Generic interchangeability

Generic Interchangeability: between science and regulation

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Contents

Chapter 1.1

General Introduction

This thesis addresses generic interchangeability. The first chapter discusses generic drugs from a historical context and why it is so important to study their interchangeability.

Pharmacological treatment has an important position in health care. In high-income countries, about 20% of all money spent on health care goes to pharmaceuticals (1). For good reason, as humanity greatly benefits from antibiotics, vaccines, and chemotherapy, to name a few. Nonetheless, pharmacological treatment has come a long way. Even late in the 19th century, treatment was primarily based on herbal remedies, and only a few effective therapeutic agents were available (2). The state of 19th-century pharmacotherapy was famously characterized in a quote by the eminent physician and Harvard professor Oliver Wendell Holmes Sr. (1809–1884): *"throw out a few specifics … throw out wine… and the vapors which produce the miracle of anaesthesia, and I firmly believe that if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, - and all the worse for the fishes"* (3).

Nonetheless, clinical pharmacology has been in development. Its scientific basis was established at the end of the 18th century by the empirical approach of Francois Magendie (1783–1855) and Claud Bernard (1813–1878) in the early 19th century. The discipline of pharmacology was further established later in the 19th century by Rudolf Buchheim (1820–1879) and Oswald Schmiedeberg (1838–1921). Within their research institute, they set high standards for the methodology of experimentation and applied physiochemical reasoning to explain the biological effects of therapeutic agents (4). The improved scientific principles in pharmacology led to conducting experiments instead of using hearsay regarding therapeutic activity.

Although this did not immediately lead to increased availability of effective therapeutic agents in the 19th century, the foundations for drug discovery were established. However, more progress could be made only due to parallel developments in physiology, pathology, and chemistry.

Regarding chemistry, the purification of morphine by the pharmacist Friedrich Sertürner (1783–1841) at the beginning of the 19th century was the start of natural product chemistry and proved that plants hold active substances that possess the therapeutic proprieties of those plants (5). Developments in synthetic organic chemistry started when Friedrich Wöhler (1800–1882) prepared urea from a nonliving origin. Further developments in synthetic chemistry and

theories of structure aided in the availability of various chemical compounds in the 19th century (6, 7). This chemistry evolution was the main driver for drug discovery until deep into the 20th century. For instance, in the 1950s, the discovery of the first benzodiazepine, chlordiazepoxide, was purely driven by synthetic chemical benchwork (8).

In parallel, the medical interpretation of the cell theory by Rudolf Virchow (1821-1902) and the germ theory by Louis Pasteur (1822–1895) laid the foundations for understanding pathology and possible targets for pharmaceutical treatment (2, 3). Nonetheless, pathophysiological reasoning became more important in drug discovery only later in the 20th century. For instance, the discovery of propranolol in the 1960s was fully based on the understanding of a clinical problem and the search for the most suitable beta-receptor antagonist (9).

Drug discovery was aided considerably by the growth of local pharmaceutical businesses into the larger-scale pharmaceutical industry. Although there were only a limited number of effective therapeutic agents available in the 19th century, increased profit from their commercialization allowed for intensified research and development in drug discovery.

An example of the move toward the modern-day research-based pharmaceutical industry was the local apothecary Merck who, in 1827, started selling morphine and other high-purity compounds refined from plants (10). Shortly after, other apothecary businesses followed (2). However, it was not until 1856 that the discovery of mauveine by William Henry Perkin (1838–1907) sparked the realization that synthetic organic chemistry could also be commercially interesting (2, 3, 6). Two decades later, in 1874, large-scale production of salicylic acid was possible, as Hermann Kolbe (1818–1884) discovered its chemical structure and method of synthesis (11).

With the upcoming large-scale production and distribution of prefabricated drug products, the need increased for a more structured control and regulation of these products. The control of medicinal products has been relevant for thousands of years. Even in ancient Greece and Egypt, institutions were tasked with controlling pharmaceutical products (2). In modern history, this was primarily organized by pharmacopeias, authoritative lists of how to prepare and use drugs, which is essentially a form of indirect quality control. The oldest documented pharmacopeia from modern times is probably the pharmacopeia

of the Italian city of Florence, issued in 1498 by the local guild of physicians and pharmacists. Actual inspections have been documented of 'syrup makers' in medieval Muslim countries in the 9th century and 'drug-shops' in the Italian city Salerno in the 10th century (12).

Earlier control and regulation were focused on fraud and adulteration, but in light of the emergence of refined natural and newly synthesized chemicals in the 19th century, they focused more on quality, purity, and safety (12). Until 1938, premarket toxicity testing was not required for drugs, at least in the United States (US). Legislation requiring premarket toxicity testing was drafted in 1933, but its acceptance in 1938 was triggered by a therapeutic catastrophe in 1937. The solvent diethylene glycol was used to meet the demand for a liquid formulation of sulfanilamide, primarily for children, but soon after, it was discovered that the liquid formulation had a significant risk of acute kidney failure (13).

In Europe, another therapeutic catastrophe in the early 1960s led to the most significant drug regulation reform. The widely used sedative and morning sickness drug thalidomide was identified in the late 1950s to cause severe congenital disabilities and was withdrawn from the market. Most European countries had some form of drug regulation in place at that time, but the thalidomide catastrophe triggered intensified drug regulation. The United Kingdom, France, Switzerland, Norway, and Sweden had already advanced drug regulations. Notably, in Norway, as early as 1928, legislation was in place that required proof of efficacy (14). From the 1960s and 1970s onwards, emphasis was placed on demonstrating a clear positive benefit versus risk of new drugs before approval in all European countries (2). In the Netherlands, the Medicines Evaluation Board, responsible for assessing the safety and efficacy of drugs, was officially installed in 1963 (15, 16). In the US, the 1962 Kefauver-Harris Drug regulation set the requirement to demonstrate safety and efficacy preapprovals (2, 12, 13, 17, 18).

Up to this point, the modern generic drug industry did not exist. At that time in the US, drugs that were not protected by a patent were produced and sold by small-scale drug manufacturers, strengthening the public image that off-patent drugs were often subject to adulteration, illegally produced, and inferior to branded drugs. Several factors enabled the rise of the modern generic drug industry in the US. First, the patent expired for numerous drugs from the 1940s and 1950s. Second, the attention drawn to the subject by the Kefauver Senate

hearings from 1959 to 1960 solidified the position of generic drugs. Third, drug efficacy studies started in 1966, affirming the therapeutic value of all drugs approved by the Food and Drug Administration (FDA), which made it easier for generic drug makers to refer to them. Fourth, as of 1969, regulatory hurdles for generic drugs were lowered by the FDA, as it was deemed sufficient to demonstrate the chemical equivalence to the newly off-patent drugs. Finally, the potential market for cheaper drugs increased with the growth of government-sponsored access to health care (19).

By then, market approval in the US for a generic drug could be obtained by specifying compliance with compendia standards for the quality of the generic drug. However, in the late 1960s, the first studies were reported, demonstrating a difference in the bioavailability of chemically equivalent drugs. In 1974, an expert panel concluded that equivalent bioavailability, or bioequivalence, could not be ensured by the current standards and regulations. Additional research was recommended to improve the assessment and prediction of bioequivalence, including a need to identify for which drug classes direct evidence of bioequivalence should be required (20). By 1984, the Hatch-Waxman Act was passed in the US, which clarified that demonstrating bioequivalence was mandatory for registration of generic drugs (17, 21). This act truly established the modern generic drug industry in the US.

The European history of the generic drug industry is not as well documented as in the US. Nonetheless, comparable factors likely influenced the growth of this industry. Most importantly, the preference for lower-cost generic drugs and the need to reduce healthcare spending are universal. In addition, the Treaty of Rome in 1957 created the European Economic Community and the start of free trade agreements across EU member states, facilitating access to a larger market for drugs (22).

In the EU, approval for market access of generic drugs was separately arranged in each member state. The requirements for the market approval of generic drugs were primarily based on scientific literature and FDA regulations (23). Although these national requirements were based on the same scientific principles, guidance for conducting and analyzing bioequivalence studies was often not specific or unavailable (24).

In 1987, the Nordic Council on Medicines took the first step toward European harmonization, in which Denmark, Finland, Iceland, Norway, and Sweden

jointly published the Nordic Guidelines *Bioavailability Studies in Man* (23, 25-27). This step was soon followed in 1991 by the commission of the European Communities, with the first European guideline on bioequivalence: *Note for Guidance: Investigation of Bioavailability and Bioequivalence* (25). The Australian regulatory agency adopted these guidelines, and although many differences between bioequivalence requirements for generic drugs existed globally, this marked the start of international harmonization (28). Since then, the harmonization of regulatory requirements for bioequivalence has been achieved in many ways but is still ongoing (29).

In general, the current guidance defines bioequivalence as two similar drug products of which the rate and extent of their bioavailability after administering the same dose do not exhibit significant differences and lie within acceptable predefined limits (30, 31). Bioequivalence studies should be performed so that all variables but the variability of the compared drug products are reduced to a minimum. As detailed in the guidance, this is usually a randomized single-dose crossover study, with two study periods and two sequences. The main outcome parameters for the demonstration of bioequivalence are the maximum plasma concentration (C_{max}) and the plasma concentration-time area under the curve (AUC), representing the rate and extent of the bioavailability. The statistical evaluation is based on 90% confidence intervals for the geometric mean ratio of C_{max} and AUC, which should lie within the acceptance interval of 80.00% to 125.00% (30, 31). The limits of this acceptance interval translate to a maximum difference of 20% for the average C_{max} and AUC. This value was arbitrarily set based on the opinion of FDA medical experts to be the maximum tolerable difference that would not lead to a significant difference in the therapeutic activity between the compared drug products (32).

The guidance on bioequivalence further describes numerous aspects of adequate bioequivalence testing, such as the study design, chosen study population, and analytical methodology. Common issues for discussion on these general requirements for the demonstration of bioequivalence from the viewpoint of a regulator are described in chapter 1.2.

In theory, adequately demonstrated bioequivalence and, thus, the absence of significant differences in bioavailability would ensure the therapeutic equivalence of a generic drug compared to an originator drug. However, some patients, physicians, and pharmacists negatively perceive the efficacy and safety of generic drugs and drug switches (33). In addition, adverse drug reactions (ADRs) associated with generic drug switches are reported regularly (34). Thus, a mismatch between theory and practice seems to exist. In this thesis, we investigate the validity of this apparent mismatch.

Thesis Aim

With this thesis, we aim to study generic interchangeability issues in clinical practice and challenge the robustness of the current bioequivalence requirements.

Thesis Outline

In the first part of this thesis, we investigate patient-reported clinical discomfort using a systemic approach. Therefore, we study the number of ADRs related to drug switches and place these into perspective by identifying the number of people switching between (generic) drug products. In chapter 2.1, we study the frequency of drug switches in the Netherlands for a selection of 20 active substances for which switch-related ADRs are most often reported. In chapter 2.2 we analyze the reported ADRs concerning the number of drug switches. Additionally, in chapter 2.3, we investigate the reasons for generic drug switching in the Netherlands in a pilot study.

In the second part of this thesis, given that demonstrated bioequivalence should ensure therapeutic equivalence, we investigate the robustness of the applied bioequivalence methodology. Using modeling and simulation, we investigate whether a conclusion of bioequivalence in a healthy population holds for a vulnerable patient population with altered pharmacokinetic characteristics. In chapter 3.1, we report the model validation of a non-parametric pharmacokinetic model of gabapentin based on the exposure data for gabapentin, following the administration of the originator and three generic drug products in healthy subjects. In chapter 3.2, we perform simulations with the gabapentin model to possibly identify patient subpopulations for whom aberrant pharmacokinetic profiles are more likely to occur upon switching to or between bioequivalent generic drug products. Last, chapter 4 provides an integrated discussion of the findings from the individual articles included in this thesis. First, in chapter 1.2 we describe the current requirements for demonstrating bioequivalence and the common issues for discussion from the regulator's viewpoint.

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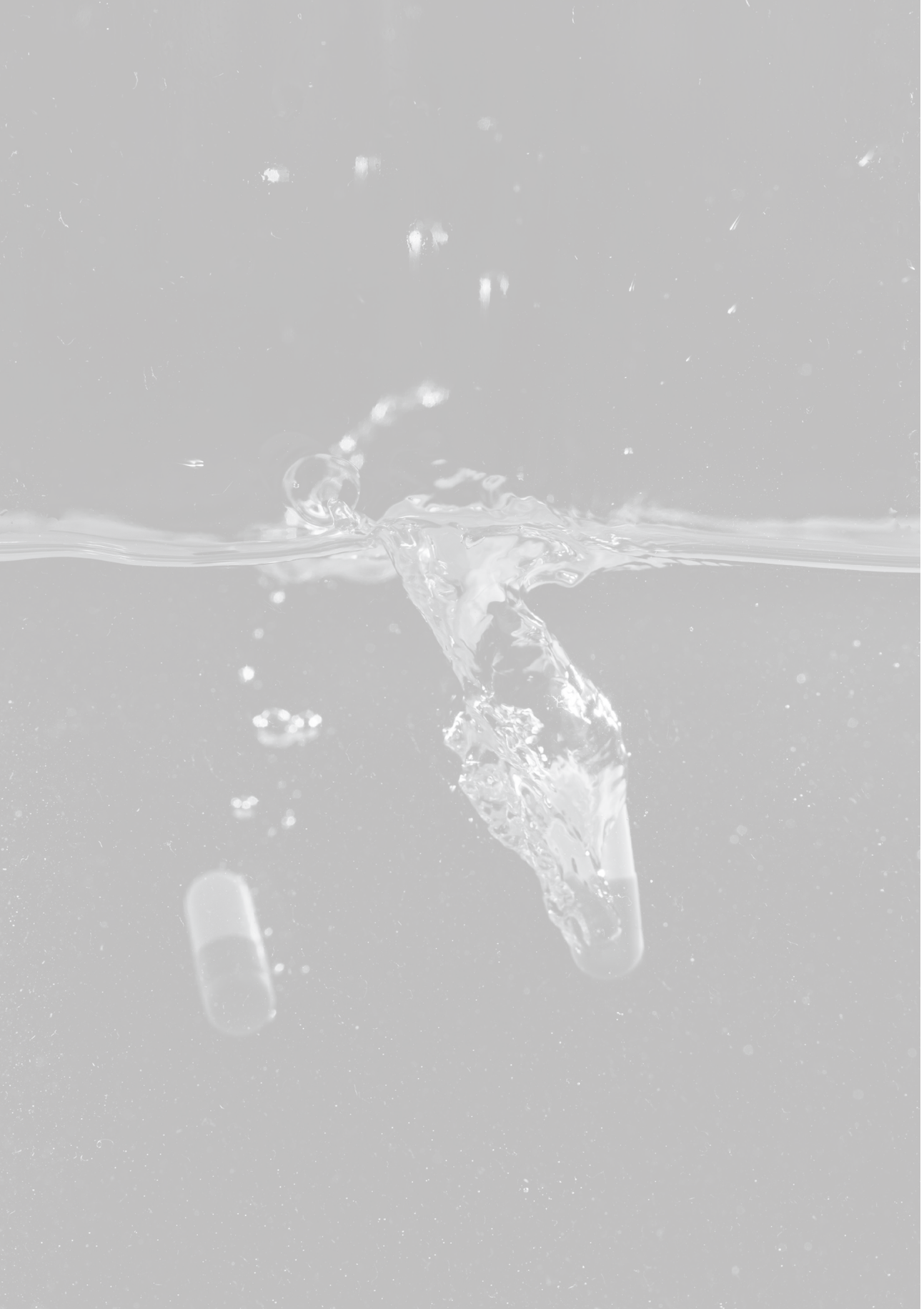

Chapter 1.2

Pharmacokinetics and generic drug switching: a regulators view

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Abstract

There appears to be a mismatch between the assumed therapeutic equivalence of generic drugs, their interchangeability, and reported clinical discomfort following generic drug use and drug switches. In this paper, we describe why we are of the opinion that the current regulatory approach to the evaluation of generic drugs based on average bioequivalence is sufficient to expect therapeutic equivalence in the clinical setting. This has often been debated, specifically since adverse drug reactions related to generic drug switches are regularly reported. We agree that clinical discomfort during a bioequivalent drug switch may indeed be caused by different exposures to the active substance. However, this difference in exposure is not a result of the characteristics or quality of generic drugs; it is caused by the pharmacokinetic within-subject variability of the active substance. Therefore, reported clinical discomfort following generic drug use and drug switches does not warrant a change in the regulatory approach to the evaluation of the bioequivalence of generic drugs. Switching from a brand-name drug to currently approved generic drugs, or between different generic drugs, will result in comparable exposure, within boundaries determined by the within-subject variability of the pharmacokinetics of the active substance involved.

A demonstration of bioequivalence is the cornerstone of generic drug registration. Two pharmaceutically comparable drug products of high quality are bioequivalent if there is statistical proof of comparable bioavailability. For immediate release drugs with systemic action, this comparable bioavailability is usually investigated in a randomized, two-period, two-sequence, single-dose crossover study. The evaluation is predominantly based on the area under the plasma concentration-time curve (AUC) and maximum peak plasma concentration (C_{max}), which reflect the extent of exposure and peak exposure and therefore allow for a comparison of exposure over time. Already in the early 1970s, the Canadian authorities used the arbitrary cut off of at least 80% bioavailability to compare different drug products (1), and the use of a confidence interval for the statistical test was proposed (2). Current guidance dictates that, generally, the 90% confidence intervals for the geometric mean ratio of C_{max} and AUC between the two products, should be within the acceptance interval of 80.00–125.00% (3).

For active substances with a within-subject variability of over 30%, the US Food and Drug Administration allows a widening of these acceptance limits for AUC and C_{max} depending on the within-subject variability of the active substance (4). In the European Union (EU), widening of the acceptance limits is similarly allowed but can only be applied to C_{max}, and it is maximized to a range of 69.84–143.19%, which is the limit when a within-subject variability of 50% is determined. In addition, both in the US and in the EU, acceptance limits can be tightened to 90.00–111.11% for active substances with a narrow therapeutic index.

Several aspects of the regulatory approach to the concept of bioequivalence have been debated over the years. Ever since the first proposal of the confidence interval limits, the width of this acceptance range has been challenged (5), mainly raising the question as to why the same arbitrary limits are applied to all active substances. Partly because of those discussions, in current regulation, a narrowing or widening of the confidence interval limits is allowed. Independent of the confidence interval limits applied, it is known that the ratio of the exposure to the active substance from the generic and brand-name drug is within a much smaller range than allowed with the above-mentioned criteria, as indicated by an analysis of 2,070 bioequivalence studies by Davit et al. in 2009 (6). In that analysis, they demonstrated that the mean estimated difference

between generic and brand-name drugs was only 4.35% for C_{max} and 3.56% for AUC. For the European situation, based on a smaller subset of 120 bioequivalence studies, comparable figures were obtained (7).

