1</td>
</tr>
<tr>
<td>Location of general practice/pharmacy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rural</td>
<td>33.4 %</td>
<td>39.6 %</td>
</tr>
<tr>
<td>- Urban</td>
<td>35.7 %</td>
<td>30.9 %</td>
</tr>
<tr>
<td>- Mixed rural-urban</td>
<td>30.9 %</td>
<td>29.5 %</td>
</tr>
<tr>
<td>Social class of neighbourhood around general practice/pharmacy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Poorer</td>
<td>13.6 %</td>
<td>14.4 %</td>
</tr>
<tr>
<td>- Residential</td>
<td>9.5 %</td>
<td>6.9 %</td>
</tr>
<tr>
<td>- Mixed (poorer-residential)</td>
<td>76.9 %</td>
<td>78.7 %</td>
</tr>
<tr>
<td>Type of general practice:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Solo practice</td>
<td>40.6 %</td>
<td>Not applicable</td>
</tr>
<tr>
<td>- Duo practice</td>
<td>21.0 %</td>
<td></td>
</tr>
<tr>
<td>- Group practice (including district health centers)</td>
<td>38.4 %</td>
<td></td>
</tr>
<tr>
<td>Type of pharmacy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Retail pharmacy</td>
<td>Not applicable</td>
<td>84.9 %</td>
</tr>
<tr>
<td>- Cooperative pharmacy</td>
<td></td>
<td>12.8 %</td>
</tr>
<tr>
<td>- Health service pharmacy</td>
<td></td>
<td>2.3 %</td>
</tr>
</tbody>
</table>

2.3.2. RESPONSES TO THE STATEMENTS

Details on the responses to the statements are given in Table 2.2. With regard to the motives of health policy makers to introduce INN prescribing, the majority of the participants agreed that it was introduced to reduce expenditures for the government (88 %) and the patient (57 %).

Most participants agreed that INN prescribing is acceptable for elderly (57 %), while 90 % disagreed with the statement that it is unacceptable for children. However, participants (88 %) stressed that in case of chronic treatment, continuity of treatment should be guaranteed.

The majority of pharmacists (75 %) and a minority of GPs (30 %) agreed that dispensing the cheapest medicinal product is only acceptable for acute treatment. For chronic treatment, dispensing the cheapest medicinal product was agreed by only 29 % of the pharmacists, while 44 % of the GPs agreed.

The majority of the participants did not agree that INN prescribing should not be allowed because the clinical outcomes between brands and generics differ too much (only 16 % agreed).
Table 2.2. Percentage of participants agreeing (agree + strongly agree) per statement for the overall survey sample and per subgroup

<table>
<thead>
<tr>
<th>Statements</th>
<th>% agree (agree + strongly agree)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total survey sample N = 745</td>
</tr>
<tr>
<td>1. Motives for the introduction of policies concerning INN prescribing</td>
<td></td>
</tr>
<tr>
<td>• To reduce pharmaceutical expenditures (health insurance institute)</td>
<td>87.6</td>
</tr>
<tr>
<td>• To make medicinal products cheaper for the patient</td>
<td>57.1</td>
</tr>
<tr>
<td>• To contribute to rational prescribing*</td>
<td>30.0</td>
</tr>
<tr>
<td>• To increase the role of the pharmacist as caregiver</td>
<td>20.8</td>
</tr>
<tr>
<td>• To optimize stock management in the pharmacy</td>
<td>14.8</td>
</tr>
<tr>
<td>2. Attitudes towards policies introduced concerning (INN) prescribing</td>
<td></td>
</tr>
<tr>
<td>• ‘In case of chronic treatment, it is important to always dispense the same medicinal product’</td>
<td>87.7</td>
</tr>
<tr>
<td>• ‘Currently, cost savings are the only aim of INN prescribing’</td>
<td>74.8</td>
</tr>
<tr>
<td>• ‘Currently, there is too much emphasis on cost savings through INN prescribing’</td>
<td>67.1</td>
</tr>
<tr>
<td>• ‘Prescribing medicines for older people by INN is acceptable’</td>
<td>56.9</td>
</tr>
<tr>
<td>• ‘At university, only INN prescribing should be taught’</td>
<td>53.5</td>
</tr>
<tr>
<td>• ‘Mandatory dispensing of one of the cheapest medicines with an INN prescription is only acceptable for acute treatment’</td>
<td>52.4</td>
</tr>
<tr>
<td>• ‘The current way of applying INN prescribing is good’</td>
<td>43.7</td>
</tr>
<tr>
<td>• ‘With INN prescribing, it is important that the prescriber receives information on the dispensed medicinal product package’</td>
<td>36.8</td>
</tr>
<tr>
<td>• ‘Mandatory dispensing of one of the cheapest medicines with an INN prescription is acceptable for chronic treatment’</td>
<td>36.7</td>
</tr>
<tr>
<td>• ‘Patients are mature enough to choose together with the pharmacist the most suitable medicinal product package’</td>
<td>33.0</td>
</tr>
<tr>
<td>• ‘Potential cost savings through INN prescribing are negated by the additional costs when complications occur due to INN prescribing’</td>
<td>29.0</td>
</tr>
<tr>
<td>• ‘The clinical differences between the different brands are too large to allow INN prescribing’</td>
<td>16.2</td>
</tr>
<tr>
<td>• ‘Prescribing medicinal product for children by INN is unacceptable’</td>
<td>10.4</td>
</tr>
<tr>
<td>3. Benefits of INN prescribing</td>
<td></td>
</tr>
<tr>
<td>• Patients do not have to pay a reference supplement</td>
<td>66.4</td>
</tr>
<tr>
<td>• With one INN prescription, multiple small packages can be prescribed/dispensed</td>
<td>63.1</td>
</tr>
<tr>
<td>• Contributes significantly to cost savings</td>
<td>56.3</td>
</tr>
<tr>
<td>• Patients can receive their medicines quicker in the pharmacy</td>
<td>55.4</td>
</tr>
<tr>
<td>• Contributes to rational prescribing</td>
<td>43.0</td>
</tr>
</tbody>
</table>
• Provides more rational stock management in the pharmacy 41.5 37.7 45.3
• Increases the role of pharmacists as caregivers* 40.4 22.0 58.8
• Shields from marketing influences 38.0 55.6 20.3
• The physician and pharmacist are more aware of the active ingredient* 32.9 44.3 21.5
• Patients are more aware of the active ingredient in the pharmacy 31.2 28.8 33.5
• Decreases the amount of prescribing errors 23.3 18.2 28.3
• Reduces the chance of dispensing errors 18.4 15.9 20.8
• Improves medication adherence 9.0 3.8 14.2

4. **Drawbacks of INN prescribing**

<table>
<thead>
<tr>
<th>Drawbacks of INN prescribing</th>
<th>GPs</th>
<th>Pharmacists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases patient confusion</td>
<td>74.5</td>
<td>81.0 67.9</td>
</tr>
<tr>
<td>Increases liability of pharmacists*</td>
<td>55.3</td>
<td>50.8 59.8</td>
</tr>
<tr>
<td>Decreases medication adherence</td>
<td>55.4</td>
<td>42.8 67.9</td>
</tr>
<tr>
<td>Compromises continuity of treatment*</td>
<td>45.2</td>
<td>49.3 41.1</td>
</tr>
<tr>
<td>Leads to more administration in the pharmacy*</td>
<td>44.0</td>
<td>27.4 60.6</td>
</tr>
<tr>
<td>Restricts flexibility of choice (only one of the cheapest can be dispensed)</td>
<td>34.6</td>
<td>29.7 39.5</td>
</tr>
<tr>
<td>Restricts free choice of therapy*</td>
<td>31.6</td>
<td>31.6 ‡</td>
</tr>
<tr>
<td>Consultation takes longer</td>
<td>15.6</td>
<td>15.6 ‡</td>
</tr>
</tbody>
</table>

*Statements, formulated in the opposite way, were recoded to align the values correctly
‡These statements were not present in the questionnaire for pharmacists, as they were not relevant for this subgroup

With regard to the benefits of INN prescribing, few participants agreed that INN prescribing improves medication adherence (only 9 %) or that it can decrease prescribing and dispensing errors (only 24 % and 18 % agreed, respectively). Two-thirds of all participants agreed that one of the benefits of INN prescribing is the guarantee that patients do not have to pay a reference supplement.

Pharmacists indicated that INN prescribing has the potential to increase the pharmacist’s role as caregiver (59 % agreed) and to rationalize stock management (45 % agreed).

With regard to the drawbacks of INN prescribing, most participants agreed that the current practice of INN prescribing causes patient confusion (76 %).

Pharmacists (61 % agreed) indicated that the current concept of INN prescribing increases the work load in the pharmacy. Most GPs did not perceive that INN prescribing extends the duration of the consultation (only 10 % agreed).

2.3.3. **SUM SCORES FOR ‘BENEFITS’ AND ‘DRAWBACKS’**

Calculating the sum score for ‘benefits’ resulted in a mean score of 41.3 for GPs and 42.8 for pharmacists. The mean sum score for ‘drawbacks’ was 21.4 for GPs and 22.2 for pharmacists.

The univariate analysis only revealed an association between demographic characteristics and the sum scores for ‘benefits’ and ‘drawbacks’ among GPs, and not among pharmacists.

The univariate analyses showed that being a younger GP, not allowing visits from (pharmaceutical) company representatives, working in a group practice, in a poorer neighborhood, in an urban area, having studied at the
Ghent University and being female was associated with the highest sum score for ‘benefits’. In contrast, being visited by company representatives, having a solo practice in a social-mixed neighborhood and being an older GP was associated with the highest sum score for ‘drawbacks’ (Table 2.3).

Table 2.3. Results of the univariate and multivariate analysis of the influence of demographic characteristics on the sum score for ‘benefits’ and ‘drawbacks’ for general practitioners

<table>
<thead>
<tr>
<th>‘Benefits’ for GPs</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Cumulative R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>B</td>
</tr>
<tr>
<td>Age</td>
<td>-0.244</td>
<td>&lt; 0.001</td>
<td>-0.105</td>
</tr>
<tr>
<td>No visits from (pharmaceutical) company representatives</td>
<td>0.236</td>
<td>&lt; 0.001</td>
<td>2.942</td>
</tr>
<tr>
<td>Group practice (including district health centers)</td>
<td>0.222</td>
<td>&lt; 0.001</td>
<td>1.716</td>
</tr>
<tr>
<td>General practice in a poorer neighborhood</td>
<td>0.166</td>
<td>&lt; 0.001</td>
<td>2.168</td>
</tr>
<tr>
<td>General practice in an urban area</td>
<td>0.145</td>
<td>0.001</td>
<td>-</td>
</tr>
<tr>
<td>Studied at Ghent University</td>
<td>0.145</td>
<td>0.001</td>
<td>2.235</td>
</tr>
<tr>
<td>Female</td>
<td>0.116</td>
<td>0.008</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>‘Drawbacks’ for GPs</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Cumulative R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
<td>B</td>
</tr>
<tr>
<td>Visits from (pharmaceutical) company representatives</td>
<td>0.315</td>
<td>&lt; 0.001</td>
<td>3.249</td>
</tr>
<tr>
<td>Solo practice</td>
<td>0.182</td>
<td>&lt; 0.001</td>
<td>0.931</td>
</tr>
<tr>
<td>Age</td>
<td>0.138</td>
<td>0.002</td>
<td>-</td>
</tr>
<tr>
<td>General practice in a social-mixed neighborhood</td>
<td>0.137</td>
<td>0.002</td>
<td>-</td>
</tr>
<tr>
<td>General practice in a rural area</td>
<td>0.096</td>
<td>0.028</td>
<td>-</td>
</tr>
</tbody>
</table>

Multivariate analysis revealed a higher sum score for ‘benefits’ (r = -0.180) was most associated with being younger and that a higher sum score for ‘drawbacks’ was most associated with being visited by company representatives (r = 0.287). Thirteen percent of the variance in the model for ‘benefits’ could be explained by age, no visits from company representatives, working in a group practice in a poorer neighborhood and having studied at the Ghent University. In the model for ‘drawbacks’, 10 % of the variance could be explained by visit from company representatives and having a solo practice (Table 2.3).

2.3.4. PERSONAL OPINIONS

Almost half of the participating GPs (44.8 %) and pharmacists (42.6 %) gave their opinion regarding the concept of INN prescribing at the end of the questionnaire (Box 2.1).

The comments revealed four different themes, covering different topics. The first theme was “The current concept of INN prescribing does not guarantee the continuity of treatment”. The second was “Medical software is not adapted for proper INN prescribing and communication between GPs and pharmacists” and the third theme “Communication problems between GPs and pharmacists”. The fourth theme “Practical implications of the new policies for pharmacists” was only applicable for pharmacists (Box 2.1).
Box 2.1. Themes and topics commented on the open question

<table>
<thead>
<tr>
<th>Theme 1: “The current concept of International Nonproprietary Name (INN) prescribing does not guarantee the continuity of treatment” - Applicable for general practitioners (GPs) and pharmacists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient confusion</strong></td>
</tr>
<tr>
<td>GP, ♂, 43 years: “INN prescribing causes major patient confusion”</td>
</tr>
<tr>
<td>Pharmacist, ♂, 59 years: “INN prescribing is most confusing for older patients”</td>
</tr>
<tr>
<td><strong>Medication adherence</strong></td>
</tr>
<tr>
<td>GP, ♂, 49 years: “I like to prescribe by INN, but my patients should always receive a product from the same manufacturer”</td>
</tr>
<tr>
<td>Pharmacist, ♂, 53 years: “Continuously switching between brands for chronic medication compromises medication adherence”</td>
</tr>
<tr>
<td><strong>Current way of naming generics (active ingredient + name of generic company)</strong></td>
</tr>
<tr>
<td>GP, ♂, 46 years: “It might be better to put the INN in large print on the medicinal package, and to standardize the packages”</td>
</tr>
<tr>
<td>Pharmacist, ♂, 53 years: “The generic company name should not be part of the medicinal product name; this causes confusion”</td>
</tr>
<tr>
<td><strong>Preference to prescribe ‘cheap medicines’ instead of by INN</strong></td>
</tr>
<tr>
<td>GP, ♂, 47 years: “As continuity of treatment is very important, I am in favor of prescribing cheap medicines instead of by INN”</td>
</tr>
<tr>
<td>Pharmacist, ♂, 60 years: “Physicians rarely prescribe by INN, usually they prescribe generics”</td>
</tr>
<tr>
<td><strong>Concerns about patients with chronic treatment</strong></td>
</tr>
<tr>
<td>GP, ♂, 36 years: “The main disadvantage of INN prescribing are the problems that can occur in case of chronic treatment”</td>
</tr>
<tr>
<td>Pharmacist, ♂, 60 years: “In case of chronic treatment, continuity of treatment supercedes limited cost savings”</td>
</tr>
<tr>
<td><strong>Medication errors</strong></td>
</tr>
<tr>
<td>GP, ♂, 29 years: “Due to frequent switching, it might occur that some of my patients take two pills of the same product (e.g. Bisoprolol Sandoz® and Bisoprolol Mylan®)”</td>
</tr>
<tr>
<td><strong>Continuity of treatment</strong></td>
</tr>
<tr>
<td>GP, ♂, 56 years: “INN prescribing does not guarantee the continuity of treatment. This is the main issue.”</td>
</tr>
<tr>
<td>Pharmacist, ♂, 34 years: “In case of INN prescribing during chronic treatment, the continuity of treatment should prevail”</td>
</tr>
<tr>
<td><strong>Dissatisfaction on policies pushed by the government</strong></td>
</tr>
<tr>
<td>GP, ♂, 48 years: “Mandatory regulation is usually not welcomed. I don’t understand the added value of the current concept of INN prescribing”</td>
</tr>
<tr>
<td>GP, ♂, 52 years: “Why do GPs have to solve the budgetary problems?”</td>
</tr>
</tbody>
</table>
### Theme 2:
"Software is not adapted for proper INN prescribing and communication between GPs and community pharmacists" - Applicable for general practitioners and pharmacists

- **Inability of medical software to easily make an INN prescription and register it properly**
  
  **GP, ♀, 32 years:**
  "Unfortunately I cannot prescribe by INN with my prescription software"

  **Pharmacist, ♂, 47 years:**
  "Apparently, GPs’ prescription software does not permit INN prescribing"

- **Feedback on the dispensed medical product package**
  
  **GP, ♀, 33 years:**
  "It would be convenient to know which medicinal product package is dispensed"

  **Pharmacist, ♂, 47 years:**
  "It should be possible with pharmacy software to automatically inform the prescriber on the dispensed medicinal product package"

### Theme 3:
"Communication problems and mutual incomprehension between GPs and pharmacists" - Applicable for general practitioners (and pharmacists)

- **Decisions made by GPs/pharmacists when making/dispensing prescriptions**
  
  **GP, ♂, 62 years:**
  "In reality, pharmacists do not always dispense the cheapest available, but those which are most profitable for them"

  **Pharmacist, ♂, 47 years:**
  "It should be made clear to physicians that INN prescribing ensures patients receiving the cheapest product available. Physicians distrust pharmacists."

- **Pharmacists put profits ahead of patient care**
  
  **GP, ♀, 44 years:**
  "It appears to me that having one of the cheapest products dispensed with INN prescribing is the same as the most beneficial product for the pharmacist"

  **GP, ♂, 50 years:**
  "Currently, INN prescribing is only advantageous for the pharmacist. Due to the current concept, pharmacists also substitute other medicinal product besides antibiotics and antifungal treatment"

- **Fee for pharmacists**
  
  **GP, ♂, 52 years:**
  "I do not understand why pharmacists receive an additional fee when dispensing an INN prescription"

  **GP, ♂, 34 years:**
  "I do not get why pharmacists get rewarded for the efforts we make"

- **Increase of the liability of pharmacists**
  
  **GP, ♂, 56 years:**
  "Maintaining the continuity of treatment and preventing errors with INN prescriptions is the responsibility of the pharmacist"

  **GP, ♂, 45 years:**
  "The liability of the pharmacist should be increased"

### Theme 4:
"The practical implications of the new policies for the pharmacists" - Applicable for pharmacists

- **Stock management**
  
  **Pharmacist, ♀, 43 years:**
  "These policies make stock management almost impossible"

  **Pharmacist, ♂, 55 years:**
  "This hinders any sort of stock management"
2.4. DISCUSSION

To the best of our knowledge, this survey was the first to jointly explore the opinions of general practitioners (GPs) and pharmacists on INN prescribing after a major policy change.

2.4.1. MAIN FINDINGS

This survey showed that participants perceived that INN prescribing was introduced to reduce the pharmaceutical expenditures of the government and the out-of-pocket fees for the patients. Our results demonstrated that most agreed that INN prescribing has its potential to be widely used a way of rational prescribing. However, all participants stressed the importance of continuity of treatment, especially in the (older) chronic patient, and the danger for patient confusion due the new policy.

Comments in response to the open question revealed communication problems and mutual incomprehension between GPs and pharmacists, although both are willing to contribute to rational medication use, including INN prescribing. Many GPs also stated that electronic INN prescribing and the correct registration of an INN prescription is currently not possible.

The multivariate analysis showed that mainly younger GPs working in a group practice, situated in a poorer area, recognized the (potential) benefits of INN prescribing. This is in contrast to the stronger perception of drawbacks by older GPs with a solo practice, receiving visits from (pharmaceutical) company representatives.

2.4.2. COMPARISON WITH PREVIOUS RESEARCH

In 2005, comparable research was performed by Biga et al. in a region in France, investigating the perception on INN prescribing of GPs, pharmacists and patients [27]. Although the French health care system (and the specific regulation on INN prescribing) differs from the Belgian system, the survey showed that INN prescribing was generally well accepted. However, GPs seemed more reluctant towards INN prescribing than pharmacists and patients.

In Belgium, similar research investigated the attitudes of GPs and pharmacists towards INN prescribing in general [31]; however, this study took place before the introduction of the new policies (winter 2011-2012). This survey
demonstrated an already existing negative attitude towards INN prescribing. Our results confirmed that this perception further deteriorated after the policy change in 2012.

2.4.3. STRENGTHS & LIMITATIONS

The first strength of this survey was the structured exploration of the opinion of GPs and pharmacists. Since the policy changes were associated with quite some commotion and dissatisfaction, the opinion of (future) primary caregivers is valuable.

The second strength was the opportunity for participants to give their own opinion with regard to INN prescribing and its related aspects in an open question. The survey was administered between February and July 2013, almost one year after the introduction of the new policy. This provided adequate time for GPs and pharmacists to explore and evaluate its implications.

Our survey sample was acceptable, especially when taking into account the representativity of the sample for all subgroups, although the GPs in our survey sample were, on average, three years younger than those in the eligible population. This can be explained by the fact younger participants may be more computer savvy and might be more prone to answer an electronic survey. We have no explanation for the slight overrepresentation of male pharmacists. It is possible that selection bias may have resulted from explicit opponents and proponents of INN prescribing choosing to participate, as they might have considered this survey as an opportunity to express their views on the subject. The frequency and depth of comments left at the end of this questionnaire is a testament of the interest in this subject.

Although our questionnaire was self-designed, it was based on literature, expert consultation and pilot testing. An ex-post evaluation showed that a limited number of statements could have been formulated more clearly. However, an analysis of the topics in the open question revealed that only the limited possibilities of medical software with regard to INN prescribing was not questioned through a statement.

Another limitation is that we only addressed GPs and pharmacists in the Flanders region of Belgium. Our results cannot be extrapolated to GPs and pharmacists in Wallonia, the French-speaking part of Belgium.

2.4.4. IMPLICATIONS FOR PRACTICE

Our results emphasized the importance of consistent treatment, especially in chronic (older) patients. GPs and pharmacists expressed their concern that the new policies may confuse patients due to the possibly that the lowest cost medicinal products will change monthly, resulting in frequent switching that could lead to nonadherence and erroneous drug use by patients. These concerns were probably founded as literature showed that differences in medicinal product name, packaging and physical attributes negatively influence medication adherence and result in medication errors, due to patient confusion and discontent [32–38]. Studies also confirmed that good communication with patients is essential when medication switches occur [39–41].

This survey also showed that medical software and electronic patient records (EPR) need to be adapted for physicians to easily make and correctly register INN prescriptions. Initiatives were already taken by the Belgian
government to implement INN prescribing in electronic prescribing and register INN prescriptions using a unique identification number [13]. Additionally, GPs reported the need for (detailed) information on the dispensed medicinal product package when prescribed by INN. Therefore, it should be possible for GPs to receive information from the pharmacist on the dispensed medicinal product package through the e-health platform and medical software [22].

One of the major comments of pharmacists was that monthly changing lists of the cheapest medicines does not facilitate rational stock management. This monthly update also results in the possibility of chronic patients receiving a medicinal product of a different manufacturer every month, which can lead to patient confusion and nonadherence, as discussed above. Therefore, we suggest a quarterly or biannual update of those lists.

The answers on the open question revealed communication problems between GPs and pharmacists, including the shift of liability from GPs to pharmacists and additional fees related to INN prescribing. Structured initiatives to improve the relationship and reciprocal understanding between both should be taken, by the government or by professional associations [42,43].

2.5. CONCLUSION

This study revealed that GPs and pharmacists consider the core concept of INN prescribing, i.e. using the name of the active ingredient(s) to identify the medicinal product and having a cheap one dispensed, as a major strength, offering many possibilities for rational drug prescribing. However, the current way in which INN prescribing is applied in Belgium leads to many concerns in primary health professionals with regard to patient confusion and medication adherence. Slightly adapting the current concept of INN prescribing to these concerns can turn INN prescribing into one of the major policies in Belgium reducing pharmaceutical expenditures and can stimulate rational drug prescribing.


12. Federal Agency for Medicines and Health Products. Federal Agency for Medicines and Health Products (FAMHP), Belgium.


25. De Apotheker. VOS tegen wil en dank. 2010


42. Royal Pharmaceutical Society Scotland and Royal College of General Practitioners Scotland. Breaking Down the Barriers: how pharmacists and GPs can work together to improve patient care. 2012

43. Centre for Pharmacy Postgraduate Education. Working together for patient safety: a full day GP and pharmacist learning event.
ATTITUDES OF MEDICINE AND PHARMACY STUDENTS TOWARDS INTERNATIONAL NONPROPRIETARY NAME PRESCRIBING IN BELGIUM

Submitted:
Elien Van Bever, Monique Elseviers, Siska Haers, Luc Van Bortel, Robert Vander Stichele.
CHAPTER 3

ABSTRACT .............................................................................................................................................................. 75

3.1. INTRODUCTION ............................................................................................................................................... 76

3.2. METHODS ....................................................................................................................................................... 76

3.2.1. Development and circulation of the questionnaire................................................................................. 76

3.2.2. Statistics ................................................................................................................................................... 77

3.2.3. Ethical considerations .............................................................................................................................. 77

3.3. RESULTS .......................................................................................................................................................... 77

3.3.1. Responses to the statements .................................................................................................................. 77

3.4. DISCUSSION .................................................................................................................................................... 80

3.5. CONCLUSION .................................................................................................................................................. 81

REFERENCES........................................................................................................................................................... 82
Objective. The aim was to investigate the attitudes of Dutch-speaking medicine students and pharmacy students towards International Nonproprietary Name (INN) prescribing. INN prescribing is using the name of the active ingredient for prescribing and started in 2005 in Belgium. It underwent major policy change in spring 2012.

Methods. An electronic questionnaire with 39 five-point Likert scale statements was administered in 2013. It was circulated via the electronic platform of all four Dutch-speaking universities in Belgium. Descriptive statistics were performed on the collected demographic characteristics and representativity of the survey sample was analyzed. Differences in attitudes between medicine students and pharmacies students were tested with a Chi²-test.

Results. We received 487 valid responses with representative samples for both groups of students, with regard to gender and age. The response rate was almost 20 % for medicine students and 46 % for pharmacy students. Although over 75 % of the students stressed the importance of a guaranteed continuity of treatment, 72 % accepted the current way INN prescribing is applied in Belgium. Despite this acceptance, students did not want INN prescribing being exclusively taught during training.

Conclusion. Students believe that the concept of INN prescribing has the potential to contribute to rational drug prescribing and utilization, provided that continuity of treatment can be guaranteed. Students wish that INN prescribing is more prominently, but not exclusively, taught at university. All this favors the rational implementation of INN prescribing in education and clinical practice.
3.1. INTRODUCTION

INN prescribing is using the active ingredient name(s), instead of the brand name or branded generic name, to identify the medicinal product. Using the INN for prescribing can contribute to rational drug prescribing and utilization. In addition, INN prescribing can also be implemented as a cost-containment policy, sometimes in combination or related to (generic) substitution [1]. At university, medicine and pharmacy students can learn about different types of prescribing: brand name prescribing, prescribing of branded generics and International Nonproprietary Name (INN) prescribing.

Since 2001, INN prescribing is legally allowed in Belgium. Initially, it was introduced to enhance rational drug utilization [2], but was turned into a cost-containment measure when the global financial crisis also affected Belgium. Firstly, starting from April 2012, the pharmacist is obliged to dispense one of the three cheapest medicinal products available when prescribed by INN. The list of cheapest products available is updated monthly. Secondly, starting from May 2012, when receiving a prescription for acute treatment with antibiotics or antifungal agents, the pharmacist is obliged to treat this as it was an INN prescribing and hence dispense one of the three cheapest medicinal products. This measure is applicable for brand name and branded generic name prescriptions [3,4].

The introduction of these two cost-containment measures was extensively criticized and received quite some attention from the (professional) media [5–10].

This study is part of a broader research which also investigated the attitudes of general practitioners (GPs) and pharmacists and is presented elsewhere [11]. The aim of this study is to explore the attitudes of medicine students and pharmacy students from the four Dutch-speaking universities in Belgium, regarding the concept of INN prescribing and the austerity measures of spring 2012 in Belgium. As these students are future prescribers and pharmacists, it is important to also know about their attitudes and opinions on INN prescribing for the successful implementation of this concept in education and clinical practice.

3.2. METHODS

3.2.1. DEVELOPMENT AND CIRCULATION OF THE QUESTIONNAIRE

A self-designed questionnaire was circulated to explore the attitudes of medicine students (3rd and 4th Master) and pharmacy students (2nd Master) with regard to INN prescribing.

The questionnaire started with questions on demographic characteristics (gender, age, postal code and university), followed by 39 five-point Likert scale statements (strongly agree/agree/neutral/disagree/strongly disagree) covering four themes: (1) motives for the introduction of policies concerning INN prescribing, (2) the attitude towards INN prescribing and the introduced policies, (3) benefits of INN prescribing and (4) drawbacks of INN prescribing. Some statements were negated to avoid leading bias.

Further details on the development of the questionnaire were presented elsewhere [11].
All questionnaires were made electronically accessible using an online survey tool (eSurvey Creator®) [12]. Between February and May 2013, the link to the questionnaire was circulated via the electronic platform of all four Dutch-speaking universities with a medical and pharmaceutical department. Two reminders were sent after the initial announcement.

### 3.2.2. STATISTICS

Descriptive statistics were performed on the demographic characteristics. Representativity of the survey sample was analyzed for gender and university. To present the answers for all statements, the percentage of students agreeing (i.e. those who answered ‘agree’ and ‘strongly agree’) with each statement, was calculated.

To test for differences in opinions between medicine students and pharmacy students, and for differences between the universities, a Chi²-test was performed.

All statistical analyses were performed using SPSS® (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) with the 0.05 significance level.

### 3.2.3. ETHICAL CONSIDERATIONS

The survey was approved by the ethics committee of the Ghent University Hospital (registration number B670201316273). For informed consent, the questionnaire started with an introduction stating the goal of the survey, explaining that all received information would be handled confidentially and that students could withdraw from the survey at any time. Each student had to give consent before starting the questionnaire by ticking an electronic box “I agree to participate in this study on a voluntarily basis”.

### 3.3. RESULTS

In total, 487 completed questionnaires were received, of which 295 by medicine students (response rate 19.8 %) and 192 by pharmacy students (response rate 45.7 %) (Table 3.1).

The mean age for medicine students was 24 years and over 65 % of them were females. For pharmacy students, the mean age was 23 years and 75 % of them were females. There was some underrepresentation of medicine students from one university (Table 3.1).

### 3.3.1. RESPONSES TO THE STATEMENTS

Details on the responses to the statements are given in Table 3.2. For medicine students and pharmacy students it was clear that INN prescribing was introduced to reduce expenditures for the health insurance (74 % agreed) and for the patient (71 % agreed). Although over three-quarters of the students agreed that it is important to always have the same medicinal product dispensed during chronic treatment, 72 % mean the current way of applying INN prescribing is good. In addition, 63 % agreed that medicines for older people can be prescribed by INN.
Students perceived as main benefits of INN prescribing that (1) patients do not have to pay an additional out-of-pocket fee (68 % agreed), (2) INN prescribing shields from marketing influences (67 % agreed) and (3) it contributes to cost savings (54 % agreed).

Students indicated as main drawbacks that INN prescribing increases patient confusion (74 % agreed) and that it does not result in improved medication adherence (only 10 % agreed that INN prescribing improves medication adherence).

No differences between the opinions of students from different universities were discovered and the opinions of medicine students and pharmacy students did not relevantly differ, for most of the statements. However, more pharmacy students (49 %) meant that patients are mature enough to choose the most suitable product, together with pharmacist, compared to only 25 % of the medicine students. More medicine students (38 % vs. 23 % pharmacy students) were convinced that INN prescribing can contribute to rational stock management in the pharmacy and more medicine students (57 % vs. 41 % pharmacy students) indicated that the liability of the pharmacist increases with an INN prescription.