Another point of debate has been that bioequivalence studies are usually conducted with healthy subjects and not with the intended patient population. It has often been questioned whether the bioequivalence conclusion, as drawn in a healthy subject population, can be extrapolated to patients. Indeed, absolute exposure may be different for patients compared to healthy subjects. However, this difference is active-substance-related and similarly influenced by, for example, patient comorbidities, for both brand-name drugs and generic drugs. As discussed by Versantvoort et al., the relative exposure between the brand-name and generic drugs will be the same in healthy subjects and patients (8). One further reason for assessing bioequivalence using healthy subjects is that in these subjects, with generally less comorbidities than patients, it is expected that less variability of exposure is observed that is unrelated to the differences between the tested drug products (3). This is relevant, since the primary goal of a bioequivalence study is to investigate differences between the tested drug products, and to measure them in the most sensitive way, other variability should be minimal. Healthy subjects are the most suitable model for that purpose. Likewise, the pharmacokinetic behavior of drugs can be markedly different in men versus women (9) or in patients with different degrees of, for instance, renal function; in this situation, this also applies to an identical extent for brand-name drugs and generic drugs. Therefore, demonstrating bioequivalence for both sexes does not seem to be necessary; bioequivalence demonstrated in males can safely be extrapolated to females and vice versa, as discussed by Gonzalez-Rojano et al. (10).

Nevertheless, it is useful to empirically test the assumption of comparable relative exposure in patients versus healthy subjects. For this purpose, a well-controlled comparative bioavailability study was recently performed with kidney and liver transplant patients, and similar tacrolimus exposure for brand-name and generic drugs was concluded, in line with the expectation based on studies in healthy subjects (11). Likewise, bioequivalence as determined in healthy subjects between different generic lamotrigine drugs (generic-generic switch) was confirmed in patients with epilepsy (12).

These findings support the current approval pathway for generic drugs and

the notion that bioequivalent drugs are expected to be therapeutically equivalent. However, this assumption is based on bioequivalence: comparable average exposure in the whole population. A treating physician or prescriber would predominantly be interested in therapeutic equivalence for their individual patient. This presumed therapeutic equivalence is often debated, for instance for cardiovascular drugs (13) and drugs for psychiatric illness (14). Although in a large observational study, no substantial differences in clinical outcomes were observed between patients who started treatment with either generic or brand-name warfarin (15), and in a clinical crossover study evaluating bupropion exposure in patients with major depression, the bioequivalence of three generic drugs to the brand-name drug and between the three generic drugs was confirmed, and no differences in depressive symptoms or side effects were noted (16), clinical evidence from unbiased randomized controlled trials, for the assumed absence of clinically relevant differences in exposure between generic and brand-name drugs, is limited (17).

Indeed, if bioequivalent drugs are therapeutically equivalent, then it is unexpected that patients experience clinical discomfort related to generic drug switches. Adverse drug reactions (ADRs) related to generic drug switches are reported regularly, as evident from case reports (18, 19), and observational studies (Glerum, et al., CTS, in press) (20). The following questions then arise: What causes this apparent discrepancy between theory (assumed interchangeability of generic drugs) and real-world observations (reported clinical discomfort upon switching to a generic drug), and could the explanation still be found in pharmacokinetic aspects underlying such a generic switch?

For example, a recent article by Concordet et al. describes issues related to a levothyroxine drug switch in France affecting more than 2.5 million patients in 2017 (20). Even though bioequivalence was demonstrated between the old and new formulation of levothyroxine used in the switch, applying the tightened 90.00–111.11% acceptance range (21), more than 30,000 ADRs were reported following this massive drug switch. Based on this levothyroxine case, Concordet et al. argue that a demonstration of average bioequivalence is not sufficient to ensure switchability. They also argue that tightening the acceptance limits for the average bioequivalence 90% confidence intervals is insufficient, as the width of the 90% confidence interval is inversely related to the number of studied subjects and therefore still may allow marked differences in exposure upon

switching (22). Moreover, according to the authors, since more than 50% of the subjects in the supporting levothyroxine bioequivalence study (21) demonstrated an individual pharmacokinetic exposure ratio outside the 90.00–111.11% confidence interval, acceptance criteria should have been a warning signal of a possible lack of individual bioequivalence and a lack of individual therapeutic equivalence. Therefore, the authors argue that a priori characterization of both the subject-by-formulation interaction and the within-subject variability, as in the concept of individual bioequivalence, would have identified switchability issues and would have allowed for a better regulatory assessment of the new levothyroxine formulation.

The Concordet articles have been extensively commented upon, with discussions mainly related to difficulties and shortcomings of the individual bioequivalence approach and of the calculation and interpretation of the number of subjects in a bioequivalence study with an individual exposure ratio outside the bioequivalence acceptance criteria (23-30). The debate clearly indicates that consensus has not been reached on the issue of the interchangeability of drugs based on demonstrated average bioequivalence.

In our opinion, within-subject pharmacokinetic variability is the most important factor in this debate. As demonstrated by Yu et al., there are clear indications that within-subject variability has far more influence than subject-by-formulation interaction for drugs for which bioequivalence has been demonstrated (31). In Yu et al.'s article, it was demonstrated for a selection of drugs that the variability of exposure following a switch from a brand-name drug to a generic drug is comparable to that observed upon repeated administration of either the brand-name drug or the generic drug. It is indeed acknowledged that in bioequivalence studies, subjects will often have an individual exposure ratio outside the acceptance criteria (32), a situation we also observe in results from bioequivalence studies filed for regulatory approval of generic drugs. However, it is crucial to realise that the same phenomenon occurs when comparing the exposure of two repeated administrations of the same brand-name or generic drug; therefore, this finding is merely a reflection of the daily clinical situation upon treating a patient, with his or her inherent within-subject variability leading to different exposures per occasion, than a reflection of differences in the quality and/or exposure of a generic drug. Experimental and analytical errors add to the observation of different exposures, as demonstrated well by the simulations in the comment article by Munafo et al. (28).

Thus, when a patient experiences clinical discomfort during a bioequivalent drug switch, it may indeed be caused by a different exposure to the active substance. However, this different exposure is not a result of different characteristics of the bioequivalent drug, but because of pharmacokinetic within-subject variability, unrelated to the different drug products. When we assume that the difference in exposure is related to the perceived clinical discomfort in a patient, this clinical discomfort is not attributable to differences between the original and switched drug, but merely to pharmacokinetic within-subject variability.

The question then remains as to why larger numbers of ADRs are reported in the case of drug switches than in the case of drug continuation. In line with the above reasoning, a potential explanation could be that patients and prescribers are more prone to report ADRs, since negative perceptions about generic drug switching and forced drug switches persist. This would imply that drug switching does not increase the actual number of ADRs, but merely increases the reporting rate of ADRs. In relation to another relatively large-scale levothyroxine drug switch, in 2007 and 2008 in New Zealand, the increased number of reported ADRs in that setting has been postulated to be caused by an increased reporting rate because of inaccurate guidance information and media attention (33). Another potential explanation for an increased number of reported ADRs related to drug switches is postulated to be a nocebo effect, particularly due to the negative perceptions of generic drugs (34, 35). However, the psychological aspects potentially affecting increased ADR reporting are outside the scope of this opinion paper, and any such hypothesis would warrant further investigation. Regardless of the true cause of the increased number of reported ADRs, clinical discomfort for an individual patient should never be underestimated and should always undergo thorough causal and clinical review, both on an individual level (doctor) and on a population level (pharmacovigilance). With regard to the individual patient specifically, it is important to stress that we do not want to disregard any clinical discomfort that a patient may experience. The discomfort exists, and it can have a significant impact on the quality of life. In highly exceptional cases, this could be a result of an allergic response to excipients used in the new drug product.

Furthermore, as a regulatory agency, we see it as our responsibility to be critical of our own rules and regulations. For this reason, we investigated bioequiva-

lence and the underlying assumptions of generic interchangeability, for instance by performing a bioequivalence study between registered gabapentin generics (36); a retrospective analysis of bioequivalence studies submitted for regulatory evaluation (31), modelling and simulation efforts towards generic drugs (37); and an analysis of 1,348 reported ADRs and 23.8 million drug switches (38), to investigate the potential consequences of generic drug switching.

So far, these and other data have not provided evidence to support a change in our current regulatory approach to the evaluation of bioequivalence, and they remain in support of the assumption that switching from a brand-name drug to currently approved generic drugs, or between different generic drugs, will result in comparable exposure within boundaries determined by the within-subject variability of the pharmacokinetics of the active substance involved.

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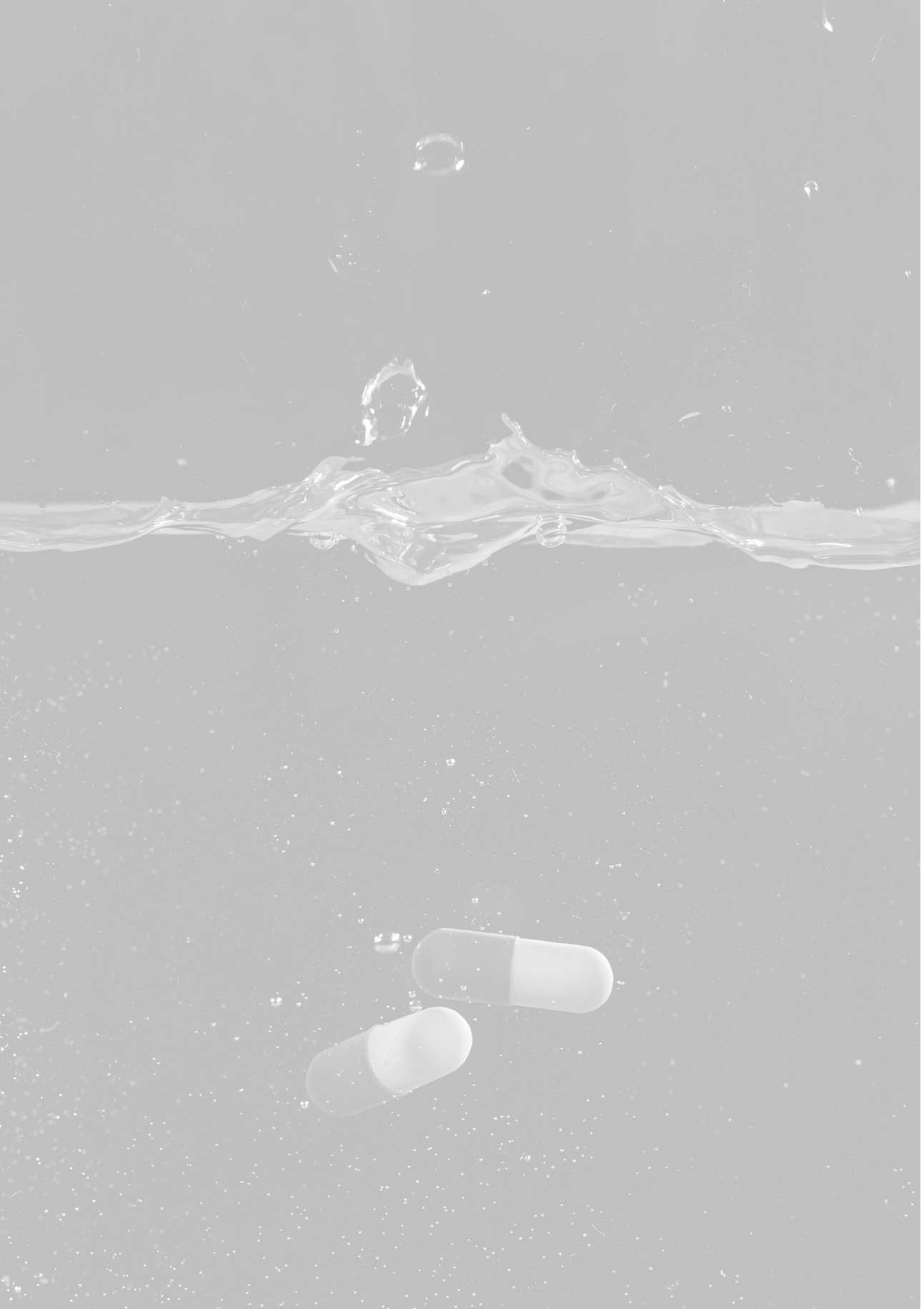

Chapter 2.1

Drug Switching in the Netherlands: A Cohort Study of 20 Active Substances

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Abstract

Background

For a patient, drug switches are not desirable (either between a brand-name drug and a generic drug, or between two generic drugs of the same active substance). Research into the causes of drug switches, and related adverse drug reactions, is hampered by the absence of quantitative data on drug switches.

Methods

We describe the frequency of drug switches in the Netherlands for a selection of active substances. A retrospective cohort study was conducted using the Drug Information System of the National Health Care Institute in the Netherlands. We studied the Dutch patient population from mid-2009 to 2016. The selection of active substances (n = 20) was made based on a report by Lareb, the Netherlands Pharmacovigilance Centre, on adverse drug reactions related to drug switching, and we used qualitative and quantitative descriptive analyses. A drug switch is defined as the replacement of a patient's prescribed drug with a similar drug from a different manufacturer.

Results

We identified 23.8 million drug switches on a total of 206 million (11.6%) similar drug dispenses. The frequency of drug switches demonstrated a yearly peak in the period from January to March. In some months, for atorvastatin, losartan, pantoprazole, and irbesartan, more than 60% of similar drug dispenses were drug switches. Most drug switches (80.3%) were between two generic drugs, and 0.12% of these involved a drug from a European parallel import. The proportion of drug switches between two brand-name drugs decreased from 14.5% to 5.53% during our study period, and of these, 86.5% involved a drug from a European parallel import.

Conclusions

Drug switching is common in the Netherlands, and most of the drug switches we studied are between generic drugs. The observed annual peak of drug switches is most likely explained by a specific Dutch reimbursement policy. Not only are the data valuable as is, but they also serve as a first step towards elucidating the reasons for the occurrence of these drug switches. In addition, these data can be used to put into perspective the adverse drug reactions associated with drug switching.

Background

The use of generic drugs is an important tool to reduce healthcare spending. For instance, in the United States (US), generic drugs cost as little as 6% of the price of brand-name drugs, mainly because of the lower cost of research, development, registration, and competition between drug companies (1, 2). In the US, 90% of all dispenses are a generic drug (3); however, the market penetration of generic drugs differs worldwide. In Japan, the market share of generic drugs was only approximately 23% at the end of 2012, but it is expected to increase (4). Furthermore, the market share varies greatly in European countries, for example between 17% in Switzerland and 83% in the United Kingdom (5).

Although the use of generic drugs is financially desirable, these drugs are not always well received. A substantial proportion of physicians, pharmacists, and the general population have a negative perception of the quality, efficacy, and safety of generic drugs and drug switches (6). In addition, adverse drug reactions (ADRs) associated with drug switches are regularly reported to Lareb, the Netherlands Pharmacovigilance Centre (7). Thus, clinical discomfort is experienced with a drug switch, and are a clear downside of the use of generic drugs from the perspective of the patient. In this paper, we use the term drug switch for a switch between 2 similar drug products of the same active substance, which can either be between a brand-name drug and a generic drug or between two generic drugs.

Drug switches are thus not desirable, and studies should be conducted to determine how the frequency of drug switches can be kept low. However, before the reasons for drug switches can be explored, a first step should be to investigate the frequency of those switches. This is largely undocumented, apart from a recent effort of the US Food and Drug Administration (FDA) (8). Therefore, we aim to study the frequency of drug switches and additionally explore some of the reasons that could influence this frequency. Furthermore, in a future study, we aim to refine previously mentioned analyses of switch-related ADRs, since the number of drug switches is missing from that analysis. Given this future aim, we limit our study to the 20 active substances described in the ADR report and focus on the Netherlands.

The Netherlands is a country with a large generic drug market share of 75.6%. Drugs are not prescribed by brand name, but by name of the active substance, and a generic drug is dispensed in 97% of cases, if a generic option is available (9). A possible reason for the large market share is that health insurance companies in the Netherlands are authorized by law to select a drug product (either a generic or brand-name drug) eligible for reimbursement from a group of interchangeable drug products with the same active substance; this is known as the 'Preference Policy' (10). Contracts between insurance companies and drug product manufacturers typically last 1 or 2 years, and the choice of drug product is predominantly based on price (11) and is thus most likely to be a generic drug. Preferred drug products change on a regular basis, and patients are forced to switch between them. Other reasons for drug switches can only be hypothesized, as no overview of the Dutch situation exists. These reasons could originate from any action of the insurer, wholesaler, pharmacy, prescriber, pharmacist, or patient; drug shortages; and patients changing healthcare insurance companies (4–10% of the Dutch population each year) (12-14). Parallel imports from drug products can also play a role. A parallel import is allowed if a drug is registered in the European Union (EU) and deemed (virtually) identical to a drug registered in the Netherlands (15).

We studied drug switches in the claims database of the National Health Care Institute in the Netherlands (ZIN). By studying the extent of drug switches and the trends in their frequency in the Netherlands, the role of influencing factors such as the Preference Policy can be postulated.

Aim of the study

The aim of this study is to describe the frequency of drug switches for a selection of active substances, in the Netherlands, in order to better understand generic drug use, and the Dutch process of drug switching and related influencing factors.

Methods

We conducted a retrospective cohort study with qualitative and quantitative descriptive analyses. The cohort is 96% of the insured Dutch population, using a selection of 20 active substances. The study is reported in line with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (16).

Drug switches

Drug switches were obtained from the Drug Information System (GIP) of the ZIN. This database contains information on reimbursed drugs prescribed by general practitioners and specialists and dispensed by pharmacists or dispensing general practitioners. It does not include drugs dispensed within hospitals in the Netherlands.

A drug switch is defined as the replacement of a patient's prescribed drug with a similar drug dispensed within the preceding 150 days, for the same active substance, same strength, and same route of administration, but with the drug product coming from a different manufacturer. The drug products before and after the switch could both be generic or brand-name drugs.

We allowed a 150-day difference between dispenses in our definition because in Dutch practice, drugs are usually dispensed for 90 days of treatment. We also allowed a safety margin of 60 days extra to account for possible non-adherence and for early dispenses. If the difference between two dispenses was more than 150 days, we assumed that the patient had stopped and started a new treatment episode. Moreover, the date of the dispense was used as the best estimate of the moment when the patient actually experienced the drug switch.

We collected data to quantify the number of repeat dispenses using identical selection criteria, but with both dispenses of a drug product coming from the same manufacturer. We use the term consecutive dispenses for the sum of repeat dispenses and drug switches.