Finally, only a minority of the students (29 %) was convinced that INN prescribing should be the only concept to be taught.
### Table 3.2. Percentage of students agreeing (agree + strongly agree) for all statements and per subgroup.
Results of the Chi²-test for different opinions between both groups of students

<table>
<thead>
<tr>
<th>Statements</th>
<th>% agree (agree + strongly agree)</th>
<th>Total survey sample N = 487</th>
<th>Medicine students N = 295</th>
<th>Pharmacy students N = 192</th>
<th>P-value Chi²-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Motives for the introduction of policies concerning INN prescribing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• To reduce pharmaceutical expenditures (health insurance institute)</td>
<td>74.0</td>
<td>74.1</td>
<td>73.9</td>
<td>0.966</td>
<td></td>
</tr>
<tr>
<td>• To make medicinal products cheaper for the patient</td>
<td>71.0</td>
<td>71.0</td>
<td>71.0</td>
<td>0.992</td>
<td></td>
</tr>
<tr>
<td>• To contribute to rational prescribing*</td>
<td>18.1</td>
<td>19.0</td>
<td>16.7</td>
<td>0.563</td>
<td></td>
</tr>
<tr>
<td>• To increase the role of the pharmacist as caregiver</td>
<td>18.9</td>
<td>15.5</td>
<td>24.4</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>• To optimize stock management in the pharmacy</td>
<td>10.3</td>
<td>13.2</td>
<td>5.7</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td><strong>2. Attitudes towards introduced policies concerning (INN) prescribing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ‘In case of chronic treatment, it is important to always have the same medicinal product dispensed’</td>
<td>78.8</td>
<td>73.8</td>
<td>86.3</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>• ‘Currently, cost savings are the only aim of INN prescribing’</td>
<td>41.4</td>
<td>38.1</td>
<td>46.6</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>• ‘Currently, there is too much emphasis on cost savings for INN prescribing’</td>
<td>47.0</td>
<td>38.7</td>
<td>60.3</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>• ‘Medicines for older people prescribing by INN is acceptable’</td>
<td>63.1</td>
<td>68.1</td>
<td>55.4</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>• ‘At university, only INN prescribing should be taught’</td>
<td>28.5</td>
<td>32.3</td>
<td>22.6</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>• ‘Mandatory dispensing one of the cheapest medicines with an INN prescription is only acceptable for acute treatment’</td>
<td>30.7</td>
<td>25.4</td>
<td>38.9</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>• ‘The current way of applying INN prescribing is good’</td>
<td>72.0</td>
<td>80.2</td>
<td>59.5</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>• ‘With INN prescribing, it is important that the prescriber receives information on the dispensed medicinal product package’</td>
<td>35.6</td>
<td>33.1</td>
<td>39.7</td>
<td>0.180</td>
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<tr>
<td>• ‘Mandatory dispensing one of the cheapest medicines with an INN prescription is acceptable for chronic treatment’</td>
<td>56.6</td>
<td>62.9</td>
<td>47.0</td>
<td>0.001</td>
<td></td>
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<td>• ‘Patients are mature enough to choose together with the pharmacist the most suitable medicinal product package’</td>
<td>34.7</td>
<td>25.4</td>
<td>49.0</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>• ‘Potential cost savings through INN prescribing are negated by the additional costs when complications occur due to INN prescribing’</td>
<td>13.4</td>
<td>11.9</td>
<td>15.8</td>
<td>0.268</td>
<td></td>
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<tr>
<td>• ‘The clinical differences between the different brands are too large to allow INN prescribing’</td>
<td>10.6</td>
<td>10.2</td>
<td>11.3</td>
<td>0.706</td>
<td></td>
</tr>
<tr>
<td>• ‘Prescribing medicinal product for children by INN is unacceptable’</td>
<td>11.8</td>
<td>12.8</td>
<td>10.2</td>
<td>0.407</td>
<td></td>
</tr>
<tr>
<td><strong>3. Benefits of INN prescribing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients do not have to pay a reference supplement</td>
<td>67.7</td>
<td>72.7</td>
<td>60.0</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>
3.4 DISCUSSION

To the best of our knowledge, this survey was the first to explore the opinion of medicine students and pharmacy students on INN prescribing.

A representative sample of students completed the questionnaire, based on gender and mean age. Differences in response rate between universities, with an underrepresentation of medicine students from one university, are difficult to explain.

Students accepted the basic concept of INN prescribing, i.e. prescribing by active ingredient name and having a cheaper product dispensed, but also stressed the need for continuity of treatment. Some differences between the opinions of medicine students and pharmacy students were found for statements related to the pharmacy and the role of the pharmacist. No differences between attitudes of students from different universities could be found.

Despite acceptance of the concept, medicine students and pharmacy students do not wish INN prescribing to be the only way taught during training. They also indicated that INN prescribing can shield from marketing influences, which favors the implementation of INN prescribing in education and clinical practice as early contact

| • With one INN prescription, multiple small packages can be prescribed/dispensed | 5.4 | 4.2 | 7.2 | 0.195 |
| • Contributes significantly to cost savings | 54.1 | 55.9 | 51.3 | 0.377 |
| • Patients can receive their medicines quicker in the pharmacy | 49.6 | 44.8 | 57.0 | 0.020 |
| • Contributes to rational prescribing | 47.5 | 51.5 | 41.3 | 0.052 |
| • Provides more rational stock management in the pharmacy | 31.9 | 37.8 | 22.7 | 0.002 |
| • Increases the role of pharmacists as caregivers* | 30.0 | 28.3 | 32.7 | 0.366 |
| • Shields from marketing influences | 67.2 | 71.0 | 61.2 | 0.044 |
| • The awareness of the active ingredient is bigger for physician and pharmacist* | 20.5 | 24.3 | 14.6 | 0.021 |
| • Patients are more aware of the active ingredient in the pharmacy | 41.1 | 39.9 | 43.0 | 0.542 |
| • Decreases the amount of prescribing errors | 28.8 | 30.1 | 26.7 | 0.463 |
| • Reduces the chance of dispensing errors | 19.3 | 16.7 | 23.3 | 0.111 |
| • Improves medication adherence | 10.0 | 10.5 | 9.2 | 0.668 |

4. Drawbacks of INN prescribing

• Increases patient confusion | 73.2 | 72.3 | 74.7 | 0.609 |
• Liability of pharmacists increases * | 50.7 | 57.1 | 40.7 | 0.002 |
• Decreases medication adherence | 37.4 | 35.8 | 40.0 | 0.405 |
• Compromises continuity of treatment* | 37.2 | 34.2 | 41.7 | 0.137 |
• Leads to more administration in the pharmacy* | 33.3 | 20.3 | 53.7 | < 0.001 |
• Restricts flexibility of choice (only one of the cheapest can be dispensed) | 28.7 | 31.2 | 26.7 | 0.486 |
• Restricts free choice of therapy* | 37.4 | 30.0 | 47.0 | 0.002 |
• Consultation takes longer | 3.6 | 4.6 | 2.0 | 0.172 |

*Statements, formulated in the opposite way, were recoded to align the values correctly
of students with pharmaceutical marketing is associated with biased attitudes [13,14]. Our questionnaire did not include statements to investigate the students’ opinion on the implementation of an INN prescribing teaching module in e-learning. It would have been interesting however to explore this opinion as e-learning plays an expanding role in medical education [15].

Although students accepted INN prescribing more than general practitioners and pharmacists for chronic treatment and for the elderly, the responses to the statements were mostly in line with those of the general practitioners and pharmacists [11]. This latter can be the result of students being influenced by or reflecting the opinions of their peers (professors at university, training supervisors). However, in contrast to their peers, students answered quite some statements with ‘neutral’, showing far less pronounced opinions towards INN prescribing. This might indicate that students not had enough practical experience to fully understand the implications of the recently introduced policies.

3.5. CONCLUSION

Students believe that the concept of INN prescribing has the potential to contribute to rational drug prescribing and utilization, provided that continuity of treatment can be guaranteed. Students wish that INN prescribing is more prominently, but not exclusively, taught at university. All this favors the rational implementation of INN prescribing in education and clinical practice.
REFERENCES


INTERNATIONAL NONPROPRIETARY NAME PRESCRIBING:

DIVERSITY IN REGULATION ACROSS EUROPE

In preparation:
Elien Van Bever, Sabine Vogler, Luc Van Bortel, Robert Vander Stichele.
ABSTRACT

**Objectives.** To give an overview of the exemptions related to INN prescribing and generic substitution. To compare the most relevant exemptions related to INN prescribing and generic substitution, as these differ widely within European countries.

**Methods.** A self-designed questionnaire was sent to drug utilization researchers in 21 European countries (BE, CZ, DE, DK, EE, ES, FI, FR, HU, HR, IE, IS, IT, LT, NL, NO, PT, SI, SK, SE and UK). Completed questionnaires were validated by the researchers and sent to country representatives from competent authorities for a second review.

**Results.** Sixteen countries (BE, DE, EE, ES, FI, FR, HU, HR, IT, LT, NL, NO, PT, SI, SE and UK) completed the questionnaire and all were validated. INN prescribing is allowed in all countries, except in Sweden. Generic substitution is allowed in six countries (HR, EE, HU, IT, NL and SI) and mandatory in Finland, France, Germany, Norway, Spain and Sweden, but exemptions apply. It is not allowed in Belgium, Lithuania, Portugal and the United Kingdom. Twelve countries (BE, DE, ES, FI, FR, HR, LT, NL, NO, PT, SE and UK) have established explicit lists of medical products which cannot be prescribed by INN or substituted. These lists differ between countries in terms of products included and whether they are binding or advisory. The most common exempted products can be categorized in eight different groups of products: anti-arrhythmia agents, antiepileptic agents, biologicals and biosimilars, cardiac glycosides, coumarin anticoagulants, immunosuppressive agents, thyroid hormones and products used with specific aids (e.g. inhalation medications, insulin pens, ...).

**Conclusion.** National prescribing regulation differs widely between European countries. In particular the wide variability in exemptions related to INN prescribing and generic substitution and the lack of a definition for narrow therapeutic index drugs highlight the need for consensus. The results of our study can serve as a basis for the competent European authorities to establish a common guideline on this subject.
4.1. INTRODUCTION

Medicines or drugs are single or combined substances for treatment and prevention of diseases [1]. Since long, medicines have been subject to specific regulation, as no substance is completely safe and medicines are not ordinary consumer products. Medicines regulation covers different pharmaceutical policies, including policies on registration, pricing, reimbursement and medicines prescribing, to promote and protect public health. This medicines regulation differs between countries in scope and implementation as characteristics on national medicines regulation are influenced by underlying attitudes of governments towards providing and financing healthcare and by their response to medical and financial crises [2,3].

Pharmaceutical policies on medicines prescribing, also referred to as ‘prescribing regulation’, describe the applicable rules and practical implementation of the allowed ways of prescribing. The allowed ways of prescribing also depend on the available types of medicinal products in each country, which are ‘brands’ and ‘generics’. Brands include innovator products, licensed products and “well-established use” products, which are all marketed under a fantasy name but differ in the type of file submitted for marketing registration. For innovators, a complete marketing authorization file (including quality data and results of toxicological, pharmacological and clinical trials) must be established, while for licensed products and “well-established use” products an abridged file can be used [4,5]. We prefer not to use the widespread term ‘copy’ as it refers to a container concept used to describe two different types medicinal products, i.e. licensed products and ‘well-established use’ products. Licensed products are those where the marketing authorization license is bought from the innovator company by another company before patient expiry. The license is then called a ‘piggy-back’ license [5]. “Well-established use” products contain active ingredients which are used within the European Union for at least ten years and for which the effect and safety is proven [6]. These products are authorized based on a bibliographic record and scientific literature [4]. Generics include branded and unbranded generics, which do not differ in marketing registration, but in the way they are named. The branded generic name can be (1) a combination of the active ingredient name and generic company name (e.g. Simvastatin Teva®) or (2) a fantasy name given by the generic company (e.g. Lipcut® is the Sandoz® generic of simvastatin, available in Finland [7]). Unbranded generics are medicinal products where the name on the package does not include the name of the generic company, but is only the active ingredient name or the INN, e.g. simvastatin.

The possible ways of prescribing can be ‘brand name prescribing’, ‘generic prescribing’ and ‘International Nonproprietary Name (INN) prescribing’. These ways do not only differ in how medicines are prescribed, but also in the type of medicinal products that can be dispensed. Brand name prescribing refers to using the brand name for prescribing and having a brand (innovator, licensed product or “well-established use” product) dispensed. Generic prescribing includes prescribing of a (branded) generic and INN prescribing, resulting in the dispensing of a generic product. INN prescribing however can also result in the dispensing of a brand product. This latter is possible when the brand product has the same price as the available generic products or when no generic products are available (yet).
Using the INN for prescribing was introduced in the mid-eighties in France, by the journal ‘La Revue Prescrire’, to contribute to rational and safe drug prescribing and utilization [8]. Although endorsed by the World Health Organization (WHO) [9], INN prescribing was never really accepted as a way of prescribing in continental Europe. However, since the global financial crisis also affected Europe in 2008, INN prescribing was forced into a cost-containment measure for pharmaceutical expenditures in many countries [10,11].

While INN prescribing is a pharmaceutical policy executed by the prescriber, generic substitution is a policy performed at the pharmacy level. Generic substitution was introduced to enhance the role of the pharmacist as care giver and to promote the use of generics [12]. Generic substitution is when the prescribed medicinal product (a brand or branded generic) is substituted in the pharmacy by another medical product (usually a generic product) which is bioequivalent. Generic substitution can occur with or without permission of the prescriber.

Regarding INN prescribing and generic substitution, national prescribing regulation often includes lists of medicinal products which can or not be prescribed by INN or products which can or not be substituted. These lists differ between countries, but regularly exempt narrow therapeutic index drugs (NTIDs) from INN prescribing or generic substitution. However, within the European Union, there is no official definition or established list of NTIDs [13,14].

Therefore, the first aim of this study was to give an overview of exemptions related to INN prescribing and generic substitution. The second aim is to compare the most relevant exemptions, as these differ widely within European countries. For the correct understanding and completeness, we start with an overview of the types of medicinal products available and the allowed ways of prescribing.

### 4.2. METHODS

#### 4.2.1. QUESTIONNAIRE

Prior to drafting the questionnaire, a preliminary literature search in PubMed and on the world wide web was performed using the European country names and search terms: “Drug Prescriptions/standards” [MeSH], “Drugs, generic” [MeSH], “Drug substitution” [MeSH], “Health policy” [MeSH], “health care system”, “prescribing regulation”, “medicines regulation”, “reference price system”. All relevant information was extracted and used as framework for the draft questionnaire. The draft questionnaire was discussed and tested in several expert meetings including general practitioners, pharmacists, drug utilization researchers and experts in pharmaceutical policies. The draft questionnaire was adjusted to the remarks of the experts. Afterwards, it was tested by a drug utilization researcher and finalized according to the remarks.

For the correct understanding and interpretation of used terms in the questionnaire, a glossary was composed. This glossary comprised definitions retrieved from other glossaries and sources (such as the MeSH database, the Merriam-Webster dictionary, the European Medicines Agency (EMA), the Food and Drug Administration (FDA) and the Pharmaceutical Health Information System Glossary 2009 [15]). When no sufficient definition was found, existing definitions were adapted or completed, or when no definition was available, one was established by the authors.
The questionnaire was divided into five sections, with 51 questions in total. However, some questions are beyond the scope of this article and therefore will not be further discussed. The first section contained questions about e.g. the types of medicinal products available, whether a reference price system is applied and whether electronic prescribing is possible. Section 2 was called “Prescribing by brand name” and contained questions on (a) the regulation of this way of prescribing, including whether it is allowed or mandatory to prescribe by brand name. Applicable exemptions related to this regulation could also be mentioned. Next were questions on (b) the items needed for a correct brand name prescription (e.g. strength, route of administration) and at last questions on (c) whether generic substitution is allowed or mandatory with a brand name prescription and which exemptions apply. Section 3 was called “Prescribing of branded generics” and section 4 “INN prescribing”. These sections were constructed similar to section 2. Section 5 “Education” focused on the way students where taught to prescribe at university. After each question and at the end of the questionnaire, space was provided for additional remarks.

4.2.2. CIRCULATING & VALIDATING THE QUESTIONNAIRE

With the help of the European Drug Utilization Research Group (EuroDURG) [16], drug utilization (DU) researchers in 21 European countries were identified and contacted by e-mail in September 2013. The DU researchers were asked to complete the questionnaire, within two months if possible. Completed questionnaires were returned to the authors and the given answers were validated with information available on websites of national health insurance institutes, medicines agencies and professional associations. Afterwards, the completed questionnaires were sent to a country representative from competent authorities for a second review. These representatives were contacted by the Head of the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies [17]. Reviewed questionnaires were returned to the authors for analysis.

4.3. RESULTS

The questionnaire was sent to 21 countries (BE, CZ, DE, DK, EE, ES, FI, FR, HU, HR, IE, IS, IT, LT, NL, NO, PT, SI, SK, SE and UK) of which 5 did not participate (CZ, DK, IE, IS and SK) and the remaining 16 completed the questionnaire. All completed questionnaires were validated by the authors and 7 of them were reviewed a second time by a representative from the competent authorities (BE, FI, FR, HU, LT, NL and NO) (Table 4.1).

4.3.1. AVAILABLE TYPES OF MEDICINAL PRODUCTS

Brands (innovators, licensed products and “well-established use” products) and branded generics were available in all 16 countries. Unbranded generics were only available in two countries: the Netherlands and the United Kingdom (UK). In the UK, unbranded generics were the most common generics.
4.3.2. ALLOWED WAYS OF PRESCRIBING

Depending on the types of medicinal products available, countries allow different ways of prescribing: brand name prescribing, generic prescribing and INN prescribing.

Brand name prescribing is allowed in all investigated countries, except in three: Estonia, Lithuania and Portugal. In these three countries, brand name prescribing is only allowed in specific situations where INN prescribing might compromise patient safety (see further).

Most countries do not make a distinction between the legal status of brands and branded generics, which implicates that regulation for prescribing branded generics is similar to the regulation of brand name prescribing. However, countries might distinguish between brands and branded generics for price and reimbursement related reasons. For example, in Belgium, physicians are allowed to prescribe both by brand name and branded generic name but reimbursement regulation for brand products and branded generics causes differences in price and reimbursement level (Table 4.2).