Active substances

The selection of 20 active substances was based on a study by Lareb in 2017 that described active substances with more than 25 ADR reports associated with drug switching between 2006 and 2016 (7). The following active substances (20) are included in this study: atorvastatin, enalapril, esomeprazole, ethinylestradiol/levonorgestrel, irbesartan, levothyroxine, losartan, metformin, methotrexate, methylphenidate, metoprolol, omeprazole, pantoprazole, paroxetine, perindopril, rivastigmine, salbutamol, salmeterol/fluticasone, simvastatin, and venlafaxine. Of note, while the total number of active substances was 20, the total number of unique Anatomical Therapeutic Chemical (ATC) codes was 21. This is because methotrexate can be used as an antineoplastic agent (ATC: L01BA01) and as an immunosuppressant (L04AX03).

We defined the time frame of our study according to the maximum availability of data, which was 7.5 years from 01 June 2009 to 31 December 2016.

Data analyses

Data were aggregated on a monthly basis, as this was expected to maximize to potential to study the influence of the Preference Policy. We performed descriptive analyses, including total number, minimum, median, and maximum number of drug switches per month. The pattern of drug switches was visually assessed using a plot of drug switches over time, an overlay plot of total drug switches per year separately, and mathematically by autocorrelation. Autocorrelation was calculated as the number of drug switches in a month, divided by the number of drug switches in a previous month, varying from 1 to 18 months, to identify the lag time in months, which results in the highest correlation.

Furthermore, the number of drug switches is expressed as a percentage of the total number of consecutive dispenses, and the numbers of generic-to-generic (GG), brand-name-to-generic (BG), generic-to-brand-name (GB), and brand-name-to-brand-name (BB) drug switches, as well as the total number of drug switches involving parallel import products, were calculated. In a bar plot, the study period was divided into tertiles to provide a general impression of changes over time. Lastly, drug switches were studied for each active substance, and the analysis for atorvastatin is presented as an example.

We identified the Dutch brand name and EU reference dates from the GIP database (17), the database of the Dutch Medicines Evaluation Board (18), and the EU reference date list (19). The EU reference date is the earliest EU-known marketing authorization for the (combination of) active substance(s).

Data management

Data were extracted from the GIP database using SAS Enterprise Guide software (version 7.1). Monthly aggregated data were exported as a Microsoft Excel workbook and imported into R software (version 3.5.0) (20) using the package 'xlsx' (21). Moreover, qualitative and quantitative descriptive analyses as well as data visualization were performed using base R and R Studio (22).

Results

Dataset

We identified 23.8 million drug switches on a total of 205.6 million (11.6%) consecutive dispenses. The median percentage drug switches of consecutive dispenses for the included active substances ranged between 15.8% for ethinylestradiol/levonorgestrel and 1.75% for levothyroxine (see Table 1). In some months, for atorvastatin, losartan, pantoprazole, and irbesartan, more than 60% of consecutive dispenses were drug switches.

The highest number of drug switches in a single month for a single active substance – simvastatin – was 149,497 on a total of 328,184 (46.7%) consecutive dispenses in January 2015. The highest number of drug switches in a single month – January 2016 – for a unique combination of drug products before and drug products after the switch was 41,659, which is 96.6% of all 43,107 atorvastatin drug switches in that month.

INN	Brand name	EU reference date	Average yearly drug switches	Average yearly repeat dispenses (not switching)	% drug switches median (range per month)
ethinylestradiol/ levonorgestrel	Microgynon®	April 1965	63,824	331,419	15.8% (7.44–48.9)
atorvastatin	Lipitor®	November 1996	264,776	1,297,895	15.0% (4.71–68.1)
salmeterol/ fluticasone	Seretide®	October 1990	104,663	689,450	14.4% (3.10–26.2)
perindopril	Coversyl®	June 1988	161,155	890,803	14.0% (4.31–34.2)
losartan	Cozaar®	September 1994	118,979	735,195	12.0% (3.94–63.6)
simvastatin	Zocor®	April 1988	559,303	3,220,461	11.8% (3.24–47.4)
paroxetine	Seroxat®	December 1990	112,555	754,569	11.8% (4.63–38.2)
pantoprazole	Pantozol®	Augustus 1994	289,171	1,897,439	10.7% (4.06–63.2)
irbesartan	Aprovel®	Augustus 1997	58,854	398,297	9.93% (0.00–60.8)
venlafaxine	Efexor®	September 1993	55,719	416,314	9.61% (5.78–39.9)
metformin	Glucophage®	March 1959	252,557	2,231,914	9.41% (2.82–32.3)
omeprazole	Losec®	April 1987	361,669	2,977,064	9.39% (3.38–28.7)
esomeprazole	Nexium®	March 2000	94,460	761,959	8.98% (4.40–48.6)
methotrexate (immunosuppressant)	Metoject®	July 2003	21,310	171,876	8.70% (4.05–35.8)
enalapril	Renitec®	January 1985	102,387	1,027,850	7.69% (2.82–23.1)
metoprolol	Lopresor®	February 1975	359,131	3,479,555	7.41% (3.58–29.9)
salbutamol	Ventolin®	January 1969	65,047	789,636	7.29% (4.24–13.7)
methylphenidate	Ritalin®	October 1954	29,472	529,279	4.81% (2.59–15.7)
rivastigmine	Exelon®	May 1998	4,051	53,243	4.02% (0.00–20.3)
methotrexate (antineoplastic)	Ledertrexate®	September 1974	2,090	60,219	2.21% (0.00–46.4)
levothyroxine	Thyrax Duotab®	January 1952	66,909	1,252,976	1.75% (0.28–26.0)

Table 1 Overview of the active substances investigated, with INN, brand name (in the Netherlands), EU reference date, average yearly drug switches, average yearly number of repeat dispenses (not switching), and percentage of drug switches of consecutive dispenses per month (median, range) from June 2009 to December 2016. Active substances are tabulated in descending order by median drug switch percentage.

Drug switch pattern

An overview of the pattern of drug switches between June 2009 and December 2016 is depicted in Fig. 1 and Fig. 2. The pattern of drug switches for the active substances included in this analysis was characterized by seasonality, with most drug switches between January and March of each year between 2010 and 2016. A statically significant positive correlation was observed with a lag of 12 months (autocorrelation = 0.597), which confirms the annual pattern.

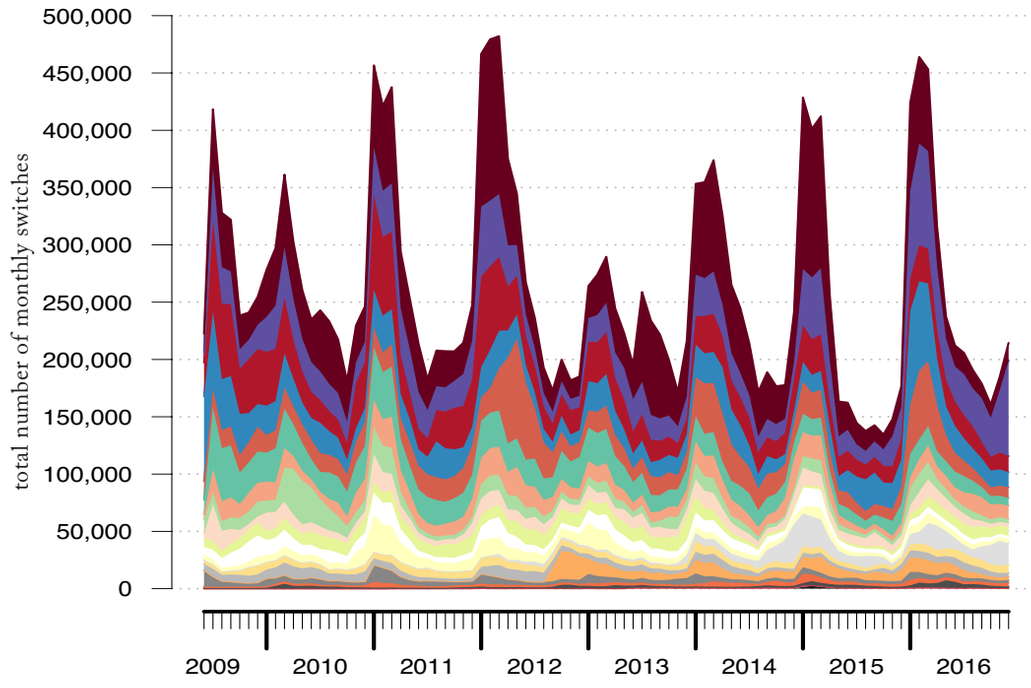

Fig. 1 Stacked area chart over time of total number of drug switches per month per active substance from June 2009 to December 2016 in the Netherlands. Active substances are ordered from top to bottom by descending total number of drug switches during the study period. The total number of monthly drug switches is on the y-axis, and the time period of the study is on the x-axis.

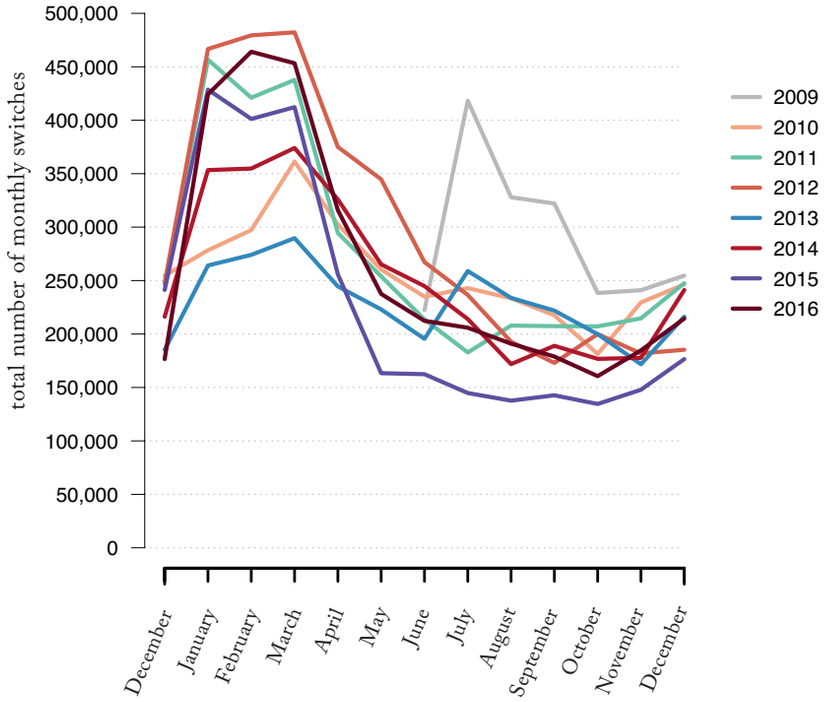

Fig. 2 Total number of drug switches per month from June 2009 to December 2016 in the Netherlands for the 20 active substances combined, as an overlay plot in the timeframe of 13 months. Each line represents 13 months of drug switches from December (previous year) to December.

Brand-name drugs versus generic drugs – type of drug switch

Of all drug switches in our study, only 7.09% (range of active substances 0.00–29.1%) were BG switches. Most drug switches (80.3%, range 0.18–100%) involved a GG switch, while GB switches accounted for approximately 3.52% (range 0.00–17.3%) of drug switches, and 9.06% (range 0.00–99.4%) involved a BB switch of drugs with the same active substance. The distribution of drug switches per drug in tertiles of the time period between June 2009 and December 2016 is illustrated in Fig. 3.

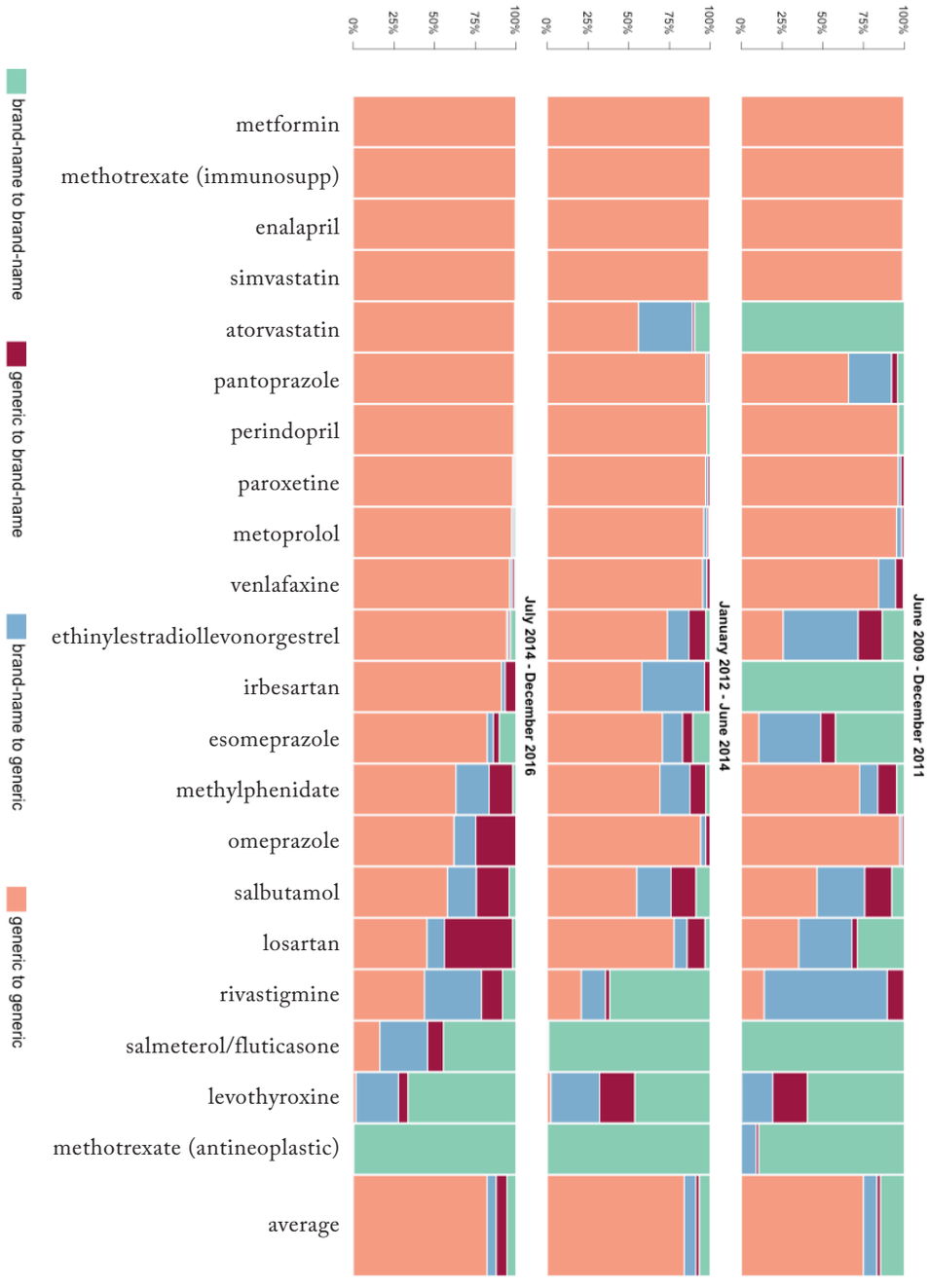

Fig. 3 (turn thesis 90 degrees clockwise) Percentage distribution of type of drug switch per active substance (green: brand-name to brand-name, red: generic to brand-name, blue: brand-name to generic, orange: generic to generic) in descending order by percentage of generic-to-generic drug switch in the last period. Bar plots are (top down) for the periods from June 2009 to December 2011, January 2012 to June 2014, and July 2014 to December 2016.

For a number of active substances included in our study, the distribution of the type of drug switch remained relatively stable over the 91 months. However, the type of drug switch involving atorvastatin, irbesartan, esomeprazole, ethinylestradiol/levonorgestrel, salmeterol/fluticasone, omeprazole, losartan, and rivastigmine changed over time. Over these 91 months, atorvastatin, irbesartan, and esomeprazole demonstrated an almost complete change from BB to GG drug switches. For ethinylestradiol/levonorgestrel and salmeterol/fluticasone, the involvement of brand-name drugs in the drug switches reduced as well. In all periods, most omeprazole drug switches were GG, but in the last period, there were GB drug switches (24.7%) and BG drug switches (13.3%) (see Table 2). Furthermore, for losartan, the number of BB and BG drug switches decreased, whereas the proportion of GB drug switches increased to 41.7% between July 2014 and December 2016. For rivastigmine, the proportion of BG drug switches decreased over the three periods (75.6% to 35.0%); however, the proportion of BB drug switches peaked (61.6%) between January 2012 and June 2014 (see Table 2). For all active substances combined, the proportion of BB drug switches decreased from 14.5% between June 2009 and December 2011 to 5.53% between July 2014 and December 2016. Conversely, the proportion of GG drug switches increased from 75.0% to 82.2% in the same period.

	June 2009 to December 2011				January 2012 to June 2014				July 2014 to December 2016			
	GG	**BG**	**GB**	**BB**	**GG**	**BG**	**GB**	**BB**	**GG**	**BG**	**GB**	**BB**
metformin	99.9	0.07	0.01	0.00	100	0.00	0.00	0.00	100	0.00	0.00	0.00
methotrexate (immunosupp)	100	0.00	0.00	0.00	100	0.00	0.00	0.00	100	0.00	0.00	0.00
enalapril	99.3	0.46	0.27	0.00	99.5	0.32	0.16	0.00	99.7	0.17	0.13	0.00
simvastatin	99.2	0.39	0.38	0.07	99.1	0.27	0.14	0.44	99.7	0.12	0.09	0.09
atorvastatin	0.00	0.00	0.00	100	56.0	33.2	1.34	9.44	99.1	0.50	0.37	0.00
pantoprazole	65.8	26.4	3.64	4.10	97.5	1.46	1.02	0.01	99.1	0.49	0.43	0.03
perindopril	96.4	0.03	0.01	3.54	98.0	0.02	0.00	2.01	99.0	0.05	0.03	0.93
paroxetine	96.3	1.67	1.98	0.00	97.2	1.55	1.23	0.00	97.9	0.74	0.74	0.61
metoprolol	95.3	3.17	1.44	0.06	96.2	2.10	0.99	0.71	97.3	0.91	0.65	1.11
venlafaxine	84.3	10.4	4.88	0.38	95.5	2.61	1.90	0.01	96.2	1.44	1.46	0.91
ethinylestradiol/ levonorgestrel	25.7	46.0	14.9	13.4	73.8	13.2	10.5	2.56	94.3	1.16	1.23	3.31
irbesartan	0.00	0.00	0.00	100	58.1	38.5	3.44	0.00	91.1	2.25	6.59	0.08
esomeprazole	10.8	38.0	9.05	42.2	70.7	12.4	6.34	10.6	82.3	3.77	3.65	10.2
methylphenidate	72.6	11.1	11.7	4.57	69.1	18.5	9.70	2.61	63.1	20.3	14.6	1.90
omeprazole	97.2	1.31	1.37	0.07	94.2	3.11	2.65	0.01	62.0	13.3	24.7	0.07
salbutamol	46.4	29.3	16.6	7.60	55.0	21.1	15.3	8.61	57.9	17.8	20.1	4.24
losartan	35.3	32.6	3.34	28.8	77.8	8.06	11.1	3.01	45.3	10.7	41.7	2.18
rivastigmine	14.0	75.6	10.3	0.08	20.9	14.8	2.67	61.6	43.8	35.0	12.9	8.33
salmeterol/ fluticasone	0.00	0.00	0.00	100	0.00	0.65	0.20	99.1	16.3	29.3	9.78	44.6
levothyroxine	0.15	19.1	21.3	59.4	2.19	29.9	21.7	46.2	1.72	26.1	5.89	66.3
methotrexate (antineoplastic)	0.00	9.04	1.66	89.3	0.00	0.03	0.00	100	0.25	0.02	0.00	99.7
average	75.0	8.31	2.22	14.5	84.1	7.14	2.18	6.54	82.2	5.59	6.63	5.53

Table 2: Percentage distribution of type of drug switch per active substance (GG = generic drug to generic drug switch, BG = brand-name drug to generic drug switch, GB = generic drug to brand-name drug switch, and BB = brand-name drug to brand-name drug switch) in descending order by percentage of generic-to-generic drug swivtch in the last period, similar to the order in Fig. 3. Periods are June 2009 to December 2011, January 2012 to June 2014, and July 2014 to December 2016.