INN prescribing is possible in 15 of the investigated countries and is not allowed in Sweden. It is mandatory for all products (except in specific situations – see further) in Estonia, Lithuania and Portugal. In Hungary, INN prescribing is only mandatory for lipid-modifying agents. In Italy, it is only mandatory for off-patent products prescribed for acute treatment or prescribed for the first time in chronic treatment. In France, Germany, Hungary, the Netherlands, Spain, Slovenia and the UK INN prescribing is allowed (but not mandatory, except for

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Table 4.1. Overview of countries contacted, participating and validated

<table>
<thead>
<tr>
<th>Countries contacted N = 21</th>
<th>Country name abbreviation</th>
<th>Participated in project N = 16</th>
<th>Questionnaire validated N = 16</th>
<th>Questionnaire reviewed 2nd time N = 7</th>
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<td>DE</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Hungary</td>
<td>HU</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Iceland</td>
<td>IS</td>
<td>×</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ireland</td>
<td>IE</td>
<td>×</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Italy</td>
<td>IT</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Lithuania</td>
<td>LT</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>the Netherlands</td>
<td>NL</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Norway</td>
<td>NO</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Portugal</td>
<td>PT</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Slovakia</td>
<td>SK</td>
<td>×</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Slovenia</td>
<td>SI</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Spain</td>
<td>ES</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Sweden</td>
<td>SE</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>UK</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
</tbody>
</table>
lipid-modifying agents in Hungary) for all products. The same applies to Finland and Norway, but it is rarely used. In Belgium, INN prescribing is allowed for most products, but exemptions apply (see further) (Table 4.2 & 4.3).

Table 4.2. Overview of the applied regulation\(^1\) of medicines prescribing and generic substitution

<table>
<thead>
<tr>
<th>Country</th>
<th>Brand name prescribing (prescribing of branded generics)(^2)</th>
<th>INN prescribing</th>
<th>Generic substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed, but with exemptions(^3)</td>
<td>× Not allowed</td>
</tr>
<tr>
<td>Croatia</td>
<td>✓ Mandatory for all products</td>
<td>✓ Allowed for all products</td>
<td>× Allowed, but with exemptions(^3)</td>
</tr>
<tr>
<td>Estonia</td>
<td>× Not allowed, only in specific situations(^3)</td>
<td>✓ Mandatory for all products</td>
<td>✓ Allowed</td>
</tr>
<tr>
<td>Finland</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products, but rarely used</td>
<td>Mandatory, but with exemptions(^3)</td>
</tr>
<tr>
<td>France</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products</td>
<td>✓ Mandatory, but with exemptions(^3)</td>
</tr>
<tr>
<td>Germany</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products</td>
<td>✓ Mandatory, but with exemptions(^3)</td>
</tr>
<tr>
<td>Hungary</td>
<td>✓ Allowed for all products, except lipid-modifying agents</td>
<td>✓ Allowed, mandatory for lipid-modifying agents</td>
<td>✓ Allowed</td>
</tr>
<tr>
<td>Italy</td>
<td>✓ Allowed, except for off-patent products prescribed for acute treatment or for the 1(^{\text{st}}) time in chronic treatment</td>
<td>✓ Mandatory for off-patent products prescribed for acute treatment or for the 1(^{\text{st}}) time in chronic treatment</td>
<td>✓ Allowed, but with exemptions(^2)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>× Not allowed, only in specific situations(^3)</td>
<td>✓ Mandatory for all products except biologicals and narrow therapeutic index drugs (antiepileptic agents and immunosuppressive agents)</td>
<td>× Not allowed</td>
</tr>
<tr>
<td>the Netherlands</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed, but with exemptions(^3)</td>
</tr>
<tr>
<td>Norway</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products, but rarely used</td>
<td>✓ Mandatory, but with exemptions(^3)</td>
</tr>
<tr>
<td>Portugal</td>
<td>× Not allowed, only in specific situations(^3)</td>
<td>✓ Mandatory for all products, except for tacrolimus, ciclosporin and L-thyroxin</td>
<td>× Not allowed</td>
</tr>
<tr>
<td>Slovenia</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products</td>
<td>✓ Allowed for all products</td>
</tr>
</tbody>
</table>
### 4.3.3. GENERIC SUBSTITUTION

More than half of the countries allow both INN prescribing and generic substitution (DE, EE, FI, FR, HU, IT, NL, NO, SI and ES), but usually either INN prescribing or generic substitution is endorsed for rational drug utilization and as cost-containment measure (Table 4.2).

Generic substitution is allowed in six countries (HR, EE, HU, IT, NL and SI) and mandatory in Finland, France, Germany, Norway, Spain and Sweden, but exemptions apply. It is not allowed in Belgium, Lithuania, Portugal and the UK (Table 4.2).

It is important to notice that most of the above described regulation is (only) applicable for reimbursable medical products and that different regulation can apply for non-reimbursable products and Over-The-Counter (OTC) products.

### 4.3.4. EXEMPTIONS AND SPECIFIC SITUATIONS

The regulation of INN prescribing and generic substitution is elaborated in different ways and extent across countries. For example, countries can apply lists of interchangeable products or lists of products not suitable for INN prescribing or generic substitution.

Twelve countries (BE, DE, FI, FR, HU, IT, LT, NO, PT, SE, SI and foreseen beginning 2015 in HR) established lists of interchangeable products for INN prescribing or generic substitution. These lists differ between countries with regard to the items (e.g. active ingredient name, brand name, strength, route of administration) used to establish the interchangeable groups. In some countries, these lists of interchangeable products are related to national reimbursement policies and in some countries only medicinal products for which generics are available are included.

| Country      | INN Prescribing | Generic Substitution | Exemptions
|--------------|------------------|----------------------|-------------
| Spain        | ✓                | ✓                    | ✓           |
| Sweden       | ✓                | ×                    | ✓           |
| United Kingdom| ✓                | ✓                    | ×           |

1 This regulation is only applicable for reimbursable medical products and different regulation can apply for non-reimbursable products and Over-The-Counter products.
2 Because there is no legal distinction between brands and branded generics. However, there might be a difference between brands and branded generics with regard to pricing and reimbursement regulation.
3 These exemptions differ between countries, but can include anti-arrhythmia agents, antiepileptic agents, biologicals and biosimilars, cardiac glycosides, coumarin anticoagulants, immunosuppressive agents, insulin and analogues and thyroid hormones. See also Table 4.3.
4 These specific situations refer to, for example, prescriptions for chronic treatment, patients with special needs (children, elderly) or sensitivity to excipients or when judged necessary by the prescriber for patient safety reasons.
Table 4.3. Overview of most common groups of products exempted from INN prescribing and/or generic substitution

<table>
<thead>
<tr>
<th>Country</th>
<th>Anti-arrhythmia agents</th>
<th>Antiepileptic agents</th>
<th>Biologicals &amp; biosimilars</th>
<th>Cardiac glycosides</th>
<th>Coumarin anticoagulants</th>
<th>Immunosuppressive agents</th>
<th>Thyroid hormones</th>
<th>Products used with specific aids $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Exempted from switching</td>
<td>All exempted from switching</td>
<td>Exempted from INN prescribing</td>
<td>Exempted from switching</td>
<td>Exempted from switching</td>
<td>Exempted from switching</td>
<td>Exempted from switching</td>
<td>Exempted from switching</td>
</tr>
<tr>
<td>Croatia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Digoxin exempted from generic substitution</td>
<td>Warfarin exempted from generic substitution</td>
<td>Cyclosporin and tacrolimus exempted from generic substitution</td>
<td>-</td>
<td>Exempted from generic substitution</td>
</tr>
<tr>
<td>Estonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exempted from generic substitution</td>
</tr>
<tr>
<td>Finland</td>
<td>Exempted from generic substitution</td>
<td>Exempted from generic substitution</td>
<td>Exempted from generic substitution</td>
<td>Warfarin exempted from generic substitution</td>
<td>-</td>
<td>-</td>
<td>Exempted from generic substitution</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>-</td>
<td>Levetiracetam, lamotrigine, topiramate and valproic acid exempted from generic substitution</td>
<td>-</td>
<td>-</td>
<td>Mycophenolate mofetil exempted from generic substitution</td>
<td>L-thyroxin exempted from generic substitution</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
<td>Substitution should be carefully considered</td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No explicit exemptions for INN prescribing or generic substitution. A list of substitutable medicinal products is available.</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No explicit exemptions for INN prescribing or generic substitution. A list of substitutable medicinal products is available.</td>
</tr>
<tr>
<td>Lithuania</td>
<td>-</td>
<td>Exempted from INN prescribing</td>
<td>Exempted from INN prescribing</td>
<td>-</td>
<td>-</td>
<td>Exempted from INN prescribing</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Country</td>
<td>Anti-arrhythmia agents</td>
<td>Antiepileptic agents</td>
<td>Biologicals &amp; biosimilars</td>
<td>Cardiac glycosides</td>
<td>Coumarin anticoagulants</td>
<td>Immunosuppressive agents</td>
<td>Thyroid hormones</td>
<td>Products used with specific aids&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>---------------------------</td>
<td>--------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>-----------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>the Netherlands</td>
<td>Class I and III exempted from substitution</td>
<td>Exempted from generic substitution when indicated for epilepsy</td>
<td>Substitution should be carefully considered</td>
<td>Exempted from substitution</td>
<td>Exempted from substitution</td>
<td>Exempted from substitution when indicated for prophylaxis of graft-versus-host disease</td>
<td>Exempted from substitution</td>
<td>Exempted from substitution</td>
</tr>
<tr>
<td>Norway</td>
<td>-</td>
<td>All exempted from generic substitution but only when indicated for epilepsy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>L-thyroxin exempted from generic substitution</td>
</tr>
<tr>
<td>Portugal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Cyclosporin and tacrolimus exempted from generic substitution</td>
<td>L-thyroxin exempted from generic substitution</td>
<td>-</td>
</tr>
<tr>
<td>Slovenia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No explicit exemptions for INN prescribing or generic substitution. A list of substitutable medicinal products is available.</td>
</tr>
<tr>
<td>Spain</td>
<td>Flecainide exempted from generic substitution</td>
<td>Carbamazepine, phenytoin and vigabatrin exempted from generic substitution</td>
<td>Exempted from generic substitution</td>
<td>Digoxin and metildigoxin exempted from generic substitution</td>
<td>Exempted from generic substitution</td>
<td>Cyclosporin and tacrolimus exempted from generic substitution</td>
<td>L-thyroxin exempted from generic substitution</td>
<td>Exempted from generic substitution</td>
</tr>
<tr>
<td>Sweden</td>
<td>-</td>
<td>Exempted from generic substitution</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Exempted from generic substitution</td>
<td>-</td>
<td>Exempted from generic substitution</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>-</td>
<td>Advised to prescribe by brand name</td>
<td>Advised to prescribe by brand name</td>
<td>-</td>
<td>-</td>
<td>Advised to prescribe by brand name</td>
<td>Advised to prescribe by brand name</td>
<td>Advised to prescribe by brand name</td>
</tr>
</tbody>
</table>

<sup>1</sup>Some countries only took into account active ingredients and medicinal products available on the national pharmaceutical market, or active ingredients for which generics were available.

<sup>2</sup>These products can be e.g. inhalation medication, prefilled syringes with adrenaline, insulin pens, ...
In twelve countries (BE, DE, ES, FI, FR, HR, LT, NL, NO, PT, SE and UK) explicit lists of medical products which cannot be prescribed by INN or substituted are established. These lists differ between countries in terms of products included and whether they are binding or advisory. Nine countries (BE, ES, FI, FR, HR, LT, NO, PT and SE) have binding lists with (groups of) products exempted from INN prescribing (BE and LT) or generic substitution. In the United Kingdom, a document from the National Health Service is available on which (groups of) products are advised to prescribe by brand name instead of by INN. In Germany, the German Pharmaceutical Society (Deutsche Pharmazeutische Gesellschaft e.V. – DPhG [18]) has established a guidance on Good Substitution Practice, which includes (groups of) products where substitution should be carefully considered. In the Netherlands, a guidance on generic substitution is established by the professional association for pharmacists (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie – KNMP [19]) and exempt antiepileptic drugs (AEDs) when prescribed for epilepsy, immunosuppressive agents and insulin and its analogues from generic substitution and advises to carefully consider substitution for other (groups of) products (e.g. cardiac glycosides, coumarin anticoagulants). Besides a binding list with products not suitable for INN prescribing, Belgium applies a second list with exemptions, the ‘NO SWITCH’ list. This list contains (groups of) products for which frequent switching during treatment is not advised. Switching can occur when dispensing an INN prescription, but not due to generic substitution, as this is not allowed in Belgium [10,14].

Exemptions for INN prescribing and/or generic substitution can be listed as specific active ingredients (e.g. cyclosporin, tacrolimus, warfarin) or as groups of products (e.g. AEDs, immunosuppressive agents). Some countries refer to these (groups of) products as narrow-therapeutic index drugs (NTIDs). However, within the Europe, there is no official definition of an NTID nor is there an exhaustive list of NTIDs. As a result, products judged as NTIDs also differ widely between countries.

Ten countries exempt antiepileptic agents and immunosuppressive agents. Both groups are exempted in Belgium, France (only specific AEDs and mycophenolate mofetil), Germany, Lithuania, the Netherlands, Spain (only specific active ingredients), Sweden and the UK. In Croatia, only cyclosporine and tacrolimus are exempted. In Norway, only AEDs prescribed for the treatment of epilepsy are exempted. Thyroid hormones are exempted in eight countries (BE, DE, FR, NL, NO, PT, SE and UK). Six countries (BE, DE, ES, FI, HR and NL) exempt coumarin anticoagulants and cardiac glycosides. Anti-arrhythmia agent are exempted by five countries (BE, DE, ES, FI and NL). Further details on exempted (groups of) products are given in Table 4.3. Besides the mentioned groups of products in Table 4.3, multiple other (groups of) products are listed as exemptions in different countries, which include controlled drugs (e.g. buprenorphine in France), medicated patches or transdermal systems (e.g. in BE, DE, FI, SE, UK), products with modified release (e.g. products containing nifedipine or morphine) and products containing multiple active ingredients (e.g. laxatives, multiphasic contraceptive pills).

Some countries (e.g. BE, IT, PT) also describe specific situations where INN prescribing, generic substitution or frequent switching might not be appropriate for practical or patient safety reasons. These specific situations refer to, for example, prescriptions for chronic treatment, patients with special needs (children, elderly) or sensitivity to excipients.
All countries applying mandatory policies on INN prescribing or generic substitution allow prescribers to deviate from the applying rules when judged necessary for patient safety reasons. In most countries, substitution of aforementioned products is also possible in exceptional situations (e.g. stock problems) with supervision of the prescriber.

4.4. DISCUSSION

To the best of our knowledge, this study was the first to investigate exemptions related to INN prescribing and generic substitution. These exemptions are mainly referred to as narrow therapeutic index drugs (NTIDs). Remarkably, these exemptions also differ widely between countries, although most of them were established because of patient safety reasons – and patients do not differ between countries. In addition, within Europe, there is no official definition of a NTID or an exhaustive list of NTIDs, neither is there a list of products which are advised not to be switched or substituted during treatment (without the supervision of a physician and/or pharmacist).

Not all European countries were included in our study. On the world wide web more complete overviews of the allowed ways of prescribing and of generic substitution are available, including data on the remaining 13 EU member states (AT, BG, CZ, CY, DK, EL, IE, LV, LU, MT, PL, RO and SK) [20,21]. These overviews confirm our data for the common countries and complement it for the remaining countries.

Despite the use of a glossary, definitions of used terms (e.g. generic products, brand name prescribing, generic prescribing) can have subtle differences between countries. These differences can be explained by variations in pricing and reimbursement regulation, which was not a topic in our questionnaire. In-depth understanding of all national aspects related to medicines and prescribing regulation is only possible when the overall picture is revealed.

When comparing (groups of) products exempted from INN prescribing and/or generic substitution, not all products and differences between countries were discussed, due to the large variety between countries. In our study, we only focused on the eight main groups of exemptions and discussed some others briefly. However, our purpose was to highlight the wide variability between European countries in exemptions related to the same pharmaceutical policies.

Furthermore, no data on the amount of prescriptions and dispensed products has been collected for the included countries. Combined with our collected information, it would be interesting to investigate for each country the effect of the applied policies (e.g. the percentage generic market share, percentage of generic substitution in the pharmacy). However, collecting these data will be a difficult task, as one way of prescribing can result in different types of products dispensed. For example, an INN prescription can lead to the dispensing of either a brand product or a generic product (branded or unbranded).