Parallel import

A proportion of all drug switches (9.5%) in our study involved a parallel product. These drug switches were mostly BB (81.9%) and BG drug switches (15.8%); however, GB (1.30%) and GG drug switches (1.04%) also occurred. Overall, 0.12% of the GG drug switches and 86.5% of the BB drug switches involved a parallel imported product.

Detailed data on drug switches – example: atorvastatin

We closely investigated the drug switches of each active substance over time, and we present atorvastatin as an example in Fig. 4 because the patent of Lipitor® expired during our study period (February 2012). Roughly 2 million atorvastatin drug switches were included in our analysis. A large peak in BG drug switches occurred after patent expiry (274,300 BG drug switches in 2012), and only some patients were switched back from brand-name drugs to generic drugs: 1.7% of all drug switches in 2012 (7,355/421,875). From July 2012 until the end of the study period, 92.7% of the drug switches (1,057,601/1,141,015) concerned GG drug switches, also exhibiting the annual pattern with a peak between January and March. Moreover, 100% (600,818/600,862) of the drug switches in the period before March 2012 were BB drug switches.

As indicated in Fig. 4, the large BG drug switch peak in 2012 is a summation of 81 different BG drug switches. All atorvastatin switches in our study involved 84 different GG drug switches, 137 BB drug switches, and 68 GB drug switches.

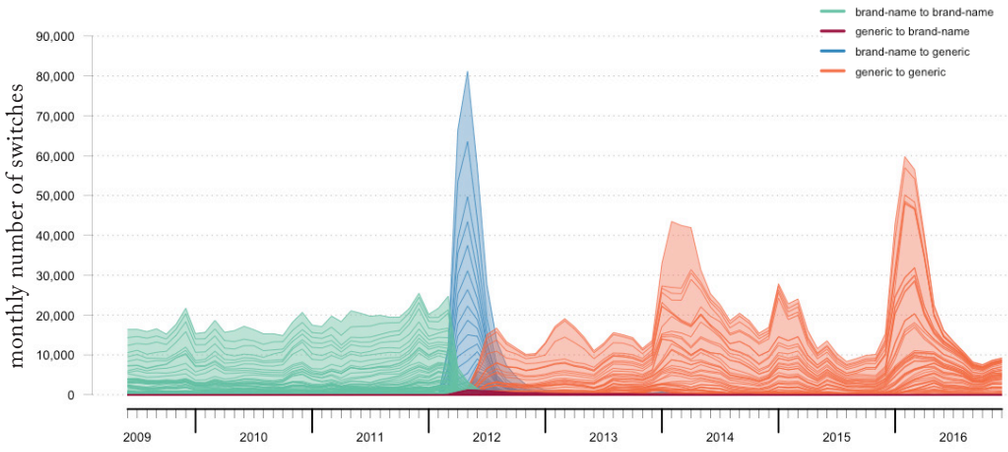

Fig. 4 Number of drug switches per month for atorvastatin, color-coded per combination of brand-name or generic drug. Brand-name to brand-name [green], brand-name to generic [blue], generic to brand-name [purple], generic to generic [orange]. Each color is a stacked area plot of the total number of drug switches, separated by solid lines for the individual contribution of switches with a unique combination of drug product before and drug product after the switch.

Discussion

This study provides new insight into the frequency of drug switches in the Netherlands. It is an essential part of characterizing the landscape of generic drug use and an important first step towards elucidating reasons for the occurrence of drug switches.

In our data, an increased number of drug switches were observed in the first 3 months of each calendar year. This increase cannot be explained by a higher overall number of drug dispenses in these months, as we did not observe a change in the number of drug dispenses throughout the year (data not shown). It can also not be explained by the number drug shortages, as these are not known to increase at the beginning of each year. Furthermore, as on average only 4–10% of the Dutch patient population changes health insurance yearly, this cannot explain the increased number of drug switches to a sufficient extent. However, the yearly increase is in line with the typical duration of health insurer-manufacturer contracts and contract renewal at the beginning of each year, as seen in the Preference Policy. Therefore, we postulate that the increased frequency of drug switches in January to March is explained by the Dutch Preference Policy.

The deviating pattern of an increased number of drug switches in the second part of 2009, as seen in Fig. 2, is likely caused by the phased introduction of the Preference Policy in that year. Until then, most contracts between manufacturers and insurers were valid for 6 months, whereas from 2009, contracts were usually of longer duration – 1 or 2 years (11).

The yearly pattern of the number of drug switches is most likely explained by the Preference Policy, but only partly. Most Dutch patients are insured by one of four large health insurance companies. Therefore, the expectation would be that there are only four (or less) preferred drug products and thus only a limited number of different drug switches for the same active substance. Nevertheless, as evident from the example of atorvastatin (Fig. 4), peaks in January to March are the result of many different drug switches involving various drug products. This was observed for the other active substances as well (data not shown). Therefore, the influence of other reasons, such as wholesaler and pharmacy practices or both local and international shortages, should be further investigated with the ultimate goal of identifying possible points for improvement towards pharmaceutical care in which the financially wanted market share of generic drugs is large, but the clinically unwanted drug switches do not occur frequently.

If a patient has complaints following the use of, or switch to, a different drug product, then, on medical grounds, a medical doctor in the Netherlands is entitled to prescribe that patient a drug product principally not covered by his or her health insurance ('medical necessity' similar to 'Dispense as Written' in the US). It is then reimbursed nonetheless and is thus also included in our dataset. Medical necessity is an interesting research topic, as it could be a surrogate for clinical problems or patient satisfaction with the use of a generic drug. In our dataset, we found an average 'switchback rate' (generic drug switched to brand-name drug) of 3.52%, with a wide range for the different active substances (0.00–17.3%). However, although a switchback is most likely the result of medical necessity, it could also be caused by other factors, such as supply shortage of the generic drug or a decrease in the price of the brand-name drug. Most importantly, medical necessity is not restricted to a brand-name drug but could also be used to prefer a specific generic drug, which further diffuses the relation between satisfaction and switchback rates. Our dataset is thus not well suited to study clinical discomfort and switchback rates or medical necessity.

Furthermore, we observed a high proportion of BB switches of drugs containing levothyroxine or methotrexate (for the antineoplastic indication) (see Fig. 3). This is most likely explained by the non-availability of generic drugs for these active substances and the availability of parallel imported brand-name drugs.

Over time, for atorvastatin, irbesartan, esomeprazole, ethinylestradiol/levonorgestrel, salmeterol/fluticasone, omeprazole, losartan, and rivastigmine, the type of switch involved fewer brand-name drugs. This observation is most likely explained by the increased availability of generic drugs after patent expiry of the brand-name drug. Indeed, generic drugs of esomeprazole were first available in 2011, those of atorvastatin in 2012, and those of salmeterol/fluticasone in 2013, after which the GG drug switch rate increased.

We only studied drug switches between active substances of the same strength and thus excluded drug switches for which both strength and manufacturer were changed. Although we thereby underestimated the number of drug switches, we believe the volume of these changes is relatively small, and this is not expected to influence our results to a great extent. Moreover, drug switches in which patients were switched between a fixed dose combination (FDC) and a combination of monotherapies were not included. Given the total number of patients for whom FDCs were dispensed in the Netherlands in the GIP database, this could affect drug switches involving perindopril, losartan, irbesartan, and enalapril (all available in FDCs with diuretics). Therefore, this study might underestimate the total number of drug switches for these active substances.

A further limitation is that we investigated only 20 (combinations of) active substances. These 20 were chosen because for these active substances, at least 25 ADRs in relation to drug switching had been reported to Lareb between January 2006 and September 2016 (7). At a later stage, our drug switch data can be used to refine the Lareb analysis. Since these are the active substances with the highest number of ADR reports related to drug switching, it is possible that we selected active substances that are switched more often than active substances not included in our study. As we do not have drug switch data for other active substances, we can neither confirm nor deny this. However, the 20 active substances represent a wide range of therapeutic classes and include 5 of the 10 most prescribed active substances in the Netherlands (2016). Therefore, we believe that, to a reasonable extent, our study findings can be generalized to other active substances in the Netherlands.

A strength of our analysis is that the drug switch data for each active substance are near complete. The data source, namely, the ZIN GIP, covers approximately 96% of the insured Dutch population (23) and all individuals living or working in the Netherlands are obliged to take out health insurance. Furthermore, the size of or our sample (almost 24 million switches) is large enough for us to be able to draw conclusions about the characteristics of drug switching in the Netherlands with sufficient certainty.

To our knowledge, this is the first nationwide quantitative analysis of drug switches at a patient level in the Netherlands. The amount of literature on this topic is limited. One other study described a quantified approach to generic switching in the Netherlands (24). However, it focused on the difference between what had been prescribed by the doctor (brand-name drug or generic drug) and what was dispensed by the pharmacist (brand-name drug or generic drug). It did not characterize the frequency of drug switches at the level of the individual patient, as in our study.

Furthermore, a recent FDA study introduced a descriptive tool to analyze novel utilization and drug switching patterns at the manufacturer level (8). That study focused on the number of new users per manufacturer, time to switch to a generic drug, and switchback rates. Extensive drug switching between drugs produced by different manufacturers was observed, with the exception that there was no distinct annual pattern. In addition, switchback rates could not be compared directly to our study, as these were presented as cumulative incidence rates (close to 20% in 2 years) but seem to be in the same order of magnitude as the rate we observed. In general, our results are consistent with those of the FDA study. The absence of an annual pattern in the American drug switching data suggests that the annual switching pattern we observed is unique to the Netherlands, which is an additional argument that the pattern is probably explained by the Preference Policy.

Although we present data specifically for the Dutch situation, our research has international relevance. Internationally, there is variability with regard to generic market penetration, generic pricing, reimbursement, and the policy for the promotion of generic drugs. Even different reimbursement policies for different types of active substances exist (25) (5, 26, 27). While we postulate a strong influence of a specific Dutch reimbursement policy the drug switch pattern does clarify the downside of a system in which generic drugs are preferred predominantly based on pricing and on frequent changes to the contracts between insurers and manufactures. Especially because of the variability of international policies, other policymakers must face comparable situations, and being aware of the Dutch situation is beneficial for their decision-making process.

Conclusion

Our results present a unique and extensive characterization of the frequency of drug switches in the Netherlands. We show that for the studied selection of 20 active substances, switching between drugs made by different manufacturers was common during mid-2009 until the end of 2016. Furthermore, we demonstrate that a large number of different drug products are involved in the drug switches, and an increased rate is observed in January to March each year, most likely explained by the Dutch health insurance Preference Policy. Not only are the data valuable as is, but they also serve as a first step towards elucidating the reasons for the occurrence of those drug switches. In addition, the data can be used to put into perspective the absolute number of ADRs associated with drug switching in the Netherlands.

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Chapter 2.2

Quantification of adverse drug reactions related to drug switches in the Netherlands

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Abstract

We performed a retrospective cohort study in the Dutch patient population to identify active substances with a relatively high number of adverse drug reactions (ADRs) potentially related to drug switching. For this, we analyzed drug switches and reported ADRs related to switching between June 1, 2009 and December 31, 2016 for a selection of 20 active substances. We also compared pharmacovigilance analyses based on the absolute, switch-corrected and user-corrected numbers of ADRs. In total, 1,348 reported ADRs and over 23.8 million drug switches were obtained from the National Health Care Institute in the Netherlands and from Lareb, which is the Netherlands Pharmacovigilance Centre. There was no correlation between the number of ADRs and the number of switches, but on average we found 5.7 reported ADRs per 100,000 switches. The number was relatively high for rivastigmine, levothyroxine, methylphenidate and salbutamol, with 74.9, 50.9, 47.6 and 26.1 ADRs per 100,000 switches, respectively. When comparing analyses using the absolute number and the switch-corrected number of ADRs, we demonstrate that different active substances would be identified as having a relatively high number of ADRs, and different time periods of increased numbers of ADRs would be observed. We also demonstrate similar results when using the user-corrected number of ADRs instead of the switch-corrected number of ADRs, allowing for a more feasible approach in pharmacovigilance practice. This study demonstrates that pharmacovigilance analyses of switch-related ADRs leads to different results when the number of reported ADRs is corrected for the actual number of drug switches.

Introduction

Generic drugs are highly similar to their brand-name counterparts. Generic drugs comprise identical active substance(s), have the same pharmaceutical form and have been shown to be bioequivalent to the brand-name drug. Limits for bioequivalence are set to achieve similar clinical safety and efficacy, and if bioequivalence has been demonstrated, then branded and generic drugs are considered therapeutically equivalent (1). From a pharmacological perspective, it is therefore unexpected that a different clinical profile is observed for a generic drug as compared to a brand-name drug, and that an adverse drug reaction (ADR) is experienced following a switch between bioequivalent drug products. However, cases of ADRs following drug switches are published (2-4); some studies on switching demonstrate increased health care utilization (5), and patients' and prescribers' perceptions of generics and generic switches are not always positive (6-10). A need exists to systematically study the perceived problems and possibly elucidate points for improvement on the pharmacological and psychological assumptions of generic interchangeability.

Lareb, the Netherlands Pharmacovigilance Centre, is responsible for pharmacovigilance signal detection in the Netherlands and regularly receives ADR reports related to generic switching. In 2017, Lareb published a report on these ADRs for active substances with at least 25 reported switch-related ADRs over a period of 10 years (11). Based on observed patterns for the absolute number of reported ADRs and a clinical review of each case, Lareb identified problems following switching: dysregulation of patients after switches of the thyroid hormone levothyroxine; breakthrough bleeding on oral contraceptives with ethinylestradiol and levonorgestrel; reduced efficacy with inhalation drugs for the treatment of asthma; salbutamol and fluticasone/salmeterol, skin reactions and curling of patches with rivastigmine; injection site pain and injection site reactions with methotrexate; and reduced efficacy with anti-epileptics.

However, as acknowledged by the authors, and as is often the case for pharmacovigilance research, studying the absolute numbers of ADRs is a classic example of a "floating numerator;" that is, the number of cases is not related to the size of the population at risk. The relative risk may be low for drugs that are often switched, but could be high for drugs that are switched less often. Furthermore, we expect that there is a background rate of reported ADRs per

number of drug switches. The background rate is difficult to discern without knowledge of the number of drug switches, specifically since we know from previous work that the number of switches fluctuates on a monthly basis (23).
The primary aim of the current investigation is to calculate the relative number of reported ADRs per number of drug switches for the 20 active substances that were described in the Lareb report, in the time period between June 1, 2009 and December 31, 2016. (Temporary) increased numbers of reported ADRs ("peaks") above the background level are of particular interest, as these could indicate a true increased incidence of clinical discomfort following a drug switch. Further investigation of such a relative peak should then be performed to determine whether a causal association between a specific drug switch and the experienced ADRs can be deduced.
In addition, we examine whether different peaks would be observed using the absolute number of ADRs or using the switch-corrected number of ADRs. We also explore the feasibility of using the number of users, instead of drug switches, for correcting the absolute number of reported ADRs, since these data are more readily available.

Methods

This is a retrospective cohort study of a selection of 20 active substances in the Dutch patient population, with qualitative and quantitative descriptive analyses. We related the number of reported ADRs obtained from the database of the Lareb, to the drug switches from the National Health Care Institute (ZIN).
Active substance selection was based on a Lareb report from 2017, in which drug switch-related ADRs were described for active substances with more than 25 ADRs in a 10-year period from 2006. The following active substances (20) are included: atorvastatin, enalapril, esomeprazole, ethinylestradiol/levonorgestrel, irbesartan, levothyroxine, losartan, metformin, methotrexate, methylphenidate, metoprolol, omeprazole, pantoprazole, paroxetine, perindopril, rivastigmine, salbutamol, salmeterol/fluticasone, simvastatin and venlafaxine.

Patient switch data

We previously performed an extensive analysis of the drug switch data for the 20 drugs (23). Similarly to that publication, a switch is defined as the replacement of a patient's prescribed drug with a similar drug dispensed within the preceding 150 days, for the same active substance, same strength, and same route of administration, but with the drug product coming from a different manufacturer. The drug products before and after the switch could both be generic or brand-name drugs. In the ZIN data, analysis of consecutive dispenses is feasible from January 1, 2009 onwards, thus we have reliable drug switch data from June 1, 2009 until December 31, 2016. Furthermore, we collected data on the total number of users of the 20 active substances from the same data source.

Reported adverse drug reactions data

We obtained all spontaneously reported ADRs received by Lareb over the years 2009–2016, submitted by patients and health care professionals, both directly to Lareb and via marketing authorization holders. Only ADR reports that, according to the reporter, were highly related to drug switching or drug substitution were included. For this purpose, reports categorized under a specific subset of the Medical Dictionary for Regulatory Activities (MedDRA) Lowest-Level Terms (LLTs) were included (Table S1). For each reported ADR, we obtained the unique anonymized identification number (ID), date of onset of the ADR, report-received date, MedDRA LLT, Anatomical Therapeutic Chemical (ATC) classification system code before switch, ATC code after switch, and sex and age of the patient.
The date of onset of the ADR was deemed most relevant to our study; however, this was not registered in 12.9% (375/2,901) of the reports. In these cases, the report-received date was used, minus the median difference between the receive date and the date of onset of all reported ADRs (53 days). We excluded 5.3% (155/2,901) of the reports, whose date of onset of the ADR was not between June 1, 2009 and December 31, 2016. Furthermore, the interest of our study was drug switching between two products of the same active substance. We therefore excluded 5.2% (144/2,746) of the ADRs in which the registered ATC code before and after switch did not match. The final number of suitable ADRs was 2,602. We did not exclude reports in which the ATC code before the switch was not registered, which was the case in 33.7% (878/2,602) of the reports.

Data analysis

Aggregated data were exported from ZIN and Lareb databases as a Microsoft

Excel workbook and imported into R software (version 3.5.1) using the package "xlsx." Qualitative and quantitative descriptive analyses and data visualization were performed using base R and R Studio.

Descriptive analyses of reported ADR data were performed and presented per anatomical subgroup of the ATC classification system and for each of the 20 selected drugs. Both the patient switch data and the ADR data were aggregated on a quarterly (3-monthly) basis, as this is a common time frame for analyses in pharmacovigilance. In the absence of switch data, ADR data before July 2009 was not included in the quarterly analyses.

The numbers of reported ADRs per number of switches were calculated by dividing the quarterly number of ADRs for each active substance by the quarterly number of switches for that active substance. Analogously, numbers of reported ADRs per number of users were calculated by dividing the quarterly number of ADRs by the number of users.

In this study, we define a peak in the number of ADRs as the value exceeding a threshold. This threshold was subjectively defined as the mean value of the number of ADRs in all quarters for all included active substances, plus 1 times its standard deviation.

Results

Number of reported adverse drug reactions

Our analyses included a total of 2,602 reported ADRs related to drug switching during the study period June 1, 2009 until December 31, 2016. Of the included ADRs, 63.9% were reported for female patients, and the mean age of the patients was 53.1 years (range 0–95 years). In Table S2 an overview is presented of the number of ADRs per ATC anatomical main group. Differences between anatomical groups are observed, with, for example, a large number of reported ADRs for the nervous system subgroup (n = 595) and a small number for dermatological drugs (n = 13). However, as the number of switches per active substance is unknown, no inferences can be made with regard to the relative risk per anatomical group.

In Fig. 1 the data is illustrated graphically, with each shaded band indicating one specific active substance. From this figure, large differences can be observed regarding the relative contribution of active substances within each anatomical group – for example, a major contribution of levothyroxine in the subgroup "systemic hormonal preparations" (H) (95% [360/379] of the total number of switches in the ATC group) and of omeprazole (41.3% [124/300]) in the "alimentary tract and metabolism" subgroup (A). The 20 active substances included in our further analyses represent 51.8% (1,348/2,602) of all reported ADRs in our dataset; they are marked in Fig. 1. Table 1 provides an overview of both the number of reported ADRs and the number of drug switches of the included active substances.

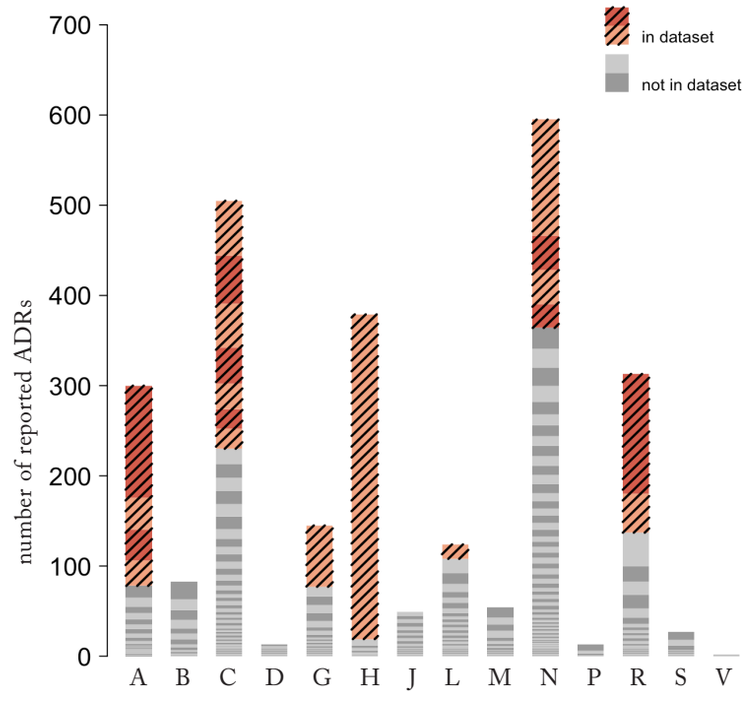


Fig. 1: Overview of all spontaneously reported ADRs related to drug switching, for all active substances, from June 2009 to December 2016 in the Netherlands, as obtained from Lareb. Each bar is a sum of all reports in a specific anatomical group. Each individual color represents the total number of reported ADRs for one specific ATC code. Colored and striped parts indicate the 20 products selected for further study.

INN	EU brand name	Total number of reported ADRs	Total number of switches
levothyroxine	Thyrax Duotab ®	360	507,396
salbutamol	Ventolin ®	133	493,270
methylphenidate	Ritalin ®	129	223,496
omeprazole	Losec ®	124	2,742,659
ethinylestradiol/ levonorgestrel	Microgynon ®	68	483,996
atorvastatin	Lipitor ®	61	2,007,886
metoprolol	Lopresor ®	53	2,723,408
simvastatin	Zocor ®	49	4,241,382
salmeterol/ fluticasone	Seretide ®	43	793,693
irbesartan	Aprovel ®	40	446,312
paroxetine	Seroxat ®	38	853,542
rivastigmine	Exelon ®	38	30,722
pantoprazole	Pantozol ®	36	2,192,881
metformin	Glucophage ®	34	1,915,225
esomeprazole	Nexium ®	28	716,320
losartan	Cozaar ®	28	902,258
venlafaxine	Efexor ®	26	422,532
enalapril	Renitec ®	22	776,436
perindopril	Coversyl ®	22	1,222,092
methotrexate	Metoject ®	16	161,603
total		**1,348**	**23,857,109**

Table 1: Overview of each specific active substance included in the analysis, including International Nonproprietary Name (INN), European brand name, total number of reported ADRs related to drug switching and total number of switches for these active substances, for the period June 2009 to December 2016 in the Netherlands.

Relative number of reported adverse drug reactions

To examine the relation between the number of reported ADRs and the number of drug switches, the quarterly number of ADRs and quarterly number of switches for the 20 selected active substances are depicted in Fig. 2. The mean number at which ADRs are reported for all active substances in our selection is 5.7 per 100,000 switches. However, no linear correlation between the number of ADRs and the number of switches was identified, and a high variability in the number of ADRs reported per quarter is observed.

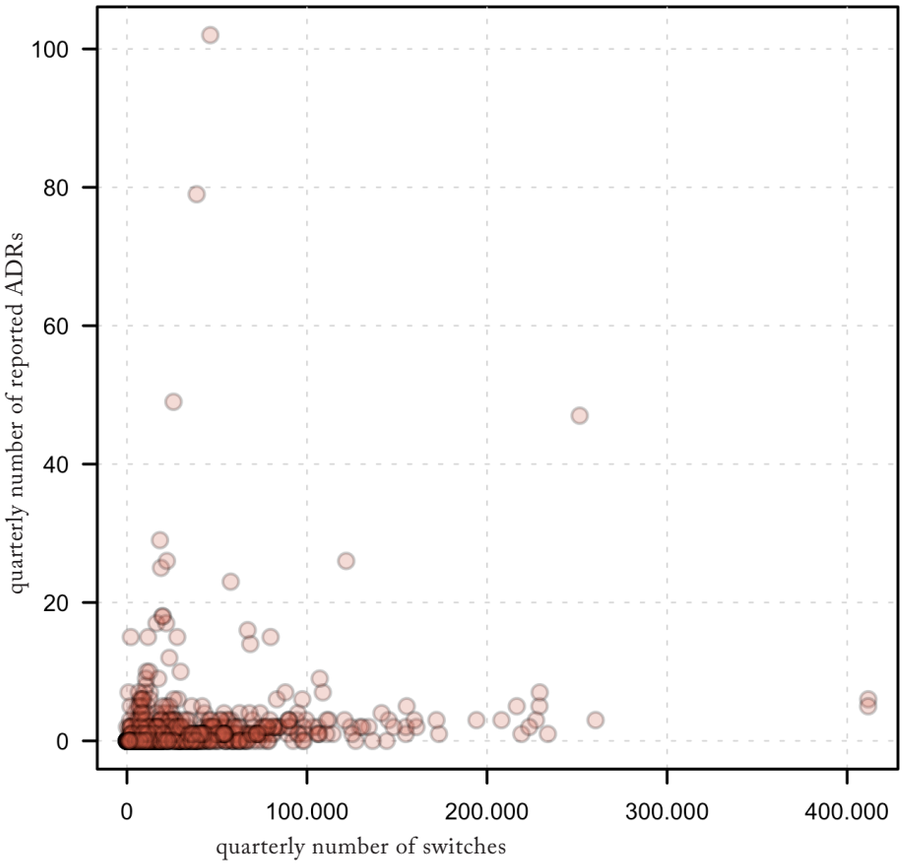
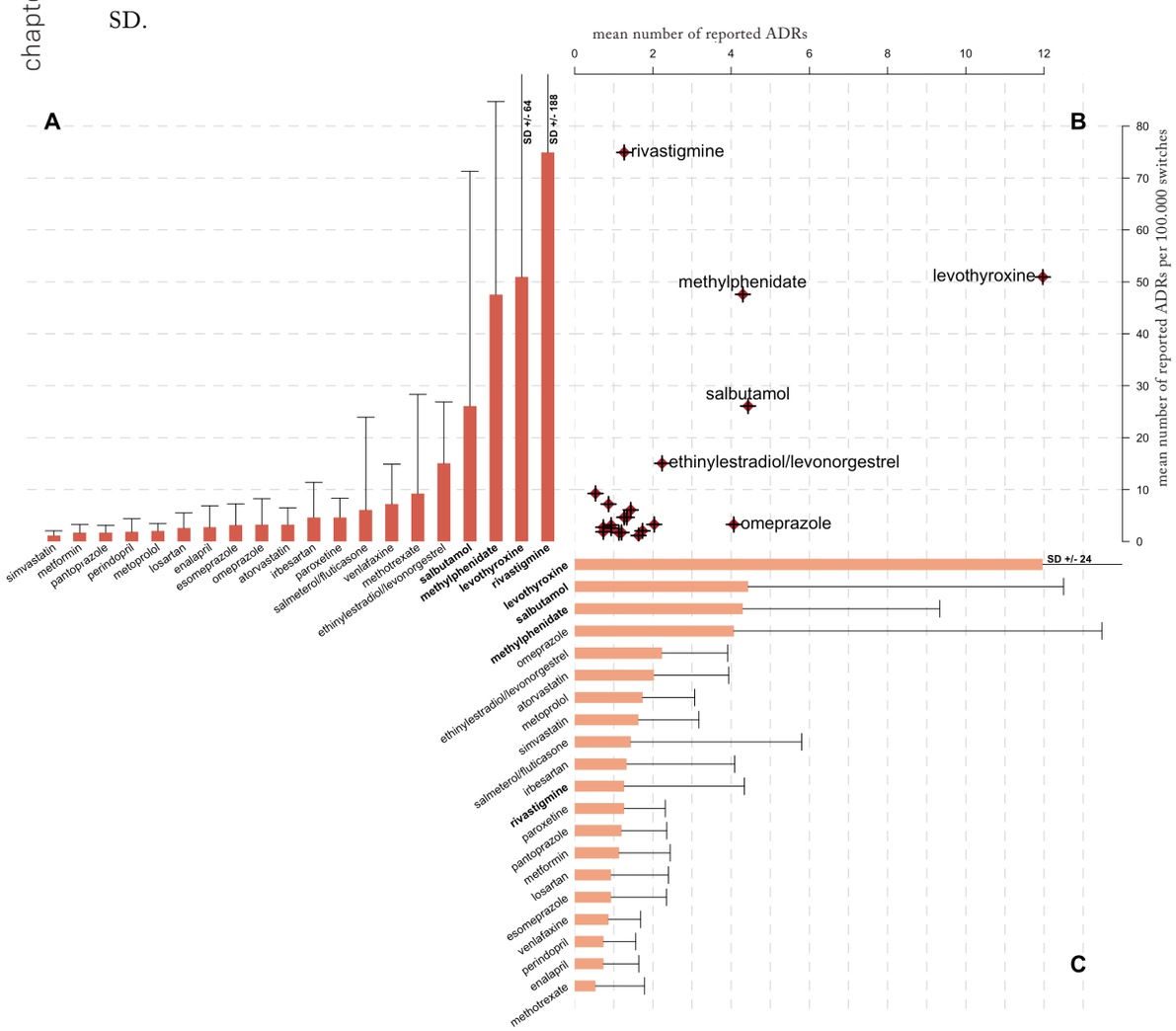


Fig. 2: Plot of the absolute number of reported ADRs related to drug switching and number of switches in the Netherlands for all included active substances (n = 20) in the dataset. Each data point is the number of reported ADRs and number of switches for one specific quarter year.

Fig. 3: (A) Bar chart of mean switch-corrected number of quarterly reported ADRs related to drug switching per 100,000 switches; error bars indicate quarterly SD. (B) Plot of each active substance, with the mean absolute number of quarterly reported ADRs on the x-axis and the mean of switch-corrected number of quarterly reported ADRs per 100,000 switches on the y-axis. (C) Bar chart of mean absolute number of quarterly reported ADRs; error bars indicate quarterly SD.



In Fig. 3, the mean quarterly reported number of ADRs and mean quarterly number of switch-corrected ADRs are compared for all 20 active substances in the dataset. Fig. 3A illustrates that there is cluster of active substances with a similar, relatively low quarterly number of ADRs per 100,000 switches. In contrast, the following four active substances demonstrate notably higher numbers: rivastigmine (74.9 +/- 188 per 100,000 switches, mean +/- SD), levothyroxine (50.9 +/- 64.2), methylphenidate (47.6 +/- 37.1) and salbutamol (26.1 +/- 45.2). The mean relative risk of reporting an ADR following a rivastigmine switch in our study period therefore appears 65-fold higher, compared to a simvastatin product switch (i.e., 74.9 versus 1.15 reported ADRs per 100,000 switches).

Comparison between relative number and absolute number of reported adverse drug reactions

Fig. 3 A and C depict the ranking of the active substances based on both mean number and switch-corrected number of ADRs. The ranking order of these two measures does not fully overlap. More specifically, for rivastigmine, for example, the mean absolute number of ADRs (1.27 +/- 3.07) is relatively low, whereas the mean number of switch-corrected ADRs is relatively high (74.9 +/- 188 per 100,000 switches). For omeprazole, it is the opposite: a relatively high mean number of ADRs (4.07 +/- 9.41) and a relatively low mean number of switch-corrected ADRs (3.28 +/- 4.97 per 100,000 switches) exist. For levothyroxine, salbutamol and methylphenidate, both the absolute number and switch-corrected number of ADRs are relatively high.

Large standard deviations on the mean values are observed. This indicates that large differences can be observed between different quarters. Studying mean values ignores the fluctuation in the data, which is essential in the (real-time) detection of temporal increases. Fig. 4 presents an example of the study over time for the number of reported ADRs (absolute and switch-corrected) related to esomeprazole. The largest absolute number of ADRs was observed in the first quarter of 2011 (six reported ADRs), and it coincides with the largest number of quarterly switches (83,254). As a result, the number of switch-corrected ADRs in the first quarter of 2011 (7.21 per 100,000 switches) is lower than the number of switch-corrected ADRs observed in the last quarter of both 2010 and 2012, the second quarter of 2015 and the first quarter of 2016 (with 8.68, 12.0, 11.96

and 12.65 reported ADRs per 100,000 switches, respectively), all representing quarters for which a lower absolute number of ADRs were reported (i.e., two or three). This exemplifies that, when corrected for the number of switches, a peak in the absolute number of ADRs does not necessarily translate into the most relevant peak in ADRs. Similarly, a lower absolute number of ADRs could be more relevant if the number of switches in a quarter is relatively low.

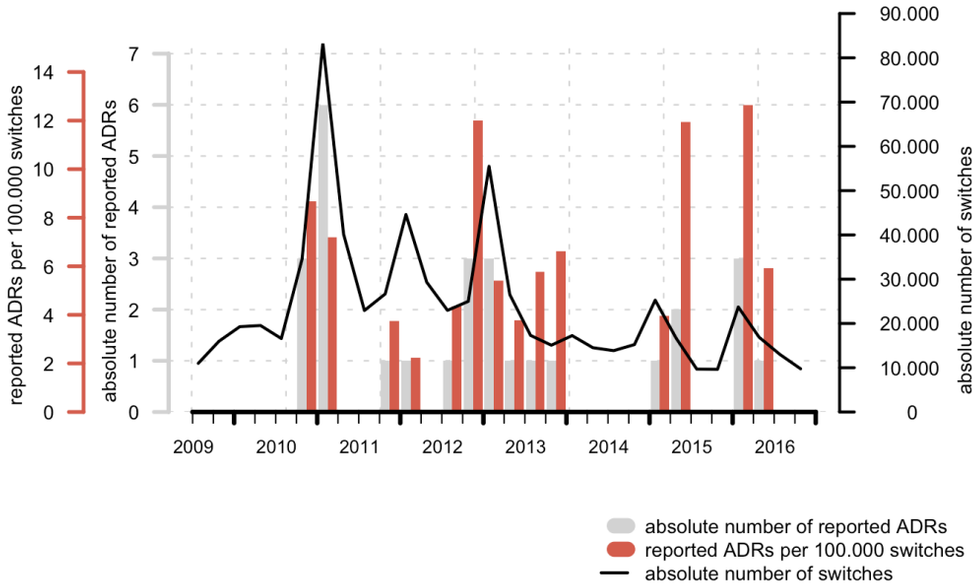
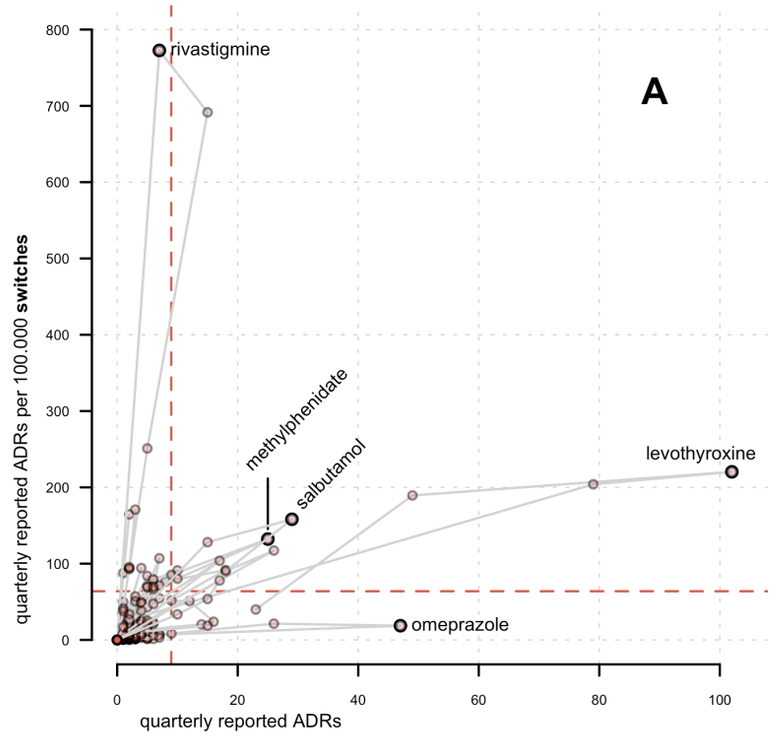
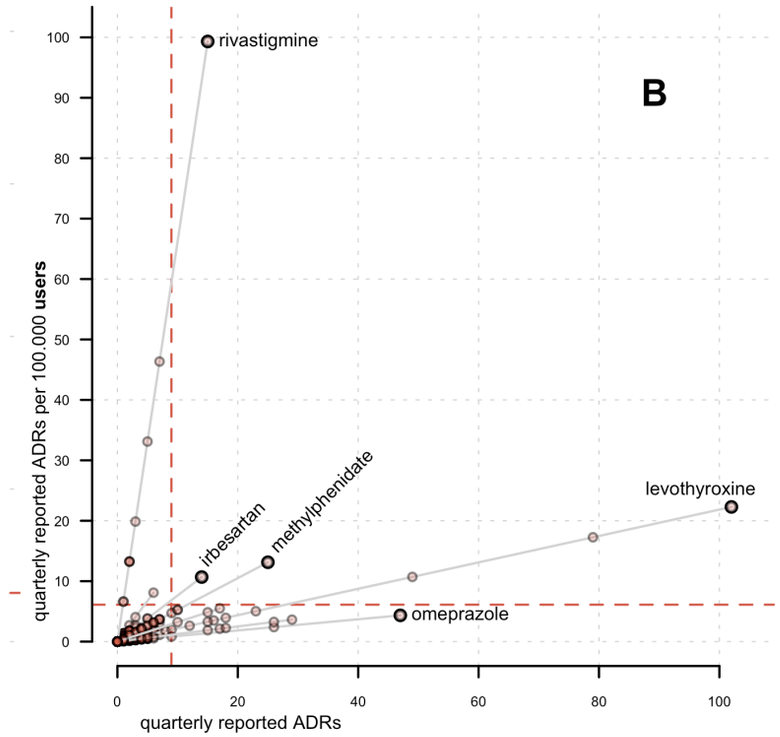


Fig. 4: (above) Number of quarterly switches (black line), absolute number of reported ADRs (gray bar plot) and quarterly number of switch-corrected reported ADRs (per 100,000 switches, color bar plot) for esomeprazole in the Netherlands.