Based on the information from 16 different European countries, we can make some recommendations for the exemptions related to INN prescribing and/or generic substitution. A European guideline might exempt anti-
arrhythmia agents, biologicals and biosimilars, cardiac glycosides, coumarin anticoagulants, thyroid hormones and products used with specific aids. In the Netherlands, immunosuppressive agents are only exempt when indicated for the prophylaxis of graft-versus-host disease. Similarly, they only exempted antiepileptic agents when indicated for epilepsy. It should be discussed whether or not to take into account the indication of certain medicinal products before exempting them.

We also recommend to describe specific situations where INN prescribing and/or generic substitution is not advised (e.g. chronic treatment). In addition, the guideline should also include the possibility for prescribers to object towards switching and/or substitution for patient safety reasons.

Finally, when establishing a guideline for patient safety reasons, it is recommendable to take into account the economic implications of exempting products and situations. It should be investigated whether the intended cost savings through INN prescribing and/or generic substitution compensate for the potential costs related to adverse drug reactions (ADRs) due to switching and/or substitution.

4.5. CONCLUSION

National prescribing regulation differs widely between European countries. In particular the wide variability in exemptions related to INN prescribing and generic substitution and the lack of a definition for narrow therapeutic index drugs highlight the need for consensus. The results of our study can serve as a basis for the competent European authorities to establish a common guideline on this subject.
REFERENCES


17. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies.
18. Deutsche Pharmazeutische Gesellschaft e.V.

19. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie
THE INTERCHANGEABILITY OF GABAPENTIN 800 MG TABLETS:

A RANDOMIZED, CONTROLLED TRIAL TO ESTABLISH INDIVIDUAL BIOEQUIVALENCE

ABSTRACT

**Objective.** To investigate interchangeability of gabapentin 800 mg tablets marketed as Neurontin® and Gabasandoz® following FDA guidelines using the individual bioequivalence (IBE) approach. To investigate interchangeability in a more real-life situation through IBE by including two different batches of each product (Neurontin® Batch ‘A’ and ‘B’, Gabasandoz® Batch ‘A’ and ‘B’).

**Methods.** Thirty healthy subjects received 6 times - in randomized order - a single dose of 800 mg Neurontin® (Batch ‘A’ or ‘B’) or 800 mg Gabasandoz® (Batch ‘A’ or ‘B’). Serum concentrations of gabapentin up to 36 hours after dosing were determined. According to FDA guidelines, IBE can be established if the 95 % upper-confidence bound (UCB) of η (i.e., a function of different variance terms) is lower than the IBE limit θI, which is 2.5. For $\text{AUC}_{0-\infty}$ and $\text{C}_{\text{max}}$, η and its 95 % UCB were calculated.

**Results.** For $\text{AUC}_{0-\infty}$ and $\text{C}_{\text{max}}$, η was 0.58 and 0.19, respectively, and the 95 % UCB was 1.32 and 0.63 (both p-value < 0.001), respectively. When including data on batch ‘B’ of Neurontin® and Gabasandoz®, η was 0.46 and -0.08 for $\text{AUC}_{0-\infty}$ and $\text{C}_{\text{max}}$, respectively. The 95 % UCB was 1.20 and 0.40, respectively (both p-value < 0.001). All UCB were below the IBE limit θI, showing IBE.

**Conclusion.** This study indicates that Neurontin® 800 mg (Batch ‘A’) and Gabasandoz® 800 mg (Batch ‘A’) are individual bioequivalent and interchangeable in clinical practice. This interchangeability remains when resembling a more real-life situation by adding an additional batch of each product (Batch ‘B’).
5.1. INTRODUCTION

Once the patent of a marketed drug product has expired, generic drug products can enter the market [1,2] of which the requirements and characteristics are secured by regulatory authorities (such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA)) [3]. For generic drug products, prior to enter the market, it is required to establish (average) bioequivalence (ABE) with the reference (marketed) drug product. Two medicinal products are considered bioequivalent if the 90% confidence interval of the ratio in bioavailability (AUC and $C_{\text{max}}$) between these products after administration of the same dose lies within a predefined interval [4]. This interval is between 80% and 125% for most medicinal products or between 90% and 111% for narrow therapeutic index drugs (NTIDs). These intervals are defined to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy, between the reference and generic drug product [5]. Notwithstanding these bioequivalence trials, issues related to switching from reference drug product to generics and between generics have been reported, especially for narrow therapeutic index drugs (NTIDs) [6], antiepileptics [7–9], antipsychotics [10–13], and antidepressants [14].

Taking these reports into account, prioritizing patients safety and in line with other European countries [15–17], the Belgian medicines agency (Federal Agency for Medicines and Health Products (FAMHP) [18]) established an exhaustive list of products for which switching from reference drug product (brand) to generic and vice versa or between generics is not advised [19,20]. This list is titled the ‘NO SWITCH’-list and is established within the framework of operationalizing electronic International Nonproprietary Name (INN) prescribing in Belgium [20]. INN prescribing in Belgium can result more frequent switching between drug products containing the same compound [21,22]. The ‘NO SWITCH’-list contains products such as NTIDs, very toxic compounds and all antiepileptic drugs (AEDs). Being on this list implies that once treatment is started with a medicinal product from a manufacturer, it is advised to continue treatment with exactly the same product. This can be advised because switching towards a medicinal product with different appearance can cause medication nonadherence [23]. In addition, it can also be advised because it is believed that products from different manufacturers are not (completely) interchangeable, in particular between-batch variability of a drug product is believed to be smaller than the variability between two bioequivalent products from different manufacturers.

The overall goal of this study was to investigate the interchangeability between a brand product (NEURONTIN® 800 mg) and its generic counterpart (GABASANDOZ® 800 mg) of gabapentin on the ‘NO SWITCH’-list. To the best of our knowledge, for none of the products on the ‘NO SWITCH’-list interchangeability has been studied using the appropriate clinical trials. In this context, a trial to establish individual bioequivalence (IBE) was performed as IBE is described as an appropriate method to investigate interchangeability between products [24]. The average bioequivalence trial design is not suitable, as it does not take into account within-subject variability [24,25].

Because of the 4-way crossover design, complex statistics and financial burden of the IBE approach and the fact that interchangeability establishment is not always needed for patients’ safety, for a majority of medicinal products, ABE currently remains the standard bioequivalence method [24,26–28]. For bioequivalence testing in
anti-epileptics, Midha et al. (2005) [29] and Bailer and Midha (2010) [30] proposed the Scaled Average Bioequivalence approach (sABE), which is ABE testing where the variance of the reference formulation is taken into account. However, this sABE approach also dictates the use of a 4-way crossover design and more complex statistics than ABE.

In this study, gabapentin, an antiepileptic drug on the ‘NO SWITCH’-list is used as study compound, with NEURONTIN® 800 mg as brand (the reference drug product) and GABASANDOZ® 800 mg as generic counterpart. Gabapentin is well absorbed without food-effect and peak plasma concentrations are reached within two to four hours after oral administration [31,32]. There is no metabolization in humans and gabapentin is eliminated as such by renal excretion [31]. The reported half-life ranged from five to ten hours [31,32].

The aim of this study was two-fold, starting with investigating for the first time IBE between one batch of the reference drug product (R1) and one batch of a generic (T1) of 800 mg gabapentin, using a four-way cross-over study design. This is in contrast to the study of Yu et al., where the so-called ‘drift’-effect was investigated between different generics of 800 mg gabapentin but IBE could not be established because of the lack of a replicated study design [32]. The second aim was to investigate the between-batch variability between two different batches of the reference drug product (R1 & R2) and two different batches of the generic (T1 & T2), using a six-way cross-over design. This additional effort was made because this design more closely resembles the real-life situation where patients consecutively receive different batches of their treatment.

5.2. METHODS & MATERIALS

All trial procedures (except the serum gabapentin analyses) were performed at the Drug Research Unit Ghent, the unit for early phase clinical drug research of the Ghent University Hospital, Belgium (www.drug-uzgent.be).

5.2.1. TREATMENTS

Four different treatments were administered. The reference products were two different batches of NEURONTIN® 800 mg [Pfizer®, New York, USA] (Batch A with number 1269012 and expiry date 12/2013; Batch B with number 1091082 and expiry date 07/2014) referred to as R1 and R2, respectively. The test products were two different batches of GABASANDOZ® 800 mg [Sandoz®, Holzkirchen, Germany] (Batch A with number CJ7435 and expiry date 11/2014; Batch B with number CT9850 and expiry date 03/2015), referred to as T1 and T2, respectively.

5.2.2. STUDY DESIGN

The study was a single blind, single dose, randomized six-way cross-over study in health volunteers. To investigate individual bioequivalence (IBE) between reference and test product, R1 and T1 were given in a replicated, two-sequence, randomized order (R1/T1/R1/T1 or T1/R1/T1/R1). This fixed design allowed an estimation of the within-subject variance and the subject-by-formulation interaction. To investigate the IBE between different batches of reference and test, two periods were added where R2 and T2 were administered in randomized order, before and/or after the fixed design with R1 and T1 (Figure 5.1), resulting in 12 possible
combinations. Therefore, randomization was performed in blocks of 12. A minimum of four days wash-out separated the single-doses of Period 1 to 6 to minimize the risk of drug carryover.

Figure 5.1. Summary of the study design with the two-sequence fixed design (R1/T1/R1/T1 or T1/R1/T1/R1) and the additional batches of reference (R2) and test (T2) before and/or after the fixed design.

With R1 NEURONTIN® 800 mg Batch A, R2 NEURONTIN® 800 mg Batch B, T1 GABASANDOZ® 800 mg Batch A and T2 GABASANDOZ® 800 mg Batch B.

In each period, subjects were confined in the clinical research unit from the evening before study drug administration until 12 hours after dosing. They were fasted overnight for at least 8 hours and received, blindfolded, a single, oral dose of 800 mg gabapentin in the morning (starting at 09:00 AM), which was taken with approximately 240 mL of noncarbonated water. Subjects received a standardized lunch, snack and dinner at respectively 4, 7 and 10 hours after dosing.

This study was conducted in two parts, starting with 12 subjects to collect data to determine the total sample size, as at that time no information on 800 mg doses was available in literature. In part two, additional subjects were included to achieve the FDA’s recommended 80% power.

5.2.3. STUDY POPULATION: IN- AND EXCLUSION CRITERIA

The subjects were non-smokers, aged between 18 and 55 years, and had a Body Mass Index of 18.0 to 30.0 kg/m². All subjects were in good physical and mental health at the time of inclusion as established by medical history, physical examination, electrocardiogram (ECG) and vital signs recording, and by results of biochemistry, hematology and urinalysis testing within six weeks prior to the first dose. Subjects had no history of hypersensitivity or idiosyncrasy to gabapentin or any other antiepileptic drugs, reported no history of alcohol or drug abuse within the last two years, no cancer or surgery of gastro-intestinal tract that might interfere with absorption and no history or presence of any significant disease. There was no use of any medication (except for contraceptive agents and paracetamol), herbal medicines or dietary supplements from 14 days prior to the first dose. Subjects refrained from any enzyme inducing drugs and products from 21 days prior to the first dose and did not participate in another clinical trial within 28 days prior to the first dose. Female subjects were not pregnant or breastfeeding, and agreed to apply a highly effective method of birth control. All subjects were
The interchangeability of gabapentin 800 mg tablets

informed, orally and in writing, about this study and gave oral and written consent prior to enter the study and were willing to comply with the study protocol requirements and to complete the study.

This study was performed in accordance with the study protocol, the ethical principles of the Declaration of Helsinki [24], International Conference of Harmonization (ICH) – Good Clinical Practice (GCP) Guidelines [25], EU-GCP directives [26] and the applicable national regulatory requirements [27]. This study was approved by the ethics committee of the Ghent University Hospital (EC/2013/210) and received EudraCT-number 2013-001157-57. The study was registered in the clinicaltrials.gov database (ID number NCT01821235).

5.2.4. MEASUREMENTS

Blood samples for pharmacokinetic measurements were taken prior to gabapentin administration, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 24 and 36 hours after dosing. For blood samples after discharge (24 and 36 hours postdose), subjects returned to the clinical research unit. Approximately 2 mL of blood was taken by an indwelling catheter in the forearm into a blood collection tube with serum cloth activator without gel separator. Prior to each sample collection, about 1 mL of blood was drawn from the catheter and discarded. After clotting for at least 30 minutes, serum was separated within 2 hours after sampling, by centrifugation at 1300 g at 20°C for 15 minutes. Serum was transferred into cryogenic vials (Biosigma®) and stored at -20°C until analysis.

5.2.5. BIOANALYSIS

The analysis of gabapentin in serum was performed with a validated ultra-performance liquid chromatography with mass-spectrometric detection (UPLC-MS-MS). Further details of this analytical method are beyond the scope of this article and are presented elsewhere [33]. All analyses were performed at the department of clinical pharmacology and pharmacy of the VU University Medical Center, Amsterdam, The Netherlands (http://www.vumc.nl/afdelingen/klinische-farmacologie-apotheek/).

5.2.6. STATISTICAL ANALYSIS

Secondary pharmacokinetic (PK) parameters were calculated using non-compartmental analysis with the PK package in R® [34,35]. The secondary PK parameters necessary for establishment of individual bioequivalence (IBE) were the area under the curve, from time 0 to infinity (AUC\textsubscript{0-inf}) and the maximum plasma concentration (C\textsubscript{max}). Other secondary PK parameters, plasma elimination half-life, T\textsubscript{max} and AUC\textsubscript{0-t}, were solely included in the descriptive part of the results. The area under the curves, and the half-life were estimated using the PK package, whereas the time to reach C\textsubscript{max} (T\textsubscript{max}) and the C\textsubscript{max} were determined from the observed plasma concentration-time profiles.

The statistical tests to establish average and individual bioequivalence were performed according to the FDA Guidance for Industry on “Statistical approaches to establishing bioequivalence” [25], from now referred to as ‘the guidance’.

Using the data from part I of the study, initial estimates were obtained for σ\textsubscript{0} (the subject-by-formulation interaction term), σ\textsubscript{T} and σ\textsubscript{R} (the within-subject variability for test and reference, respectively). Based on these
initial estimates, a simulation study was performed in R® to determine the total sample size necessary to comply with the FDA’s proposed power of 80%. The R® script included the generation of 1000 virtual clinical trials, with a pre-specified sample size (for 12, 14, 16, ..., 40 subjects) with within-product variability and subject-by-formulation interaction randomly sampled from the initial estimates of the \( \sigma_D \), \( \sigma_T \) and \( \sigma_R \) distributions and allowing for a \( (\mu_T - \mu_R) \) to be equal to 5% (according to the guidance). Afterwards, for each of the virtual clinical trials, the IBE criterion was calculated and the power was estimated by calculating the relative frequency of virtual clinical trials, in each of the sample size categories, which concluded IBE.

Afterwards, in the final analysis, average bioequivalence (ABE) was assumed if

\[-\theta_A < (\mu_T - \mu_R) < \theta_A\]

with \( \theta_A = \ln(1.25) \) and \( \mu_T \) and \( \mu_R \) being the population average log-transformed AUC or \( C_{\text{max}} \) for the test and reference formulation, respectively. The 90% confidence intervals for the ABE criteria were estimated using SAS® version 9.4 [36], by fitting the data using a linear mixed-effects model according the guidance.

Once average bioequivalence was established, the analysis to investigate IBE between R1 and T1 for \( AUC_{0-\text{inf}} \) and \( C_{\text{max}} \) was performed. According to the guidance, IBE is established once the 95% upper confidence bound (UCB) of \( \eta \) is lower than the specified limit \( \theta_I \). \( \eta \) is a function of population measures, described in the guidance and includes \( \mu_T \) and \( \mu_R \), subject-by-formulation interaction variance and within-subject variance of the test and reference drug product. The IBE limit \( \theta_I \) was calculated as follows:

\[\theta_I = \frac{(\ln 1.25)^2 + \varepsilon_I}{(\sigma_{W0})^2}\]

with \( \varepsilon_I = 0.05 \) and \( \sigma_{W0} = 0.2 \). \( \varepsilon_I \) is the sum of the maximum allowed estimate of the subject-by-formulation interaction (\( \sigma_D^2 \), i.e. maximum 0.03) and the difference in the within-subject variability (\( \sigma_{WT}^2 - \sigma_{WR}^2 \), i.e. 0.02). \( \sigma_{W0}^2 \) is the specified constant within-subject variance. As gabapentin is a low variability product with a wide therapeutic range, the constant-scaling approach was used as recommended in the guidance.

Since no analytical solution has been documented in literature to calculate the 95% upper confidence bound (UCB) of \( \eta \), a script was written in R® [34] to estimate the confidence interval from a bootstrap distribution.

Afterwards, we included additional data on the oral administration of R2 and T2. Similar to the previous part, the analysis started with calculating the ABE, and once established, the IBE analysis was performed. In addition to the general structure of the linear-mixed effects model proposed, an additional variance term, i.e. \( \sigma_{\text{batch}} \), was included to account for the additional variability by introducing two different batches (R2 and T2), instead of just one batch of each product.

In addition, to establish whether the between-batch variability was different from the variability between two bioequivalent products, an independent samples T-test was performed, using SPSS® (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) with the 0.05 significance level. The
absolute differences of $\text{AUC}_{0-1}$, $\text{AUC}_{0-\text{inf}}$, $\text{C}_{\text{max}}$ and $\text{T}_{\text{max}}$ between the two batches of the reference product ($|R1 – R2|$) and the reference and test product ($|R1 – T1|$, $|R1 – T2|$, $|R2 – T1|$ and $|R2 – T2|$) were used.

### 5.2.7. SAFETY ANALYSIS

Adverse events (AEs) were checked and reported at every visit, from signing the Informed Consent Form (ICF) onwards until the last study-related visit (follow-up). For each AE, the duration and intensity was documented and the causality to the study treatment was evaluated.

### 5.3. RESULTS

#### 5.3.1. STUDY POPULATION

Part I of this study was performed between March and May 2013 and part II between August and October 2013. This two-part study enrolled, in total, 30 healthy subjects, of which 29 completed the study. Part I included 12 subjects (3 men and 9 women) and part II 18 (7 men and 11 women). One participant in part II (allocation number 022) withdrew consent for further blood sampling and medication intake during the fourth period of the study.

Demographic characteristics of the study population are shown in Table 5.1.

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<th>Height (cm)</th>
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<td>35.1</td>
<td>71.0</td>
<td>169.8</td>
<td>24.5</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>12.4</td>
<td>13.0</td>
<td>9.6</td>
<td>3.5</td>
</tr>
</tbody>
</table>

F: female; M: male
*Data of these subjects were not used in the statistical analysis due to incomplete data

5.3.2. PHARMACOKINETICS

Due to problems during blood sampling, blood samples are missing for two subjects (allocation number 013 and 014). Therefore, data on 27 subjects were used for the estimation of the secondary pharmacokinetic parameters and the bioequivalence criteria (Table 5.1).

Mean plasma concentration time-curves per treatment are shown in Figure 5.2 and mean AUC₀⁻₃₆, AUC₀⁻∞, Cₘₐₓ, Tₘₐₓ and T₁/₂ for each treatment are presented in Table 5.2. In 1.7 % of the cases, the gabapentin concentration was below the lower limit of quantification at 12 hours postdose, in 16.4 % of the cases at 24 hours postdose and in the remaining cases at 36 hours postdose.

The mean AUC₀⁻∞ for the different treatments ranged from 85.64 to 86.73 mg.h/L, the mean Cₘₐₓ from 5.19 to 5.23 mg/L and the mean T₁/₂ ranged from 10.88 to 10.89 hours for all four treatments (Table 5.2).

For R1 and T1, the difference between average log-transformed AUC₀⁻∞ and Cₘₐₓ and their 90 % confidence intervals are shown in Table 5.3. Both were within the 80 % and 125 % ranges, thereby not rejecting ABE.

Table 5.2. Mean (SD) of AUC₀⁻ₓ, AUC₀⁻∞, Cₘₐₓ, Tₘₐₓ and T₁/₂ with N = 27

<table>
<thead>
<tr>
<th>Product</th>
<th>Reference/Test</th>
<th>AUC₀⁻₃₆ (mg.h)/L</th>
<th>AUC₀⁻∞ (mg.h)/L</th>
<th>Cₘₐₓ (mg/L)</th>
<th>Tₘₐₓ (h)</th>
<th>T₁/₂ (h)</th>
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<tr>
<td>NEURONTIN® 800 mg</td>
<td>Reference 1</td>
<td>79.35 (28.11)</td>
<td>86.15 (31.79)</td>
<td>5.20 (1.42)</td>
<td>4.32 (1.45)</td>
<td>10.88 (1.95)</td>
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<td>Batch A</td>
<td>Reference 2</td>
<td>79.96 (28.67)</td>
<td>86.73 (32.24)</td>
<td>5.23 (1.43)</td>
<td>4.35 (1.47)</td>
<td>10.88 (1.94)</td>
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<tr>
<td>NEURONTIN® 800 mg</td>
<td>Test 1 (R1)</td>
<td>78.84 (27.63)</td>
<td>85.64 (31.36)</td>
<td>5.19 (1.41)</td>
<td>4.29 (1.44)</td>
<td>10.89 (1.96)</td>
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<tr>
<td>Batch B</td>
<td>Test 2 (R2)</td>
<td>79.59 (28.21)</td>
<td>86.35 (31.85)</td>
<td>5.21 (1.42)</td>
<td>4.34 (1.46)</td>
<td>10.88 (1.95)</td>
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<tr>
<td>GABASANDOZ® 800 mg</td>
<td>Test 1 (T1)</td>
<td>80.56 (29.21)</td>
<td>86.58 (31.95)</td>
<td>5.22 (1.43)</td>
<td>4.35 (1.47)</td>
<td>10.89 (1.96)</td>
</tr>
<tr>
<td>Batch A</td>
<td>Test 2 (T2)</td>
<td>80.59 (29.22)</td>
<td>86.59 (31.96)</td>
<td>5.23 (1.44)</td>
<td>4.35 (1.46)</td>
<td>10.89 (1.95)</td>
</tr>
</tbody>
</table>

AUC₀⁻₃₆: area under the drug concentration-time curve from time zero to 36 hours; AUC₀⁻∞: area under the drug concentration-time curve from time zero to infinity; Cₘₐₓ: peak plasma concentration; Tₘₐₓ: time to peak concentration; T₁/₂: elimination half-life.

The 95 % upper-confidence bounds (UCBs) of the IBE criteria for AUC₀⁻∞ and Cₘₐₓ are shown in Table 5.4. Both were below IBE limit of 2.5, as proposed by the FDA, thereby confirming individual bioequivalence between NEURONTIN® 800 mg Batch A (R1) and GABASANDOZ® 800 mg Batch A (T1) (Figure 5.2).
The interchangeability of gabapentin 800 mg tablets

Figure 5.2. Plasma concentration-time curve of gabapentin

![Plasma concentration-time curve of gabapentin](image)

*N = 27 healthy volunteers. Mean (± SD) concentration, with R1 = NEURONTIN® 800 mg Batch A (mean of both administrations), R2 = NEURONTIN® 800 mg Batch B, T1 = GABASANDOZ® 800 mg Batch A (mean of both administrations) and T2 = GABASANDOZ® 800 mg Batch B*

When including an additional batches of each product (NEURONTIN® 800 mg Batch B (R2) and GABASANDOZ® 800 mg Batch B (T2)), ABE was also established (Table 5.3). The 95% UCBs for AUC₀-ᵢᶠ and Cₘₐₓ also remained below the IBE limit of 2.5 when adding data of the two additional batches, confirming individual bioequivalence for all products (Table 5.4).

Table 5.3. Average bioequivalence (ABE) analysis results for AUCₐ₀-ᵢᶠ and Cₘₐₓ parameters and bioequivalence (BE) conclusion

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<thead>
<tr>
<th></th>
<th>AUC₀⁻ᵢᶠ</th>
<th>Cₘₐₓ</th>
</tr>
</thead>
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<tr>
<td></td>
<td>(µT – µR)</td>
<td>90 % CI</td>
</tr>
<tr>
<td>4-way crossover design with R1 and T1</td>
<td>-0.038</td>
<td>-0.108 – 0.032</td>
</tr>
<tr>
<td>6-way crossover design with R1, R2, T1 and T2</td>
<td>-0.041</td>
<td>-0.110 – 0.028</td>
</tr>
</tbody>
</table>

With R1 NEURONTIN® 800 mg Batch A, R2 NEURONTIN® 800 mg Batch B, T1 GABASANDOZ® 800 mg Batch A and T2 GABASANDOZ® 800 mg Batch B. µT and µR are the average log-transformed AUC₀⁻ᵢᶠ and Cₘₐₓ for the test and reference formulation, respectively. 90 % CI is the 90 % confidence interval for (µT - µR).
Table 5.4. Individual bioequivalence (IBE) analysis results for $\text{AUC}_{0\text{-inf}}$ and $C_{\text{max}}$ parameters, with IBE limit $\theta = 2.5$ and bioequivalence (BE) conclusion

<table>
<thead>
<tr>
<th>Design</th>
<th>$\eta$</th>
<th>95 % UCB</th>
<th>BE conclusion</th>
<th>p-value ($\eta &gt; \theta$)</th>
<th>$\eta$</th>
<th>95 % UCB</th>
<th>BE conclusion</th>
<th>p-value ($\eta &gt; \theta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-way crossover design with R1 and T1</td>
<td>0.58</td>
<td>1.32</td>
<td>Pass</td>
<td>&lt; 0.001</td>
<td>0.19</td>
<td>0.63</td>
<td>Pass</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6-way crossover design with R1, R2, T1 and T2</td>
<td>0.46</td>
<td>1.20</td>
<td>Pass</td>
<td>&lt; 0.001</td>
<td>-0.08</td>
<td>0.40</td>
<td>Pass</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

With R1 NEURONTIN® 800 mg Batch A, R2 NEURONTIN® 800 mg Batch B, T1 GABASANDOZ® 800 mg Batch A and T2 GABASANDOZ® 800 mg Batch B. $\eta$ is a function of population measures for the estimation of IBE, and 95 % UCB is the 95 % upper confidence bound of $\eta$.

The absolute differences in $\text{AUC}_{0\text{-tr}}$, $\text{AUC}_{0\text{-inf}}$, $C_{\text{max}}$ and $T_{\text{max}}$ between the two batches of the reference product ($|R1 - R2|$) and between the reference and test product ($|R1 - T1|$, $|R1 - T2|$, $|R2 - T1|$ and $|R2 - T2|$), did not differ significantly, showing no larger difference between batches of NEURONTIN® 800 mg and GABASANDOZ® 800 mg than between different batches of the same product.

Figure 5.3. Within-subject variability of $\text{AUC}_{0\text{-inf}}$ after replicate administration of reference and test

Reference is NEURONTIN® 800 mg Batch A and test is GABASANDOZ® 800 mg Batch A. The bold line shows the estimated population difference ($\Delta \mu$) of $\text{AUC}_{0\text{-inf}}$
5.3.3. SAFETY & TOLERABILITY

All treatments were moderately to generally well tolerated. Most reported adverse events (i.e. in more than 50% of the subjects) were somnolence (n = 24), dizziness (n = 22) and headache (n = 21). All reported adverse events were mild to moderate in intensity.

There was one serious adverse event (SAE). After withdrawing consent, the subject with allocation number 022 was hospitalized and diagnosed with substance induced psychotic disorder (caused by abuse of illicit drugs). This SAE was considered not related to the study drug by the investigator and the subject’s treating physician.

5.4. DISCUSSION

To the best of our knowledge, this study is the first to investigate individual bioequivalence (IBE) between a brand and generic product of gabapentin 800 mg, including two different batches of each product.

The end-of-study analysis showed that NEURONTIN® 800 mg (Batch A) is bioequivalent to GABASANDOZ® 800 mg (Batch A) on both the average and individual level. Average and individual bioequivalence was also proven when data on two different batches of each product (NEURONTIN® 800 mg Batch B and GABASANDOZ® 800 mg Batch B) were included, resembling a more real-life situation.

These results can strengthen the confidence of health professionals and patients in bioequivalence and interchangeability between brands and generics, in particular for gabapentin.

Between-batch variability ($\sigma_{\text{batch}}$) was not statistically significantly different from 0, which means that no between-batch variance could be detected (Figure 5.3). In addition, no statistically significant differences could be detected when comparing within-subject differences between two batches of the reference product ($|R1 - R2|_1$) compared to differences between the reference and test product ($|R1 - T1|$ and $|R1 - T2|$) for $\text{AUC}_0-t$, $\text{AUC}_0-\infty$, $\text{C}_{\text{max}}$ and $\text{T}_{\text{max}}$. This challenges the view that between-product differences would be larger than between-batch differences of one product (Figure 5.3 and 5.4).

Although our results demonstrate IBE for gabapentin 800 mg, these results can probably not be extrapolated to other compounds, including other AEDs, as gabapentin has a relatively simple pharmacokinetic profile (good absorption, no protein binding, no metabolization) [31].

As only one generic product of 800 mg gabapentin was available on the Belgian market, we did not include a second generic and could therefore not investigate whether a so-called ‘generic drift’ effect (i.e. larger differences between generics because each generic is only proven to be bioequivalent to the reference/innovator product) between different generics was present. However, previous studies with gabapentin could not detect a ‘generic drift’ effect using a brand and three generics of 800 mg gabapentin [32,37]. Additionally, it has been shown from a large sample of bioequivalence studies that generic drift is unlikely to cause widespread problems [38].
Despite strict regulation by governmental authorities and many studies confirming bioequivalence between brands and generics, prescribers, mainly neurologists, remain reluctant towards generic AEDs and switching from a brand to a generic AED [39,40]. It should be asked whether this is because interchangeability between brands and generics is not proven or because of the uniqueness of epilepsy as disease. The first reason can be refuted by our results, at least for gabapentin. When it comes to the second reason, a distinction can be made between AEDs prescribed for epilepsy or for other indications (e.g. neuropathic pain). This latter is the case for most of the gabapentin prescriptions [39,41] which opens the way for additional pharmaceutical cost savings.

A third reason for the reluctance against switching of AEDs can be the differences in tablet color and shape and product packaging between brand and generics. Variations in tablet appearance are proven to increase the risk of medication nonadherence, which can have serious consequences, in particular for patients with epilepsy [23]. Therefore, we are in favor of streamlining medicinal product appearance and packaging.

5.5. CONCLUSION

Although successful treatment is not only based on the clinical outcome of the medicinal products, but also on correct medication use and adherence, we can conclude that, provided correct medication use and adherence, switching between the brand and the generic product of 800 mg gabapentin, available on the Belgian market, should be possible without affecting the clinical outcomes.
REFERENCES


18. Federal Agency for Medicines and Health Products. Federal Agency for Medicines and Health Products (FAMHP), Belgium


36. SAS® software, Version 9.4 of the SAS System, Cary, NC, USA.


GENERAL DISCUSSION
# GENERAL DISCUSSION

1. MAIN FINDINGS

2. IMPLICATIONS FOR PRACTICE

   2.1. Points of attention for Belgium

      2.1.1. Inconsistencies

      2.1.2. Fixed package sizes

      2.1.3. Continuity of treatment

      2.1.4. Antiepileptic drugs

      2.1.5. Rational stock management

      2.1.6. Reasons for reluctance towards INN prescribing

      2.1.7. Education

      2.1.8. Potential savings

   2.2. Points of attention for Europe

      2.2.1. INN prescribing & generic substitution

      2.2.2. Uniformization of medication appearance

      2.2.3. Pharmacovigilance

   2.3. INN prescribing in hospital setting

   2.4. Therapeutic substitution

   2.5. Biologicals & biosimilars

3. IMPLICATIONS FOR FURTHER RESEARCH

4. STRENGTHS & LIMITATIONS

5. FINAL VIEW

REFERENCES
With this doctoral thesis, we aimed to investigate the different aspects of the concept of International Nonproprietary Name (INN) prescribing and its related policies, in Belgium and Europe. INN prescribing was introduced as an instrument to promote rational drug prescribing. It has a legal foundation in many European countries, but never really found foothold as an alternative way of prescribing, next to brand name prescribing and branded generic name prescribing. However, when the global financial crisis also affected Europe in 2008, INN prescribing was, together with generic substitution, one of the key pharmaceutical policies implemented or elaborated to reduce pharmaceutical expenditures. These forced cost-containment policies were not welcomed by all stakeholders, as they feared e.g. a negative influence on patients’ health. The implementation and elaboration of these policies also varied widely across European countries. In addition, there is a diversity in medicinal products and situations exempted from INN prescribing and generic substitution for practical and patient safety reasons.

This research investigated how INN prescribing in Belgium was prepared for the implementation in electronic prescribing and the electronic medical record. We describe the corresponding detailed operational rules, which include an exhaustive list of exemptions, and the reference database, containing the classified therapeutic arsenal to be implemented in commercial software. We showed the strengths and limitations of INN prescribing perceived by Flemish general practitioners, pharmacists, medicine students and pharmacy students. An overview of the regulation of INN prescribing and generic substitution in different European countries was made, including a comparison of the exemptions related to these policies. Finally, differences in pharmacokinetic outcomes due to switching between medicinal products was investigated through an individual bioequivalence trial with gabapentin 800 mg tablets.