Fig. 5: (right page) (A) Absolute number of quarterly reported ADRs per active substance on the x-axis and number of switch-corrected quarterly reported ADRs per 100,000 switches on the y-axis; gray lines connect values for quarters of a single drug in chronological order. (B) Absolute number of quarterly reported ADRs per active substance on the x-axis and number of user-corrected quarterly reported ADRs per 100,000 users on the y-axis; gray lines connect values for quarters of a single active substance in chronological order, and dashed lines are the threshold values, defined as the mean number of the absolute or switch-corrected reported ADRs + 1 SD. The total number of quarterly data points per active substance is 30.





To further examine the question as to whether different peaks would be observed using the absolute number of ADRs versus the switch-corrected number of ADRs, the absolute number of quarterly ADRs was plotted against the switch-corrected number of ADRs for all 20 included active substances (Fig. 5A). This allows for a visual assessment of the difference between the two methods of "peak detection." The figure illustrates a number of data points clustered at the lower values of both axes and a number of data points deviating from that cluster. To interpret the results, we arbitrarily defined a threshold above which a data point is considered to be a peak or a part thereof.

Data are available for 30 quarter years for each individual active substance, amounting to 600 quarters. On the one hand, based on the absolute number of ADRs, 4.3% (26/600) of the quarters would be identified as a peak. On the other hand, based on the switch-corrected ADRs, 5.7% (34/600) of the quarters would be identified as a peak. Furthermore, 2.5% (15/600) of the quarters would be identified by both methods, and 1.8% (11/600) of the peaks that were identified based on the absolute number of ADRs was not identified by the switch-corrected ADR method. The latter 1.8% could be characterized as false positives of the absolute ADR method, or a "type 1" error, as these peaks would erroneously be identified as peaks when in fact they are explained by an increased number of switches. Similarly, 3.2% (19/600) of the ADR peaks would only be identified with the switch-corrected ADR method and not by the absolute number of ADRs method. These could be defined as "type 2" errors or false negatives of the absolute number of ADRs method.

In Fig. 5A, the reported ADR peaks for the following five active substances visually stand out: rivastigmine, methylphenidate, levothyroxine, omeprazole and salbutamol. For rivastigmine, a large switch-corrected ADR peak is observed for 7/30 quarters, but only one of these seven quarters (14.3%) is above the threshold for the absolute number of ADRs. Likewise, for methylphenidate, 26.7% (8/30) of the quarters is above the switch-corrected ADR threshold but not above the threshold for the absolute number of ADRs. These data indicate false negatives in the absolute number of ADRs method.

For levothyroxine, 9/30 quarters are above the threshold for the absolute number of ADRs, of which 55.6% (5/9) is not identified by the switch-corrected ADR method, thus indicating false positives in the absolute number of ADRs method. Likewise, for omeprazole, 10% (3/30) of the quarters is above the threshold for the absolute number of ADR; however, none of these three were identified by the switch-corrected ADR method, again indicating false positives for the absolute number of ADRs method. For salbutamol, no false positives or negatives are identified, as the same five quarters are identified by both methods.

User-adjusted analysis

Data on the absolute number of drug switches is only available in the Netherlands in retrospect. This may hinder the use of the number of switches during real-time pharmacovigilance analyses. A more practical approach to put the number of ADRs into perspective would therefore be to use the number of users instead of the number of switches.

The absolute number of quarterly ADRs and the user-corrected number of quarterly ADRs are depicted in Fig. 5B. Comparing Fig 5A and 5B, similar trends are observed for the values of rivastigmine, levothyroxine, methylphenidate and omeprazole. Table 2 provides a detailed comparison of the number of ADRs above and below the threshold using either switch-corrected or user-corrected ADRs, as compared to the outcome for the absolute number of ADRs method, and it shows a similar trend using both methods.

	Absolute number of reported ADRs below threshold		Absolute number of reported ADRs above threshold	
	switch adjusted	user adjusted	switch adjusted	user adjusted
reported ADR number above threshold	3.17% (19/600)	1.50% (9/600)	2.50% (15/600)	1% (6/600)
reported ADR number below threshold	92.5% (555/600)	94.2% (565/600)	1.83% (11/600)	3.33% (20/600)

Table 2: Comparison between percentages of quarters above or below the threshold of either the switch-corrected or user-corrected reported ADR methods for the 20 selected active substances in this study. False negatives are marked in light gray, and false positives are marked dark gray.

Although numerical differences can be observed with respect to the number of false positives and false negatives between both methods, the overall impression is that both methods result in similar findings regarding the number of active substances with identified peaks and the percentage of quarters with values above or below the threshold. Similarity in the outcome of the switch-corrected and user-corrected ADR methods depends on the correlation between the quarterly number of users and the quarterly number of switches. Supplementary Figure S1 is a depiction of the correlation and there is a linear correlation (R^2 = 0.72) with a significant slope (p = $2.48*10^{-6}$). On average, approximately 91 quarterly switches per 1,000 users are observed for the 20 active substances included in our analysis.

Discussion

Pharmacovigilance is a useful tool in the identification of clinical consequences of (generic) drug switching. Given the importance for each individual patient, every reported ADR should always undergo thorough causal and clinical review. We combined the number of drug switches and the number of related ADRs for a period of 7.5 years between June 1, 2009 and December 31, 2016. We demonstrated that in this period, rivastigmine, levothyroxine, methylphenidate and salbutamol have a relatively high number of switch-related ADRs. Without switching data, the potential exists to draw false positive (noted, e.g., for omeprazole) or false negative (noted, e.g., for rivastigmine) conclusions. We also revealed that, without switching data different active substances in our selection of 20 would be identified as having a high prevalence of switch-related ADRs. The use of switch-corrected ADR data should be considered in pharmacovigilance analyses to avoid misinterpretation of switch-related ADR signals.
This is the first systematic, nationwide analysis of clinical discomfort from drug switches, using reported ADRs and the specific population at risk. Others have used indirect measures of discomfort, such as switchback rates (12). In a study on temporal trends in ADR reporting before and after generic introduction, the peak reporting numbers for five antiepileptic active substances were calculated as being in the range of 50–450 per 100,000 dispensed prescriptions (13). In that study, ADRs were not selected on specific LLTs and are expressed by number of prescriptions, which makes it difficult to compare to our study. In

a recent analysis of a large switch in France between two levothyroxine drug products, an ADR reporting rate of 1.44% is mentioned (14). This is based on an estimated 2.1 million patients switching and 31,411 reported ADRs over a period of 13 months. The relative number of 1,440 / 100,000 switches in 13 months is higher than in our study, as we found a peak of 220 ADRs per 100,000 switches in 3 months for levothyroxine. The authors postulate a causal relation between the high number of reported ADRs and the proportion of subjects outside the bioequivalence limits, as found in a pharmacokinetic study. This relation is heavily debated (15-18). In a similar situation for levothyroxine in 2007 and 2008 in New Zealand, the increased number of reported ADRs was attributed to other factors, such as inaccurate information and media attention (19). Others have postulated an analytical framework that is comparable to our approach, and this confirms the potential of combining spontaneously reported ADRs and health care claims data for the detection of generic issues (20).
In our dataset, we did not identify a correlation between the quarterly number of drug switches and the quarterly number of reported ADRs using data for all 20 active substances. This finding suggests that the increased number of ADRs is not merely a result of an increased number of switches. Thus, in many cases, the rate of reported ADRs indeed does change (temporarily), which may be an indication of an issue related to drug switches for those active substances. The reason for an increased rate of reported ADRs can be either an increase in the number of occasions on which a patient experiences a clinical consequence of a drug switch or a larger portion of the patients reporting their experienced ADR. Furthermore, the absence of a correlation between the number of switches and the number of ARDs questions the idea that the same general “background ADR reporting rate” is present for all active substances for which ADRs related to drug switches are reported.
Further in our study, we demonstrated that correcting the number of ADRs by number of users, instead of number of switches, is a suitable alternative, since a comparable number of ADR peaks over time were identified by both methods. This is not an unexpected finding, as the number of switches is related to the number of users (see Fig. S1). The number of users is, however, a mean value, and unlike the number of switches in the Netherlands, it does not demonstrate changes over a short period of time. Therefore, the user-corrected ADR method cannot put into perspective the temporal increases in reported ADR

peaks. This is not of great influence on our analysis, presumably since there is no strong correlation between peaks in the number of ADRs and peaks in the number of switches.
On average, in our dataset of 20 active substances in the Netherlands, we found 364 switches per 1,000 users per year. In a study on the frequency of switching and adherence of inhalation medication, a yearly percentage switch of approximately 5% of total users was identified (21). This is low compared to our results, perhaps since multiple switches per patient and switches between generics were not accounted for in that publication. We are unaware of other literature references to drug switch frequencies.

Study limitations

This study is based on data from spontaneous ADR reporting, which is known to be subject to underreporting, varying by type of active substance and type of ADR (22). This limits the generalizability of our study, as we are not able to calculate an absolute risk of ADRs following drug switches, only a relative number of reported ADRs. Moreover, changes in the number of reported ADRs over time could simply be changes in the reporting rate and not true changes in the number of experienced ADRs. However, we believe that spontaneous reports are the most objective and systematically acquired data available to study clinical discomfort regarding drug switches. Furthermore, conclusions on the calculated number of reported ADRs can still be drawn relative to other active substances in the dataset.
We present data for 20 active substances only. Nevertheless, these 20 active substances have the largest number of reported ADRs in the Netherlands and therefore provide an adequate number of ADRs on which to base calculations. As described in our previous study (23), we believe these 20 active substances represent a valuable sample, since active substances are included with both high and low numbers of switches, as well as high and low numbers of users. The active substance selection includes not only 5 of the 10 most prescribed active substances in the Netherlands in 2016 (between 688,000 and 1 million users), but also data for rivastigmine, which has on average only 15,102 users.
In theory, a more detailed level of analysis is possible using the Lareb and ZIN data sources, for instance analysis of manufacturer-specific switches or analysis of ADRs reported for a specific patient subgroup. Although interesting, more detailed analyses are limited because of the smaller number of ADRs that can be included in them. In addition, the data obtained for our study did not support manufacturer-specific analysis, as this information was not registered by Lareb in the first part of the study period. Furthermore, subgroup analyses could not be performed, as the ZIN data were aggregated, and patient characteristics were not included.
We used all reported ADRs for which a certain LLT was registered. This limits the study, as allocation of LLTs to ADR reports is a subjective action. "Substitution" is particularly ambiguous terminology, as various interpretations are offered in literature. However, we gathered all ADRs from the same pharmacovigilance center and are therefore confident that the terminology and interpretation is consistent and similar within our study data.
The threshold for peak identification was arbitrarily chosen as the mean plus 1 SD. This is a common approach when analyzing data such as those in this study; however, it is only a mathematical approach to peak identification. Conclusions drawn from these data can therefore differ if different threshold values are chosen, and the best threshold for actual pharmacovigilance analyses may be a subject for further research.

Future directions

In this study, we demonstrate the importance of incorporating the number of drug switches when analyzing switch-related ADRs. Although we consider each reported ADR to be important, and we know that ADRs can have a significant impact on quality of life on an individual level (24), we believe that an ADR is less informative in analyzing the clinical discomfort of drug switching when a large number of switches underlies that specific ADR.
Our recommendation is to incorporate the number of drug switches in drug switch-related ADR pharmacovigilance analyses, when feasible. If not, it would at least be desirable to incorporate the number of users, which is a reasonable alternative to the number of switches. Alternatively, it may be interesting to use an estimated number of drug switches by simulating the number of drug switches, based on the number of users, seasonality (known to occur in the Netherlands), and other factors that are unknown at this point. Further validation of either methodology is recommended.

Conclusion

We demonstrate that adjusting the absolute number of reported ADRs for the number of drug switches leads to identification of different ADR peaks between June 1, 2009 and December 31, 2016, at least in our selection of 20 active substances with a relatively large number of ADRs, in the Netherlands. By using the switch-corrected number of ADRs in pharmacovigilance analyses, the likelihood of identifying relevant switch-related ADR peaks may be increased. Therefore, the use of switch-corrected ADR data in routine pharmacovigilance analyses appears to be advisable. Although the number of switches is theoretically the best measure to put the reported ADRs related to drug switching in perspective, in the absence of such data, the mean number of users could be a useful alternative measure.

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Supplementary Figure and Tables

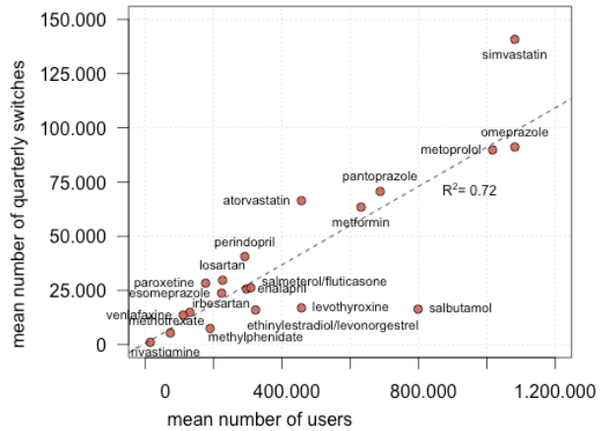

Fig. S6: Mean number of users versus mean quarterly number of drug switches for the 20 drugs included in this study over the period July 1, 2009 to December 31, 2016 in the Netherlands. The dashed line is a linear model regression.

Preferred Term	Lowest-Level Terms
Product substitution issue	Product substitution issue
	Product substitution issue brand to brand
	Product substitution issue brand to generic
	Product substitution issue generic to brand
	Product substitution issue generic to generic
Therapeutic response unexpected	Therapeutic response unexpected with drug substitution
Drug level changed	Generic drug substitution altered drug level
	Product substitution altered drug level
Therapeutic response changed	Generic substitution altered therapeutic response
Therapeutic response increased	Increased therapeutic response with drug substitution
Therapeutic response decreased	Reduced therapeutic response with drug substitution
Product substitution	Substitution therapy
	Product substitution
Product substitution error	Product substitution error

Table S1: Overview of included (MedDRA) Lowest-Level Terms and Preferred Term of the reported ADRs.

Code	Content	Number of reported ADRs
A	Alimentary tract and metabolism	300
B	Blood and blood-forming organs	83
C	Cardiovascular system	505
D	Dermatologicals	13
G	Genito-urinary system and sex hormones	145
H	Systemic hormonal preparations, excluding sex hormones and insulins	379
J	Anti-infectives for systemic use	49
L	Antineoplastic and immunomodulating agents	124
M	Musculoskeletal system	54
N	Nervous system	595
P	Antiparasitic products, insecticides and repellents	13
R	Respiratory system	313
S	Sensory organs	27
V	Various	2
	Total	**2,602**

Table S2: Overview of all reported ADRs related to drug product switching per ATC code for all drugs from June 2009 to December 2016 in the Netherlands, as obtained from Lareb.

Chapter 2.3

Reasons for patients' generic drug switching at the pharmacy counter

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Generics and Biosimilars Initiative Journal (GaBI Journal) 2021;10(3):119-22

Abstract

Background

Patients may experience clinical discomfort as a result of drug switches between drug products with the same active substance. Although a large market share of generic drugs is financially favourable, reduction of the number of drug switches should be strived for. However, specific causes for the drug switches are currently undocumented.

Objective

To document reasons for patients' drug switches between drug products with the same active substance.

Method

Observational field research was conducted in a total of 16 Dutch pharmacies during November and December 2019. In these pharmacies, a single researcher registered reasons for drug switches at time of occurrence, during a full working day.

Results

In total, 207 drug switches were registered. Most drug switches were caused by nationwide drug shortages (32%, n = 66) and the Dutch price-based tender system (23%, n = 47). Other important reasons were as follows: deals between pharmacists and wholesalers (12%, n = 25), distribution issues at wholesalers (11%, n = 22) and a financially favourable margin for pharmacists (11%, n = 21).

Conclusion

This study indicates that drug shortages and the Dutch price-based tender system are likely to be the main causes of drug switches in the Netherlands. However, other reasons, such as drug product distribution issues and local economic incentives, were also identified.

Introduction

Drug switches between drug products with the same active substance occur frequently and mostly between two generic drug products (1). Drug switching should not be clinically problematic, as interchangeability is supported by the demonstration of bioequivalence (2). However, a number of patients, physicians, and pharmacists seem to have a negative perception of generic drugs and drug switching (3), and indeed for some drugs adverse reactions related to drug switches have been reported (4). This clinical discomfort should be avoided.
Nonetheless, generic drugs are cheaper and important to reduce the costs of pharmaceutical care. In search of an optimum balance between clinical discomfort to the patients and financial benefits to the health care system, patients would benefit from a system in which generic drugs have a large market share but the number of drug switches is small. A first step towards reduction of the number of drug switches is to elucidate how they arise.
The reasons for the occurrence of drug switches are currently undocumented. Logically, drug shortages will result in drug switches, but other reasons can be sought in any action by health insurers, prescribers, wholesalers and/or patients which can influence the choice of the dispensed drug product. These can differ between countries as a result of national legislation and healthcare system. However, in many countries similar policies and financial incentives are in place to promote the use of generic drugs. For instance, a number of countries have tender systems in place which favour the cheaper drug product for reimbursement from a group of interchangeable drug products (5).
This study is performed in the Netherlands. There, generic drugs have a large market share and there is a price based tender system to promote generic drug use (6), as well as mandatory prescribing by international non-proprietary name (INN). The number of drug shortages has increased in the Netherlands in the last decade (7), as a result of several issues with regard to production, distribution, and quality, but also since the Netherlands is a less favourable sales market due to low prices and a small population size. In this study, we prospectively gathered data at the pharmacy counter, both qualitatively and quantitatively, regarding the underlying reasons for drug switching in the Netherlands.

Methods

Observational field research was conducted in Dutch pharmacies during November and December 2019. A total of 400 pharmacies were approached from the database of the Utrecht Pharmacy Practice network for Education and Research (UPPER) (8). Pharmacies were preselected by geographical spreading, limited travel time, and the research protocol was approved by the UPPER Institutional Review Board. In a pilot study drug switches were registered during a 6-hour visit to a local pharmacy.

Drug switches were recorded by one researcher (M.H.) at each pharmacy's counter, for one full day. A drug switch was defined as the replacement of a patient's drug product with a drug product containing the same active pharmaceutical ingredient, the same strength, the same dosage form and the same route of administration, but from a different manufacturer (brand or generic). Drug switches for drugs destined for home delivery or storage in the pharmacy's service lockers were included in the study, whereas pre-packed and pre-sorted packets for polypharmacy patients were excluded from the study for practicality. The researcher used notification systems but was also depended on pharmacy personnel to notice drug switches.

Pharmacy characteristics (predominant healthcare insurer, ownership status) were registered. Per drug switch, the reason, the INN, the dose, the manufacturer, and patient's health insurance company were registered. Pharmacists were interviewed regarding their view on drug switching and the reasons behind drug switching. Descriptive data analysis was used.

Nationwide shortages were identified from Farmanco – the drug shortage report system from the Dutch Pharmacists Association – which contains manufacturers' confirmed shortages lasting longer than 14 days (9). If a drug switch was because of a drug shortage that was neither a result of local pharmacy practice, nor nationwide, then the reason for the switch was considered a distribution issue at the wholesale level.

Results

Out of 400 approached pharmacies, 19 were willing to participate (4.8%); for 16 pharmacies visits could be scheduled and were included in the study. These pharmacies differed by predominant health insurance company: Zilveren Kruis/Achmea (6), Menzis (4), Zorg en Zekerheid (3), VGZ/CZ (2) and Salland (1) and ownership: pharmacy chain (4), franchise (5), independent (7).

In total, 207 drug switches were registered; 13 on average per day per pharmacy (range: 4–24). As expected, most drug switches were between generic products (86%, 177/207). Moreover, 6% (12/207) of switches was from a brand-name product to a generic product. Drug switches between two brand-name product (e.g. imported from another European country) accounted for 4% (8/207), and switching from a generic product to a brand-name product accounted for 3% (7/207) of the drug switches. Finally, 1% (3/207) of the drug switches was between compounded products (see Table 1).

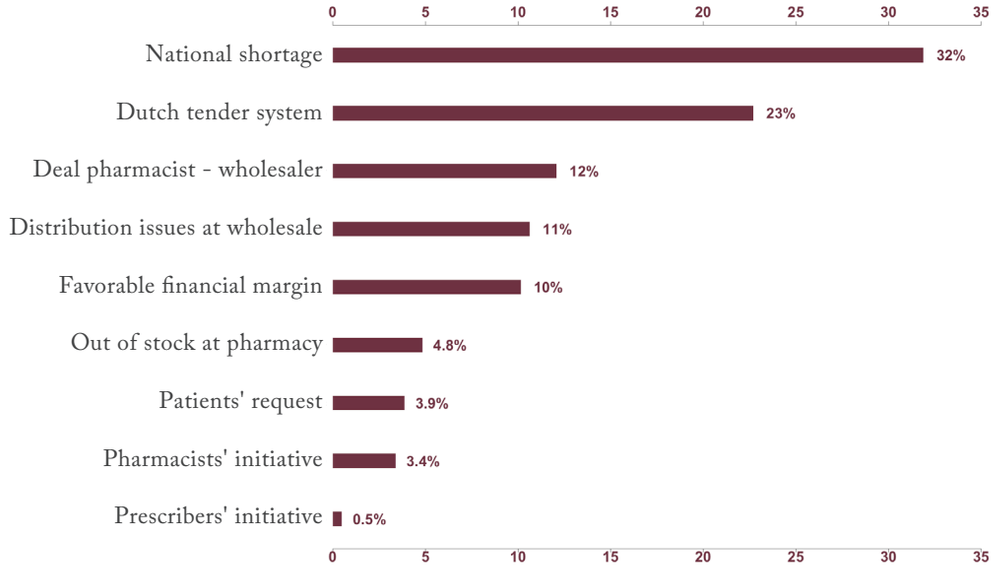

Figure 1: Characterization of registered drug switches and underlying reasons.

As depicted in Figure 1, most drug switches were a result of nationwide shortages (32%, 66/207) or the Dutch tender system (23%, 47/207). Agreements between wholesalers and pharmacists to dispense a drug product from a specific manufacturer were responsible for 12% (25/207) of the registered drug switches. In addition, 11% (22/207) of the drug switches were presumably caused by wholesalers' distribution issues, resulting in shortage at the pharmacy, while favourable financial margins were the reason for 10% (21/207) of the drug switches. Moreover, local out-of-stock issues at the pharmacy, not caused by wholesalers' distribution issues, were indicated as the reason for 5% (10/207) of

the drug switches. Finally, 4% (8/207) were at the request of the patient, while 3% (7/207) were initiated by the pharmacists, and only one by the prescriber.

Drug switch type	Number of drug switches	Share of total
Generic product to generic product	177	86%
Brand-name product to generic product	12	5.8%
Brand-name product to brand-name product	8	3.9%
Generic product to brand-name product	7	3.4%
Other	3	1.4%
Total	**207**	**100%**

Table 1: Summary of drug switch type

During the interview, 12 of the 16 pharmacists indicated that the number of registered drug switches was an underestimation of a normal days' practice, whereas 4 pharmacists indicated it was representative. Fifteen pharmacists reported an annual increase in the number of drug switches. Furthermore, based on daily experience, 11 and 5 of the 16 pharmacists estimated that drug shortages and the Dutch tender system, respectively, were the main causes for drug switches. In addition, 9 pharmacists were of the opinion that generic drugs are interchangeable, while four believed that these are not interchangeable, and three pharmacists had a neutral position on interchangeability.

Discussion

To our knowledge, this study is the first to investigate reasons for occurrence of drug switches in the Netherlands. In our sample, we found that the two main reasons for drug switching are nationwide drug shortages and the price-based tender system, which combined are responsible for approximately 55% of the drug switches in the Netherlands. It could be argued that 'distribution issues at wholesalers' and 'out-of-stock issues at the pharmacy' should also be characterized as shortages, which would increase the share of 'shortages' from 23% to 47% (98/207) of the total number of drug switches. Economic drivers contribute significantly to the number of drug switches, which were most clearly identified in 22% of the total number of drug switches (i.e., deals between pharmacist and wholesalers [12%] and financially favourable margins related to reimbursement [10%]).

The first study limitation is the small sample size, which could impact generalizability of the results. In addition, pharmacy visits were only in November and December while the influence of the Dutch tender system on drug switching is likely bigger in January to March (1). Study repetition should include more pharmacies and visits spread throughout the year. However, because we aimed to study the entire range of reasons for drug switching, the research period was still deemed adequate and perhaps more sensitive to identify issues other than the Dutch tender system.

Second, the study is limited by the semi-systematic approach, as the researcher was partly dependent on pharmacy personnel to notice drug switches. Three pharmacies did not use an automatic notification system for drug switches, which increased this dependency. Furthermore, we excluded drug switches for polypharmacy patients in pre-packed and pre-sorted packets. It must also be noted that we only succeeded in scheduling visits on 'not too busy' days. These limitations may have resulted in an underestimation of the total number of drug switches. Indeed, during the interview, 75% of the pharmacists (12/16) indicated that the registered number of drug switches was likely an underestimation. However, it is not expected that different reasons for drug switches would have been identified.

Overall, we present an exploration of the complex Dutch landscape of reasons for drug switching, which is, in some cases, related to policies or market structure specific to the Netherlands. Nonetheless, these findings are of international relevance. The search for an optimized drug market system, in which generic drugs simultaneously have a large market share but a low number of drug switches, is not restricted to the Netherlands. Moreover, policies and financial incentives, such as mandatory INN prescribing, or price-driven tender systems for drug reimbursement are effective in many countries. They would therefore likely result in a similar number of drug switches and similar reasons for those switches. Policymakers worldwide could thus utilize the results of our study. The results should open up the discussion about the acceptability of economic or distribution issues that cause drug switches, which in some cases result in clinical discomfort for patients. This is, however, a difficult discussion, as the issues are likely not easily solved and are perhaps essential for the financial viability of the pharmaceutical market.

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Chapter 3.1

Interchangeability of generic drugs: a non-parametric pharmacokinetic model of gabapentin generic drugs

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Abstract

Substitution by generic drugs is allowed when bioequivalence to the originator drug has been established. However, it is known that similarity in exposure may not be achieved at every occasion for all individual patients when switching between formulations. The ultimate aim of our research is to investigate if pharmacokinetic subpopulations exist when subjects are exposed to bioequivalent formulations. For that purpose, we developed a pharmacokinetic model for gabapentin, based on data from a previously conducted bioavailability study comparing gabapentin exposure following administration of the gabapentin originator and three generic gabapentin formulations in healthy subjects. Both internal and external validation confirmed that the optimal model for description of the gabapentin pharmacokinetics in this comparative bioavailability study was a 2-compartment model with absorption constant, an absorption lag time and clearance adjusted for renal function, in which each model parameter was separately estimated per administered formulation.

Introduction

Generic medicines are drugs comparable to their originator counterparts, containing similar amounts of active substance(s). Generic drugs can only be marketed when pharmaceutical comparability to the originator has been demonstrated and the patent of the originator has expired. Financial investment for the development of generic drugs is markedly lower as compared to that for development of a new active substance medicinal product (i.e. originator drug), as there is no need to repeat the studies on safety and efficacy of the active substance. Therefore, generic drugs are usually sold for lower prices, generally resulting in health care cost savings.

About 80% of all pharmacy filled prescriptions in the United States are filled with generic drugs (1). In Europe, market shares of generic drugs may differ between countries (2). In the Netherlands, 72.4% of all drug prescriptions in 2015 were for generic drugs, while these accounted only for 16.5% of total drug associated costs (3). If available in the Netherlands, 97.1% of the prescriptions are filled with generic drugs. This high percentage in the Netherlands is presumably partly a result of the way health insurance companies execute national law and in the case of drug shortages, pharmacists are often forced to substitute with other equivalent (generic) drugs (4,5).

Registration of generic drugs requires proof of bioequivalence to the originator. If generic drugs contain an equal amount of active substance(s), proof of bioequivalence can be provided by statistically confirmed comparable bioavailability. Bioequivalent formulations are subsequently expected to demonstrate essentially similar efficacy and safety under identical circumstances.

Even though evidence for clinical inequivalence could not be identified for cardiovascular and antiepileptic drugs (6,7,8), a large portion of patients and health care professionals have doubts regarding quality, safety and efficacy of generic drugs and hold a negative opinion towards generic drug substitution (9). For instance in the field of epilepsy, many issues regarding seizure control are reported and various clinical guidelines recommend to avoid generic drug substitution (10).

To demonstrate bioequivalence, usually a randomized crossover study with pharmacokinetic endpoints is conducted, comparing two formulations of which one is the originator. Bioequivalence is confirmed when 90% confidence intervals of

the geometric mean ratios for area under the curve (AUC) and peak concentration (C_{max}) are within pre-specified limits, which are normally 80.00 to 125.00%, as for instance described in the 'guideline on the investigation of bioequivalence' by the European Medicines Agency (EMA) (11) and the draft guidance 'bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA' by the Food and Drug Administration (FDA) (12). The bioequivalence approach however, is based on average values and only accounts partially for the variation observed for an individual's pharmacokinetic parameters. In theory, high ratios for AUC and / or C_{max} outside the 80.00-125.00% margin could be observed upon administration of different formulations in a single individual, even though these formulations were proven to be bioequivalent. Ultimately, we want to investigate those individual deviations and to challenge the appropriateness of the current bioequivalence requirements in regulatory approval of drugs, by investigating whether pharmacokinetic subpopulations exist, demonstrating low or high ratios for AUC and/ or C_{max} when exposed to bioequivalent formulations of gabapentin, using a non-parametric pharmacokinetic modeling approach. The study described in this paper represents the first step in which we build and validate a pharmacokinetic model for gabapentin based on pharmacokinetic data from a previously conducted comparative bioavailability study comparing gabapentin exposure following administration of the gabapentin branded formulation and three generic gabapentin formulations currently marketed in the Netherlands.

Results

In the first step of the modeling, 4 different structural models were considered. By addition of a Tlag in the 1 compartment with absorption constant model, the AIC decreased (-219) (Table 1a). Likelihood of the model with a 2nd compartment was higher compared to the 1 compartment model; the AIC was reduced (AIC from 3802 to 3669). Model fit further improved with the Tlag introduced in the 2-compartment model, with no significant changes in bias and precision. Overall, a reduction of the AIC of 233 was observed by introduction of the 2nd compartment and Tlag parameters. Based on AIC, bias and precision as well as the VPCs, it was concluded that a 2-compartment model with addition of Tlag best explained observed data. The regression equation of the observed versus the predicted concentration is y=0.997x + 0.0295 with an R2 of 0.887 (bias: -0.0194 and imprecision: 0.851).

Model	Parameters	AIC	ΔAIC	Bias	Imprecision
Structural models					
1 comp + Ka	Ka, V, Ke	3802		0.0018	0.8543
1 comp + Ka + Tlag	Ka, Tlag, V, Ke	3583	-219	-0.0114	0.8467
2 comp + Ka	Ka, V, Ke, KCP, KPC	3669	-133	0.0103	0.8638
2 comp + Ka + Tlag	Ka, Tlag, V, Ke, KCP, KPC	3569	-233	0.0194	0.8514
Level of separation					
Separation of Ka	Ka1, Ka2, Ka3, Ka4, Tlag, V, Ke, KCP, KPC	2546	-1023	-0.0052	0.8284
Separation of Tlag	Ka, Tlag1, Tlag2, Tlag3, Tlag4, V, Ke, KCP, KPC	3576	+7	-0.0362	0.8540
All parameters separated ('96 pseudo subjects')	Ka, Tlag, V, Ke, KCP, KPC	1588	-1981	-0.0214	0.7888
Covariates selection					
Weight	Ka, Tlag, V, Ke, KCP, KPC	1613	+25	-0.0884	0.8063
Renal	Ka, Tlag, V, Ke, KCP, KPC	1585	-3	-0.0280	0.7795
Weight + Renal	Ka, Tlag, V, Ke, KCP, KPC	1600	+12	-0.0653	0.8262

Table 1: Model selection statistics: Akaike Information Criterion (AIC), bias (mean error) and imprecision (mean squared error) are shown.

The second step in this modeling exercise was refinement to include structure with regard to the 4 different formulations. Based on the chosen base model (2 compartment, Ka, Tlag) a comparison to 3 additional models was made. These models were; (1) separation of Ka per formulation, (2) separation of Tlag per formulation and (3) separation of all parameters (Ka, Tlag, V, KCP, KPC and

Ke) per formulation. Numerical results of this comparison are depicted in Table 1b, and show that model fit was improved by allowing separate estimates for Ka per formulation but not when allowed for separation on Tlag. The likelihood of the model was strongly improved for the 'pseudo subject' model, in which each parameter was independently estimated per treatment period, the AIC was reduced by 1981 (from 3569 to 1588) compared to no separation at all. Therefore, this model was chosen as the final structural model for further refinement. The regression equation of the observed versus the predicted concentration for this model is y=0.995x + 0.022 with an R2 of 0.98 (bias: -0.0214 and imprecision: 0.7888).

The third step in the model building process was covariate selection. Based on stepwise linear regressions, weight and renal function were selected as the covariates with the potential to improve model fit. Weight (mean 71.0, range 52.7 - 97.0 kg) was tested as a multiplicative term on V (Equation 1).

$$V0 = V * WEIGHT$$

Equation 1: Weight as a multiplicative term on V

Renal function was estimated by creatinine clearance (mean 120, range 71.2-183 ml/min), which was estimated from the serum creatinine concentration, by using the Cockcroft-Gault equation. There is no indication that gabapentin undergoes metabolism in humans. Instead, it is eliminated unchanged solely by renal excretion (13). A multiplicative term of renal function (CrCl) on the renal clearance (Kr) is therefore expected to adequately represent clearance (Ke) (Equation 2).

$$Ke = Kr * CrCl$$

Equation 2: Clearance (Ke) as a multiplicative term of renal function (CrCl) on renal clearance (Kr)

From Table 1c; The covariate weight as a multiplicative term on V did not significantly improve the likelihood of the model (AIC +25), indicating no

significant dependency of volume of distribution on weight. However, the model fit improved with renal function correlated to gabapentin clearance by a multiplicative function of renal function on the elimination constant. An AIC reduction of 3 was computed, when renal function on elimination was included in the model. A combination of both weight on volume and renal function on clearance did not further improve model fit (AIC+ 12) relative to the model with renal function only.