This thesis can serve as a basis for European and national regulatory authorities to evaluate, optimize and harmonize the regulation on INN prescribing and generic substitution.

1. MAIN FINDINGS

Chapter 1 describes the Belgian project to prepare the implementation of INN prescribing in electronic prescribing and the electronic medical record. It shows that a structured approach, involving all stakeholders is crucial. For projects involving different stakeholders (such as regulatory authorities, innovative and generic pharmaceutical industry, software vendors, health care professionals and academia), it is important to take into account and combine all different interests. If not, this might jeopardize a successful outcome (Chapter 2). Transparently reporting the implementation approach can be useful for other countries as it provides important lessons learned.

In Chapter 2, the results of an opinion survey with general practitioners (GPs) and pharmacists are presented. The general opinion was that INN prescribing can contribute to rational drug prescribing and utilization and to reduce pharmaceutical expenditures. However, INN prescribing should be carefully elaborated, and not solely be turned into a cost-containment measure. The GPs and pharmacists indicated that the policies introduced in spring 2012 impaired continuity of treatment and could therefore compromise patient safety. GPs also
mentioned a need to implement INN prescribing in their medical software (Chapter 1). This study showed that many issues can be avoided by first consulting the stakeholders who will be affected by the new policies (Chapter 1).

The medicine students and pharmacy students in Chapter 3 confirmed the opinions of their peers (Chapter 2), but they also recognized the potential benefits of INN prescribing. Students wish that INN prescribing is more prominently, but not exclusively, taught during training. Their attitudes favor a more thorough and rational implementation of INN prescribing in education and in clinical practice.

In Chapter 4, we explored the differences between European countries with regard to INN prescribing regulation and the related concept of generic substitution (which is not allowed in Belgium). Some countries allow both INN prescribing and generic substitution, but usually only one is endorsed or is even mandatory. Similarly to the Belgian regulation (Chapter 1), most countries selected medicinal products which are not suitable for INN prescribing and/or generic substitution. Although most countries exempt medicinal products referred to as narrow-therapeutic index drugs (NTIDs), for example antiepileptic drugs (AEDs), immunosuppressive agents, cardiac glycosides and thyroid hormones, these national lists of NTIDs also differ widely. This variation might be explained because of the lack of an official European definition and exhaustive list of NTIDs. Therefore, countries such as Belgium, had to rely on definitions and information from outside Europe and from national regulating authorities within Europe, with own definitions and already established lists of exemptions (Chapter 1).

A potential rationale for exempting certain products from INN prescribing and/or generic substitution (Chapter 4) was studied in Chapter 5. The results of the clinical trial showed that the brand and generic product of 800 mg gabapentin are bioequivalent, also on the individual subject level. This means that switching between this brand and generic product does not result in differences in pharmacokinetic parameters (AUC0-inf and Cmax) and that both products are thus interchangeable. The AED gabapentin was used as the test molecule, as AEDs are, by principle, frequently exempted from INN prescribing and/or generic substitution (Chapter 1 & Chapter 4). These results can strengthen the confidence of health professionals and patients in bioequivalence and interchangeability between brand and generic products. The results also provide valuable information for regulatory authorities occupied with elaborating the regulation on INN prescribing and/or generic substitution.

2. IMPLICATIONS FOR PRACTICE

To make from INN prescribing the success story it can be, there are several points that need further attention. Changes to the concept of INN prescribing might also be needed, both in Belgium and Europe. The points of attention and changes involve different aspects, such as harmonization of the regulation, guaranteeing the continuity of treatment, smooth implementation in electronic prescribing and in medical and pharmaceutical education.

Below we discuss these points of attention and make suggestions for changes in Belgium and Europe.

120
2.1. POINTS OF ATTENTION FOR BELGIUM

In Belgium some inconsistencies between the regulation on INN prescribing and other regulation and reimbursement policies need to be clarified. This is necessary to avoid confusion and reluctance of prescribers and to benefit from INN prescribing as an alternative, high-quality way of prescribing.

2.1.1. INCONSISTENCIES

Controlled drugs

The first inconsistency is related to the Belgian law on controlled drugs [1,2] which obliges the prescriber to specify the total amount of product to be dispensed and write it in full (e.g. ‘thirty tablets’ instead of ‘30 tablets’). However, the total amount of product to be dispensed is not a standard item on an INN prescription, where this amount is determined by combination of daily dose and duration of treatment. Writing the total amount of product to be dispensed in full is a precautionary measure to avoid confusion and misreading when prescriptions are written by hand. However, nowadays, most prescriptions are electronically written and printed, which decreases the chance of confusion substantially. It should be discussed by the regulatory authorities how to manage this inconsistency. It might be possible that the total amount of units to be dispensed is calculated and added automatically by the prescribing software or is added manually by the prescriber in case of a paper prescription. In addition, controlled drugs can also be exempted from INN prescribing, as is the case in some European countries (e.g. France and Spain).

Pro re nata use

The second inconsistency is related to pro re nata (PRN) use (if-needed use), where it is difficult to determine the exact amount of intakes and duration of treatment. We suggest that in this case, the prescriber indicates a maximum amount of units to be dispensed per day and per treatment period.

Groups of cheapest medicinal products available

Next are some important differences between the rules for the operationalization of INN prescribing applied by the Belgian medicines agency (FAGG/AFMPS), described in Chapter 1, and the rules applied by the health insurance institute (RIZIV/INAMI) for defining the groups of cheapest medicinal products available. Although the health insurance institute refers to the rules described in Chapter 1 for making an INN prescription, it applies different rules for dispensing an INN prescription.

The first difference is that the groups of cheapest medicinal products available contain an additional key element, i.e. package size. This element had to be included in response to the policies introduced in 2012 and to define which products are the cheapest (based on the price per unit). The package size also links the reimbursement rules to INN prescribing.

The second difference is the operationalization of the third key element, method of administration, for the groups of cheapest products available. The method of administration, described in Chapter 1, refers to a list of...
General Discussion

23 single terms and 13 combination terms to categorize the Belgian therapeutic arsenal into groups of interchangeable products. Different terms are used for determining the groups of cheapest products available, such as ‘solid oral’, ‘solid oral, delayed action’, ‘liquids’ and ‘injections’ [3]. These different terms are not in line with the terms used to make a correct INN prescription. It leads to fragmentation of the groups of cheapest medicines, which could have been avoided, by aligning with the rules for the operationalization of INN prescribing.

Thirdly, the third key element is not always referred to as ‘method of administration’ in the documents and on the website of the health insurance institute. It is sometimes referred to as ‘way of administration’ or ‘method/way of administration’. This jumble of terms and definitions should be avoided in order not to further contribute to confusion and reluctance against INN prescribing.

Reimbursement policies

Finally, some inconsistencies with several reimbursement policies need to be addressed. For reimbursable medicinal products, the duration of treatment is limited to 92 days [4]. As a result, when the daily dose is one unit per day, large medicinal product packages containing more than 92 units cannot be prescribed by INN and are not eligible for reimbursement. This is because in a ‘once daily’ regimen, the duration of treatment would exceed those 92 days. However, dispensing one large package is usually cheaper than dispensing multiple smaller ones. Therefore, we recommend to extent the limit in duration of treatment to make it possible to prescribe and dispense the largest available package for products with a ‘once daily’ regimen.

Another reimbursement policy related to INN prescribing states that the amount of units dispensed cannot exceed the amount of units determined on the prescription, in order to obtain reimbursement. Therefore, it might occur that a much smaller package need to be dispensed if there is no suitable package size available. This might result in an abrupt discontinuation of the treatment and in additional, but unnecessary, consultations. This might occur if a physician prescribes, for example, a 14-day treatment with 3 times a day 50 mg diclofenac. In this case, 42 tablets should be dispensed. However, on the Belgian market only packages of 30 and 50 tablets are available. As a result of the above described reimbursement policy, the patient should be dispensed a package of only 30 tablets, which implies a treatment of only 10 days. To avoid such situations, we suggest to determine which packages sizes can be dispensed based on specific ranges of units (e.g. 30 to 50 tablets prescribed means that packages up to 50 tablets can be dispensed).

2.1.2. FIXED PACKAGE SIZES

The above described inconsistency with the current reimbursement policies also addresses the problem related to the available and fixed packages sizes.

Package sizes are mainly suitable for the recommended daily dose and duration of treatment. However, economical and practical aspects, with regard to the production, packaging and distribution process, are also taken into account by the pharmaceutical companies. As a result, available package sizes are not always in line with the prescribed treatment, which can lead to substantial waste of medicinal products. When patients are
(unnecessarily) dispensed a large package, they also have access to excessive amounts of medicinal products at the same time. This can lead to potential dangerous situations such as overdosing.

**Individual medication packaging**

A possible solution for INN prescribing and non-adjusted package sizes can be individual medication packaging (IMP). IMP is when one or multiple medicinal products for one patient are taken out of their primary package and rearranged in a closed individual package format for administration at a certain point of time. IMP for ambulatory care is in Belgium possible since December 2012 [5]. It was introduced to contribute to the role of the pharmacist as caregiver and is mainly used for (older) patients with polypharmacy. The aim is to detect and solve medication errors in order to prevent adverse drug reactions, to reduce overconsumption and to improve patient safety and medication adherence [6]. Currently, IMP is a developing concept as it is only advised for certain groups of patients and only possible for predefined (groups of) medicinal products (such as solid products for oral administration, e.g. tablets, capsules) [7]. However, before considering IMP, related practical and economical aspects should be taken into account. These aspects concern investments related to specific infrastructure (space, equipment, quality control, transport) and staff which are necessary for a qualitative IMP process [6–8]. In Belgium, pharmacies offering IMP receive a standard fee (e.g. per dispensing, per patient or per period) from the health insurance to compensate for the investments made [9].

INN prescribing can be linked to IMP. This implies a step back from fixed package sizes, which are usually related to a specific manufacturer. However, it should be discussed whether the advantages of IMP and INN prescribing can outweigh the additional investments and costs.

### 2.1.3. CONTINUITY OF TREATMENT

Maintaining continuity of treatment, in particular for chronic treatment, is another point of attention for INN prescribing regulation. To address this, different scenarios are possible. In the first scenario, with regard to the obligation to dispense one of the three cheapest medicinal products with an INN prescription, an exemption can be introduced, for example for treatments exceeding a period of 28 days. The second scenario involves a quarterly or biannually update of the lists of cheapest medicinal products, instead of a monthly one.

Frequent medication switches can result in reduced treatment persistence [10,11] and can confuse patients [12,13]. Confused patients are at risk for erroneous drug use, e.g. involuntary duplicate intake [14], medication non-adherence [15], unnecessary complications, therapeutic failure and even disability and death [16]. The resulting costs can override the savings made by INN prescribing and generic substitution [12]. Patient confusion is mainly caused by changing appearance of the switched medicinal products, e.g. changes in pill color [17–20]. Therefore, a third scenario involves the compulsory improvement of medicinal product packages and their appearance, as is also mentioned by other researchers [11,17,19–21]. We suggest a standardization of products packages in terms of color and labelling, with a more prominent position for the INN. For the appearance of the medicinal product, a standardization in terms of color, shape and taste is recommended.
2.1.4. ANTIEPILEPTIC DRUGS

As described in Chapter 1, all available AEDs in Belgium are on the NO SWITCH-list. The main reason for including AEDs on this list was patient safety, as many of the AEDs are considered as NTIDs or very toxic molecules. No distinction was made between AEDs with or without NTI and therefore also AEDs such as gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, stiripentol, tiagabine, topiramate and vigabatrine were included. However, the results of the clinical trial presented in Chapter 5 challenge the place of AEDs without NTI on the NO SWITCH-list, in particular gabapentin (800 mg tablets). Besides the distinction between AEDs with and without NTI, also the indication for prescribing AEDs is important. There is no doubt that epilepsy is an unpredictable disease which causes uncertainty in patients and can have serious consequences when therapy fails. However, some AEDs can also be prescribed for other indications, e.g. gabapentin for the treatment of neuropathic pain, pregabalin for neuropathic pain and anxiety disorders and topiramate for the prophylaxis of migraine in adults. It can be questioned whether also a distinction based on indication should be made.

The results of Chapter 5 also indicate that the differences in pharmacokinetic outcomes between branded and generic gabapentin 800 mg tablets can be neglected and are probably not the cause of a potential therapy failure in case of a medication switch. As described above, a possible explanation for therapy failure after switching between bioequivalent products can be the lack of medication adherence. However, it must be said that our clinical trial was performed in healthy volunteers and only used a single dose treatment.

2.1.5. RATIONAL STOCK MANAGEMENT

INN prescribing can contribute to a more rational stock management in the pharmacy. However, as indicated by pharmacists in Chapter 2, this is currently not possible as the lists of cheapest products available change on a monthly basis. Therefore, the above suggested quarterly or biannual update of these lists might contribute to rational stock management.

In addition, public tenders for outpatient care can be another option to improve stock management and to stimulate price competition for medicinal products. Tendering can be defined as a method where large volumes of medicinal products are bought from the manufacturer with the best offer [22]. It is frequently used in hospital settings. Tendering can contribute to transparency in the use of public budgets and is mostly implemented for a period of one year or longer [22,23].

In addition, pharmacists mentioned that the policy of May 2012, for acute treatment with antibiotics or antifungal agents, can also be extended towards other groups of medicinal products, in order to contribute to rational stock management. However, extending this policy towards medicinal products for chronic treatment will implicate a major change and should be carefully considered. If the Belgian regulatory authorities are planning to extend this policy towards other groups of medicinal products, these groups should be carefully chosen, in order to assure patient safety, to prevent serious adverse drug reactions and potential extra costs. These extra costs can derive from additional consultations and medical tests and from the treatment of ADRs, due to frequent medication switch [24,25]. Some precautionary measures, such as the NO SWITCH-list and the
possibility for the prescriber to deviate from the obligatory switch, were already taken when introducing the policy, but it remains important to manage the other issues described above. In addition, data confirming the overall financial benefits of (automatic) switching towards the cheapest product available is currently lacking [26].

2.1.6. REASONS FOR RELUCTANCE TOWARDS INN PRESCRIBING

The results of Chapter 2 and Chapter 5 showed that the reluctance of prescribers towards INN prescribing is usually not the result of a distrust in the quality of generics, which previously existed [13,19,27–30]. The possible explanation for the limited success of INN prescribing is twofold. Firstly, parallel to the introduction of INN prescribing, also the quota for prescribing cheap medicines were introduced and prescribers can be penalized if they do not meet their quota. Secondly, INN prescribing was never stimulated by providing a financial compensation for prescribers nor was it related to a minimum percentage of INN prescriptions that had to be prescribed. In contrast, pharmacists receive a (small) fee for each INN prescription which is dispensed. Fixing the imbalance for provided fees related to INN prescribing can be a progress in the right direction [31], also for improving the relationship and collaboration between physicians and pharmacists.

In addition, the policies introduced in 2012 imply that only the three cheapest medical product packages are reimbursed. When patients wish to receive their regular medicinal product, they are obliged to pay the full price of the medicinal product package. This detrimental obligation and restriction of the patients’ and prescribers’ free choice can also contribute to the existing reluctance.

Electronic INN prescribing

Furthermore, as commented in our study presented in Chapter 2, making an INN prescription with prescribing software or documenting it correctly in the patient’s medical file is (often) not possible. Therefore, INN prescribing should be implemented in medical software as soon as possible and, later on, also being rolled-out in e-prescribing. The largest part of the preparatory work is already done, as described in Chapter 1. It should also be possible for the prescriber to receive detailed information on the dispensed medicinal product package. Additionally, to assure continuity of treatment with INN prescriptions, every pharmacist (and the GP of the patient) should also have access to a shared patient’s pharmaceutical file. The first private initiative to accomplish such a shared pharmaceutical file between pharmacies was already taken in 2014 [32]. However, sharing information between pharmacies and other health professionals is not possible yet [33]. Providing access to patient-specific information for physicians, pharmacists and also the patient is necessary to guarantee patient safety, but privacy and protection of personal information should also be taken into account.

Liability

The importance for the prescriber to receive detailed information about the dispensed medicinal product package is also related to liability. Prescribers can still be accountable if the dispensed medicinal product results in an ADR, even if a switch was performed at dispensing level and without the prescriber’s permission [13].
Within the framework of the recently applied reimbursement policies for INN prescribing and/or generic substitution, it might be appropriate to review the liability conditions for each stakeholder involved in the drug utilization process (e.g. the regulatory authorities, the health insurance institute, pharmaceutical industry, the prescriber, the pharmacist, the patient).

2.1.7. EDUCATION

Medicine and pharmacy students recognized the potential benefits of INN prescribing. Therefore, more focus on INN prescribing in education can stimulate young physicians to prescribe by INN, in order to further reduce the pharmaceutical expenditures. The beneficial effect of teaching INN prescribing is already proven in England, with 83% of all prescriptions written by INN in 2009 [34].

However the suggestions described above are recommended from a Belgian point-of-view, they can also be applicable to other European countries, provided adjustments towards each country’s specific health care system and prescribing regulation.

2.1.8. POTENTIAL SAVINGS

As the last point of attention, the savings accomplished by introducing the new policies on INN prescribing in spring 2012 should be discussed. One year after the introduction, a saving of €9.8 million for the health insurance and €3.7 million for patients was estimated [35]. Although every saving is beneficial and can result in scarce resources being more efficiently used, these savings should be interpreted taking into account the annual pharmaceutical expenditures. These were €2,700 million for the health insurance and €500 million for patients in 2012 [36]. This means that the new introduced policies lead to a saving of only 0.36% and 0.75% for the health insurance and patients, respectively.

2.2. POINTS OF ATTENTION FOR EUROPE

2.2.1. INN PRESCRIBING & GENERIC SUBSTITUTION

In Europe, INN prescribing is, at the moment, only regulated at the national level. However, the results of this thesis indicate that there is a need for European guidelines and regulation to harmonize the differences in national regulation.

We make suggestions for topics to be addressed in these European guidelines with regard to INN prescribing. However, these suggestions may also be applicable for generic substitution, provided that it is allowed.

Firstly, we suggest to establish an official definition of a NTID within Europe and an exhaustive list of active ingredients considered as NTID. There is a strong need for this definition and corresponding list as shown in Chapter 1. This need is also confirmed by the results of Chapter 4, as many countries considered different active ingredients as NTID when establishing their regulation on INN prescribing and/or generic substitution.
Secondly, because of the large differences between European countries in (groups of) medicinal products exempted from INN prescribing and/or generic substitution, we believe a scientific-based, European guideline might be useful. In this way, information can be provided on which (groups of) medicinal products are not advised to be prescribed by INN or to be substituted. Based on the results of Chapter 4, a European guideline might exempt anti-arrhythmia agents, biologicals and biosimilars, cardiac glycosides, coumarin anticoagulants, thyroid hormones and products used with specific aids. For immunosuppressive agents, it should be discussed whether these should only be exempted when indicated for the prophylaxis of graft-versus-host disease, as suggested by the Netherlands. Whether to exempt antiepileptic agents which are only indicated for epilepsy should also be discussed and in particular gabapentin, taking into account the results of Chapter 5. In addition, more clinical trials to establish individual bioequivalence, such as ours described in Chapter 5 and access to results of clinical (bioequivalence) trials performed by sponsors can provide additional information to make these decisions. This latter is already attributed as since 21 July 2014 sponsors are obliged to publish clinical trial summary results in the European Clinical Trial (EudraCT) database, managed by the European Medicines Agency [37].

Thirdly, similar to some national regulation, we recommend that the European guideline also describes specific situations in which INN prescribing and/or generic substitution are not advised and includes the possibility for prescribers to prohibit it (e.g. for patient-specific reasons). When establishing this guideline, it might be useful to study, evaluate and take into account all the situations described in national regulation, in particular the difference made between medicines for acute and chronic treatment e.g. in Italy.

2.2.2. UNIFORMIZATION OF MEDICATION APPEARANCE

National standardization of medication appearance and packages might reduce patient confusion and contribute to medication adherence. Standardization on a European level might also be beneficial, in particular when medicines are imported from other (European) countries. Medication import can occur in two situations. The first is when certain medicinal products are not available in a country, because it has no marketing authorization (yet) or it is temporarily or not yet available. This is mainly applicable for hospital pharmacies. The second situation refers to parallel import of medicinal products. Parallel import is when medicinal products manufactured for a national market in a European country are imported and sold in another European country, mainly for commercial reasons [38–40].

Within the framework of medication import, we believe that it can also be useful to standardize the Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL) per group of interchangeable products and within Europe. Differences in information in SPCs and PILs of interchangeable products exist both on a national and European level [41,42]. These differences might also confuse patients and therefore compromise medication adherence.
2.2.3. PHARMACOVIGILANCE

Chapter 1 described INN groups comprising interchangeable products and labelled by three key elements (the therapeutic moiety/INN, the strength and the method of administration). This universally applicable concept can also be useful in pharmacovigilance, e.g. the Periodic Safety Update Report (PSUR) synchronization list. The synchronization list is the result of a work sharing and synchronization project under the auspices of the Heads of Medicines Agencies (HMA) and the European Risk Management Strategy Facilitation Group (ERMS FG) [43]. Currently, this list is only based on one element: the INN [44]. Adding ‘strength’ and ‘method of administration’ to the INN and assuring accurate identification and codification procedures can provide more detailed information and more in-depth review of the benefit-risk balance of medicinal products.

2.3. INN PRESCRIBING IN HOSPITAL SETTING

The regulation on INN prescribing and generic substitution described in this thesis is mainly, if not only, established for outpatient care. However, INN prescribing and generic substitution are concepts which can be and are used in a hospital setting. The regulation of these concepts should distinguish between (1) the medicinal products exclusively used in hospitals and (2) medicinal products available in the hospital and used in both outpatient and inpatient care. The implementation and operationalization will depend on whether electronic prescribing or paper prescribing is used and whether therapeutic substitution is possible (see further). The regulation will also be influenced by which medicinal products are available in the hospital, sometimes determined by tendering, and whether medicines formularies are applied (which mainly include brand products).

Medication management is an important part of seamless care, which is the continuity of care between different healthcare settings [45,46]. INN prescribing can result in budget savings when applied at discharge as the cheapest medical product will be dispensed for newly prescribed medication. It can also contribute to maintaining continuity of treatment as the patient’s regular home medication will be dispensed. Provided some suggestions to assure continuity of treatment mentioned above are taken into account, INN prescribing in hospital setting (at discharge) can contribute to seamless care.

2.4. THERAPEUTIC SUBSTITUTION

Therapeutic substitution can be defined as switching the prescribed medicinal product towards another product with assumed equivalent therapeutic effect. The other product may be within the same therapeutic class (e.g. switch from omeprazole towards pantoprazole) or can be from another class (e.g. switch from a proton pump inhibitor (PPI) towards a H2-antagonist) [13].

Therapeutic substitution occurs often automatically when patients are admitted to hospital, where formularies are applied for practical reasons (e.g. stock management, availability of space, budgets). Automatic therapeutic substitution should be possible between medicinal products from the same therapeutic class where no significant difference could be detected. It mainly occurs for medicinal products such as H2-antagonists, PPIs, statins, ACE-inhibitors, insulins and laxatives [47,48]. Therapeutic substitution can contribute to cost savings in both in- and outpatient care, but only when applied in a rational way and taking into account a patient centered
approach (e.g. seamless care). However, whether therapeutic substitution by non-clinicians (e.g. at the public pharmacy) should be possible has to be investigated and discussed carefully.

2.5. BIOLOGICALS & BIOSIMILARS

A biological medicinal product (also referred to as a ‘biological’) is defined as a product which contains a biological substance. This substance is produced by or extracted from a biological source. Biological substances and their production process are subject to physico-chemical and biological tests, in order to control their characteristics and to determine their quality. Examples of biologicals are recombinant proteins, monoclonal antibodies, medicinal products derived from human blood and plasma and immunological medicinal products [49,50].

A similar biological medicinal product (also referred to as a ‘biosimilar’) is defined as a product similar to its reference biological product. The active substance of a biosimilar is a known biological active substance and is similar to the reference medicinal product. Biologicals and biosimilars are in general indicated for the same conditions and are expected to have the same safety and efficacy profile [49,50].

It is clear that due to their biological origin, biologicals and biosimilars are not ordinary medicines, containing reproducible chemical compounds. The current scientific and technological innovations result in more biologicals and biosimilars being introduced, which makes the assignment of INNs and establishment of bioequivalence more complex and challenging [51]. This latter and whether biologicals and biosimilars should have the same INN is being extensively discussed by different stakeholders, including proponents and opponents [52–57]. Therefore, this issue is investigated and anticipated by the WHO Program on INNs, in order to guarantee transparency, effective data collection and a pharmacovigilance system that prioritizes patient safety [51].

In anticipation of decisions on the nomenclature and appropriate methods for the establishment of interchangeability, biologicals and biosimilars are exempted from INN prescribing and/or generic substitution in some European countries (e.g. Belgium, Finland, Lithuania and Spain).

3. IMPLICATIONS FOR FURTHER RESEARCH

The INN nomenclature was established in a logical way in order to contribute to rational drug naming, prescribing and dispensing. The INNs have distinct sound and spelling and pharmacologically related active ingredients can be recognized by their common suffix. It might be useful to make scientists, including health professionals, more aware of the strengths of the INN nomenclature and the advantages of using the INN for prescribing.

In Chapter 2 and 3, the attitudes of (future) physicians and pharmacists towards INN prescribing one year after the introduction of the austerity measures in Belgium were investigated. It would be interesting to explore the current attitudes of the GPs and pharmacists who participated in 2013 and investigate whether and how their attitudes have changed. For the medicine and pharmacy students, a follow-up study should explore whether and how their attitudes have changed after some years of practical experience. For both future studies a questionnaire or a qualitative approach with e.g. semi-structured interviews or focus groups can be used.
Chapter 4 compares the exemptions related to INN prescribing and/or generic substitution between 16 European countries. The comparison of the percentage of INN prescriptions and/or prescriptions substituted per country could add valuable information to this research. However, this will be a serious endeavor as data on how medicinal products are prescribed (by brand name, by branded generic name or by INN) and which products are dispensed (brand product or generic product) need to be collected. The data should be compared within the framework of each country’s prescribing and reimbursement regulation. In addition, data on generic drug utilization and the cost savings through INN prescribing and/or generic substitution might be compared for all European countries.

Furthermore, the evolution of policies involving INN prescribing and/or generic substitution within each country can be investigated in future research. It should be interpreted together with the effect of the policy changes on the percentages of INN prescriptions and/or substitution and the achieved cost savings. This can provide an insight in important lessons learned from other countries.

4. STRENGTHS & LIMITATIONS

This thesis was the first to investigate thoroughly different aspects of INN prescribing in Belgium and Europe from a scientific point of view.

It provides detailed information on how Belgium prepared INN prescribing for the implementation in electronic prescribing, which can serve as a basis for other countries planning to operationalize electronic INN prescribing. This thesis addressed the shortcomings of the Belgian regulation of INN prescribing and provides suggestions for improvements. It also contains an overview of important differences in the regulation of INN prescribing for 16 European countries. It shows the need for a European guideline on this topic in order to harmonize the differences between countries and suggestions for topics to be addressed in this guideline are given.

During this research, a clinical trial in 30 healthy volunteers was performed to investigate interchangeability between a brand and generic product and thus the potential pharmacokinetic rationale for exempting certain products from INN prescribing and/or generic substitution. The results of this study can contribute to the confidence of health professionals and patients in generics and interchangeability, provided correct medication use and adherence. This study also provides detailed information for researchers interested in performing individual bioequivalence studies. Although different (groups of) medicinal products are exempted, we only investigated interchangeability for gabapentin, an AED which is frequently exempted from INN prescribing and/or generic substitution, despite it is not considered as an NTID.

The aim was to present an internationally applicable research. However, in certain aspects this thesis focusses on Flanders and Belgium. Therefore, some outcomes might be perceived as reflecting a regional and national perspective. Despite this, large parts of this thesis can be applicable and useful for other European countries, provided correct interpretations and adoptions.
In this thesis, we focused on INN prescribing (and generic substitution) in outpatient care. However, it would also be interesting to investigate whether INN prescribing is applied in hospitals, how it is regulated and whether there are differences between different hospitals and across European countries. In addition, an overview of how regulatory authorities and hospitals across Europe try to accomplish seamless care could be useful in order to share good ideas and pitfalls.

For the 16 European countries in this thesis we did not investigate pricing and reimbursement policies, nor did we investigate the percentages of generic drug utilization. A full pharmaco-economic appraisal of prescribing regulation, and in particular INN prescribing regulation is still to be performed.

Finally, the issues related to assigning INNs and establishing interchangeability of biologicals and biosimilars are currently being extensively discussed in different media. As biologicals and biosimilars cannot be treated as ordinary medicines, they were beyond the scope of this thesis and therefore not further discussed.

5. FINAL VIEW

The concept of INN prescribing comprises many potential benefits, as described throughout this thesis. However, we also addressed a number of attention items related to INN prescribing. These need to be addressed at national and European level in order to make INN prescribing an attractive, high quality way of prescribing with advantages for physicians, pharmacists, patients and the health insurance.

To turn INN prescribing into the preferred method for rational drug prescribing, the different interests from all stakeholders need to be aligned. Implementation of INN prescribing should foster rational prescribing, decrease pharmaceutical expenditures, without compromising patient safety and without restraining innovation in pharmaceutical industry, and promote and protect the health of all European citizens.
REFERENCES

1. Koninklijk besluit houdende regeling van de slaapmiddelen en de verdovende middelen en betreffende risicobeperking en therapeutisch advies. 31 december 1930.


37. European Medicines Agency. Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014.


44. Heads of Medicines Agencies. List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised - September 2014.


52. GaBI Journal - Generics and Biosimilars Initiative Journal


# LIST OF TABLES & FIGURES

| Figure 1 | All International Nonproprietary Names (INNs) for Angiotensin-Converting Enzyme (ACE) inhibitors, with their common suffix ‘-pril’ | 20 |
| Figure 2 | Timeframe for the regulation of INN prescribing, the ‘reference reimbursement system’ and the quota for prescribing ‘cheap’ medicines in Belgium | 22 |
| Figure 1.1 | Timeline for the INN prescribing project | 39 |
| Figure 1.2 | The INN group principle and the decision-support illustrated by (a) alprazolam divisible tablets, (b) ceftazidime I.M. injection and (c) gabapentin capsules | 41 |
| Table 1.1 | Denominators to express the strength of pharmaceutical forms | 43 |
| Table 1.2 | Single term options for the third key element ‘method of administration’ in English, Dutch & French and combination term options in English | 44 |
| Table 1.3 | Pharmaceutical products and categories with the ‘NO SWITCH’ label | 46 |
| Figure 1.3 | Screenshot from the reference database | 49 |
| Table 2.1 | Demographic characteristics and representativity (for mean age and gender) of the survey sample | 62 |
| Table 2.2 | Percentage of participants agreeing (agree + strongly agree) per statement for the overall survey sample and per subgroup | 63 |
| Table 2.3 | Results of the univariate and multivariate analysis of the influence of demographic characteristics on the sum score for ‘benefits’ and ‘drawbacks’ for general practitioners | 65 |
| Box 2.1 | Themes and topics commented on the open question | 66 |
| Table 3.1 | Demographic characteristics and representativity of the survey sample | 80 |
| Table 3.2 | Percentage of students agreeing (agree + strongly agree) for all statements and per subgroup. Results of the Chi²-test for different opinions between both groups of students | 81 |
| Table 4.1 | Overview of countries contacted, participating and validated | 91 |
| Table 4.2 | Overview of the applied regulation of medicines prescribing and generic substitution | 92 |
| Table 4.3 | Overview of most common groups of products exempted from INN prescribing and/or generic substitution | 94 |
| Figure 5.1 | Summary of the study design with the two-sequence fixed design (R1/T1/R1/T1 or T1/R1/T1/R1) and the additional batches of reference (R2) and test (T2) before and/or after the fixed design | 106 |
| Table 5.1 | Demographic characteristics of the study population | 109 |
| Table 5.2 | Mean (SD) of AUC₀⁻ᵗ, AUC₀⁻∞, Cₓₘₐₓ, Tₘₐₓ and T₁/₂ with N = 27 | 110 |
| Figure 5.2 | Plasma concentration-time curve of gabapentin | 111 |
| Table 5.3 | Average bioequivalence (ABE) analysis results for AUC₀⁻∞ and Cₓₘₐₓ parameters and bioequivalence (BE) conclusion | 111 |
| Table 5.4 | Individual bioequivalence (IBE) analysis results for AUC₀⁻∞ and Cₓₘₐₓ parameters, with IBE limit θ = 2.5 and bioequivalence (BE) conclusion | 112 |
| Figure 5.3 | Within-subject variability of AUC₀⁻∞ after replicate administration of reference and test | 112 |
| Figure 5.4 | Within-subject variability of AUC₀⁻∞ after administration of two different batches of the reference product | 114 |
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