Thus, the final model for description of the gabapentin pharmacokinetics in the bioequivalence study was a 2-compartment model with absorption constant, an absorption lag time and elimination adjusted for renal function in which each model parameter was separately estimated per administered formulation (Equation 3).

$$(delta/delta\ T)\ ammnt\_depot = Fabs * dose\ (T - Tlag) - Ka*ammnt\_depot$$

$$(delta/delta\ T)\ ammnt\_blood = ammnt\_depot * Ka + ammnt\_peripheral * KPC - ammnt\_blood * (KPC + Ke)$$

$$(delta/delta\ T)\ ammnt\_peripheral = KCP * ammnt\_blood - KPC * ammnt\_peripheral$$

$$concentration\_blood = ammnt\_blood / vol\_blood$$

$$Ke = Kr * CrCl$$

$$error = sqrt(lambda^2 + sigma^2)$$

$$sigma = C0 + C1*X\_central$$

Equation 3: Final model equations

The observed versus the predicted concentration plots are shown in Figure 1, both for the population prediction and the individual prediction. The regression equation is y=0.995x + 0.0256 with an R^2 of 0.98 (bias: -0.0280 and imprecision: 0.7795).

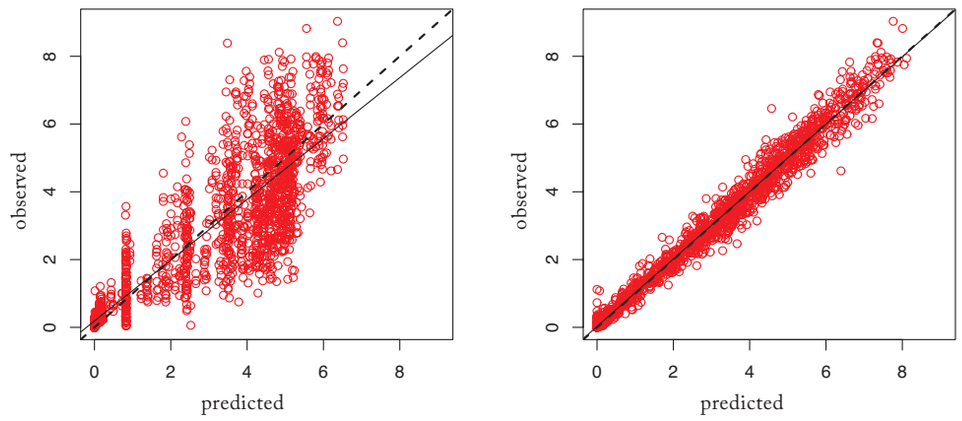

Figure 1: Population (left) and individual (right) predicted versus observed values for the final 2-compartment model with absorption constant, an absorption lag time, elimination adjusted for renal function and all parameters separately estimated per formulation, line of identity (dashed line) and linear regression (solid line).

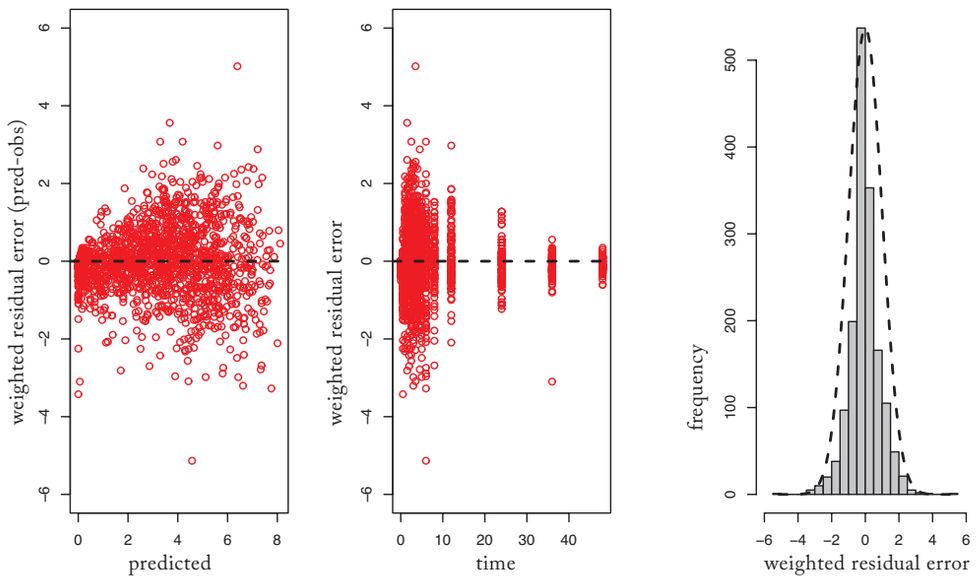

Figure 2: Residual plots; weighted residuals vs. predictions (left), weighted residuals (predicted - observed) vs. time (middle) and a histogram of residuals with an overlay of a normal curve (right).

Residual plots for the final model are shown in Figure 2. Weighted residuals demonstrate an even spread over the concentration range as well as over the time span. A slight tendency can be observed with some under predictions in the lower concentration range. However, as can be seen from the histogram of residuals, the majority of residuals are centered around zero. The D'Agostino-Pearson test for non-normality tests not significant (p = 0.587), thus the assumption is made that the residual error follows a normal distribution.
A visual predictive check (VPC) was performed for the final model, as depicted in Figure 3. The scatterplot VPC with prediction intervals shows a good correlation but some added variability on the distribution and elimination phase.

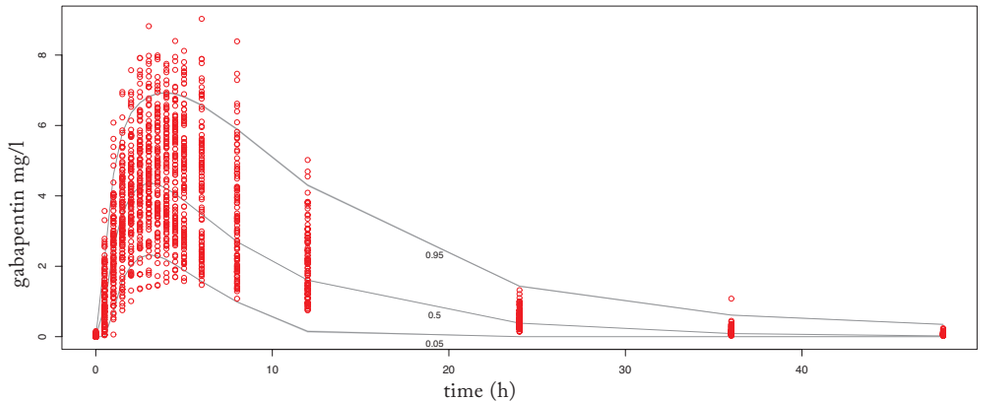

Figure 3: Scatterplot VPC, observed data from the study is represented in circles, prediction intervals (quantiles 0.05, 0.5 and 0.95) determined from 1000 simulations as solid lines.

An overview of estimated pharmacokinetic parameters from both the observed concentrations and from predicted time-observation profiles is provided in Table 2. Despite a small under prediction of the model concentrations (mean deviation from C_{max}: 7.95%, AUC_{0-t}: 5.08%, AUC_{0-inf}: 6.23%) and some added variability on half-life (mean +/- SD, observed: 8.24h +/- 2.82, predicted: 8.84 +/- 10.67), no obvious deviation is observed for the parameters.

	Formulation 1	Formulation 2	Formulation 3	Formulation 4
C_{max} (mg/l) observed	5.33 +/- 1.79	5.43 +/- 1.86	5.48 +/- 1.44	5.62 +/- 1.65
C_{max} (mg/l) predicted	4.99 +/- 1.71	4.87 +/- 1.65	5.11 +/- 1.36	5.16 +/- 1.52
AUC_{0-t} (h.mg/l) observed	63.42 +/- 25.72	61.55 +/- 24.70	61.16 +/- 20.80	62.08 +/- 22.91
AUC_{0-t} (h.mg/l) predicted	59.92 +/- 24.71	58.87 +/- 24.01	58.88 +/- 19.83	57.92 +/- 22.04
AUC_{0-inf} (h.mg/l) observed	64.49 +/- 25.68	62.39 +/- 24.68	62.45 +/- 20.88	63.03 +/- 23.13
AUC_{0-inf} (h.mg/l) predicted	60.18 +/- 24.62	59.12 +/- 23.92	59.02 +/- 19.87	58.29 +/- 22.01
T_{max} (h) observed	4.0 (2.50-8.0)	4.25 (2.0-8.0)	3.50 (1.5-6.0)	3.75 (1.5-8.0)
T_{max} (h) predicted	3.5 (1.8-8.8)	3.7 (2.2-6.4)	3.0 (1.6-6.2)	3.7 (1.6-6.0)
$T_{1/2}$ (h) observed	8.12 +/- 2.70	8.08 +/- 2.08	9.08 +/- 3.63	7.66 +/- 2.63
$T_{1/2}$ (h) predicted	7.66 +/- 5.94	7.92 +/- 6.85	7.53 +/- 4.25	12.24 +/- 18.81

Table 2: Non-compartmental analysis derived pharmacokinetic parameters C_{max} AUC0-t, AUC0-inf, Tmax and T1/2 from observed concentrations and individual Bayesian posterior final model predicted time-observation profiles, per treatment. All parameters are mean +/- SD, but Tmax median and range.

Parameter	wMedian and 95%CI	BOV
Ka (h-1)	0.26 (0.23-0.31)	35 %
Tlag (h)	0.30 (0.21-0.35)	75 %
V (l)	90.0 (83.5-106)	34 %
KCP (h-1)	0.16 (0.12-0.36)	110 %
KPC (h-1)	0.82 (0.30-1.69)	68 %
Ke (h-1)	0.32 (0.29-0.36)	34 %

Table 3: Estimated parameter values for the final model, weighted median, 95% confidence interval around the median (CI) and Between Occasion Variability, % (BOV). Ke recalculated from rate per ml/min creatinine clearance.

Estimated pharmacokinetic parameter values obtained with the final model are tabulated in Table 3. Parameter values are summarized as median and the 95 % CI around the median, as calculated by a probability weighted Monte Carlo simulation (n=1000) from the support point distribution. The Between Occasion Variability (BOV) is calculated as the population mean from the estimates of each subjects' 4 pseudo subjects coefficient of variation.

External validation of the model was performed with data obtained from a separate pharmacokinetic (bioequivalence) study with an oral 800 mg gabapentin formulation which was submitted to the MEB in support of a generic application. The NonParametric Adaptive Grid algorithm (NPAG) distribution from the final model was used as input ('prior') for the external data, to construct an observed versus predicted concentration plot, as shown in Figure 4. A high correlation can be observed, with a regression equation y=0.925x – 0.0294 with an R^2 of 0.952.

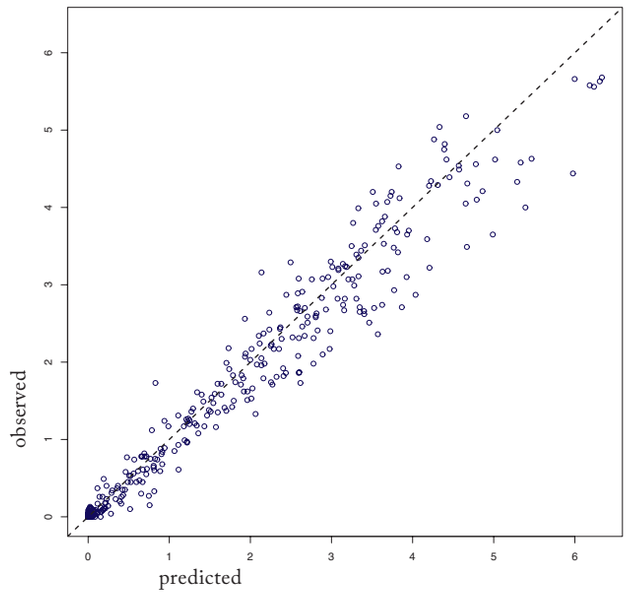

Figure 4: Individual predicted versus observed values from separately obtained gabapentin validation data (800 mg bioequivalence study).

Discussion

Both internal and external validation confirmed that the optimal model for description of the gabapentin pharmacokinetics in this comparative bioavailability study was a 2-compartment model with absorption constant, an absorption lag time and clearance adjusted for renal function, in which each model parameter was separately estimated per administered formulation.
The ultimate goal of our model is to perform simulations for the identification of pharmacokinetic subpopulations or outliers with an aberrant exposure to gabapentin outside the 80.00-125.00% margin when switching between bioequivalent formulations. Since the aim of our research is to investigate the influence of formulation on bioequivalence, one could argue that our model selection was biased towards a model with parameters separately estimated per formulation. However, we used a structured method of model selection and objective assessment of the selection parameters and thereby avoid such bias. Further, by separation of all model parameters per administered formulation we chose the most naïve approach to the data. Therefore, we were able to construct the best possible model for the explanation of these data.
The rationale for the models with separation only of Ka and Tlag is based on the general assumption regarding generic drugs that only the absorption phase and not the distribution or elimination phase is influenced by possible formulation differences. However, a limitation of those models is that the parameters for the distribution and elimination phase are fixed to the same value, for each subject. This is not an adequate representative for the true values for these parameters, as natural variability between occasions is expected to be present in any study, even where subjects serve as their own controls. By allowing separation of all parameters of the absorption, distribution and elimination phase, we allow for this inter-occasion variability. An additional randomized 5th period in the gabapentin study, with a repeated administration of 1 of the 4 formulations, solely dissimilar by occasion, would have allowed to compute an estimation of the true inter-occasion variability directly derived from the pharmacokinetic data. With the current study design, which is the usual for regulatory establishment of bioequivalence, it is not possible to separate variability due to occasion vs. variability from formulation. However, the absence of a 'true' estimation of the inter-occasion variability is not necessarily a weakness of the data and the

model. Within the current 'pseudo subject' model, the inter-occasion variability is not fixed to the amount we would have computed based on repeated administration of 1 formulation between 2 occasions. This model is without any assumptions on the inter-occasion variability.
Population pharmacokinetic models can be statistically classified as parametric or nonparametric. We choose to perform non-parametric population pharmacokinetic modeling, even though it is common practice to use parametric modeling in drug development and evaluation. In drug application dossiers submitted to regulatory authorities, the parametric program NONMEM is the most frequently used. However, an advantage of the non-parametric approach is that no assumptions are made with regard to the distribution of described parameter values. Entire joint distributions with probabilities are estimated based on the data, instead of estimating a parameter mean or median (population standard value 'Theta') and deviation (individual random effect 'Eta') (14). The absence of those assumptions in the non-parametric approach allows discovery of non-pre-specified subpopulations. This theoretical characteristic of non-parametric modeling was confirmed by Neely et al., by accurately detecting a bimodal elimination and one pharmacokinetic outlier19. Considering the aim of our study, it is justified that non-parametric modeling is the most appropriate method, optimizing our chances of identifying pharmacokinetic subpopulations.

model uncertainties

The polynomial coefficients for the error model should ideally be determined by the bioanalytical lab based on observed variation at standard concentrations. However, in absence of detailed information about the accuracy and precision of this bioanalytical method, we estimated the error polynomial coefficients based on data from other bioanalytical gabapentin methods seen in registration files of the MEB. The chosen polynomial coefficients represent a coefficient of variation between 2.75-0.95%. The Lambda term was fitted by NPAG in the final model to be 0.2990, indicating low amount of process noise and a well-executed pharmacokinetic characterization.
Gabapentin has been modeled before, using a combined approach of parametric (NONMEM) and non-parametric modeling (15). The final model from this study was a 1-compartment model with a fixed absorption constant (0.44 h-1)

and a non-linear bioavailability parameter. Our final model deviates from the previously described model by absence of a function for the absorption, an additional distribution compartment and renal function correlated clearance. An explanation for reaching another optimal model could be the richer data input (i.e. 96 occasions of 17 blood samples each in our case versus 25 occasions of 10 blood samples each in the previous study). In our research, non-linearity of the bioavailability was not explored as only 1 dose strength was administered. The estimated Ka in our study (median 0.26, range 0.11-1.09 h-1) was within the same extent. Another parametric model found was a one compartment model with absorption constant (0.053 - 0.461 h-1) and lag time (0.48 - 2.29 h-1), with covariates creatinine clearance and race (Black versus other) on gabapentin clearance and weight and population (healthy subjects versus patients) on volume of distribution (16). Again, an explanation of the observed differences could be a richer data input compared to this study (average 1.6 samples per patient).
In addition to Ka and Tlag, a relative bioavailability term (F, proportion) was explored to be included in the model. Due to the high correlation of F with Ka and the inability to accurately estimate F in the absence of intravenous data, it was concluded to estimate Ka and treat F as a fixed (but random) population parameter, to avoid unnecessary complication of the estimated absorption. As an alternative, it was planned to estimate F as a relative term. The F could then be estimated relative to 1 of the formulations, but this became irrelevant with the introduction of the 'pseudo subject' model.
Creatinine clearance was used to estimate renal function using the Cockcroft-Gault equation. Although validity of the estimation by Cockcroft-Gault is questioned in certain patient populations such as elderly and overweight subjects (17), we believe this is an accurate estimator for our data, which is obtained in young healthy adult volunteers with normal weight (included subject were in the age range of 21–55 years and their mean BMI was in the range of 19.9–30.0 kg/m2).
The external validation was performed using a gabapentin dataset obtained from the registration files of the MEB. In this study, no serum creatinine values were presented. To allow for a Cockcroft Gault estimation of the creatinine clearance, average serum creatinine values (male and female) from the 4-way study were used. This was believed to be the best available estimate of the renal function. With the external data, a high correlation was observed and

external validation of our model could be inferred.
To conclude, gabapentin pharmacokinetic data was shown to be best described by a 2-compartment model with an absorption constant and absorption lag time, with clearance adjusted for renal function and each model parameter separately estimated per administered formulation. The final model adequately describes observed data, does not show deviating trends in the goodness of fit diagnostics and is in line with current pharmacokinetic gabapentin knowledge. The model as described is considered fit for further analyses and simulations. Such future simulations using the model will be aimed to identify potential subpopulation of individual patients with increased risk for altered pharmacokinetics as a result of switching between bioequivalent formulations.

Methods

Gabapentin pharmacokinetic data

Gabapentin pharmacokinetic data was previously gathered in a 4-way crossover comparative bioavailability study, comparing 4 different oral immediate release formulations of 800 mg gabapentin that were previously accepted to be bioequivalent and therefore registered by the Dutch Medicines Evaluation Board (MEB) (18). In that study, twenty-four healthy volunteers (14 females and 10 males) were enrolled and completed the study. The mean age was 35 years (range: 21–55), mean body mass index was 23.6 kg/m2 (range: 19.9–30.0) and mean creatinine clearance 120 ml/min (range: 71.2-183.3). Gabapentin levels were measured in plasma samples, drawn pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 36 and 48 hours post-dosing, during each period. Adverse events and vital signs were monitored, standard laboratory evaluations were performed. Pharmacokinetic parameters C_{max} AUC_{0-t}, AUC_{0-inf}, T_{max}, $T_{1/2}$, K_{el} and AUC_{0-t} /AUC_{0-inf} were computed and an ANOVA was performed using ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf}. The 90% confidence intervals were calculated for C_{max}, AUC_{0-t} and AUC_{0-inf}. Bioequivalence was confirmed between all different formulations.

Model building in Pmetrics

A total of 1610 concentration time points was included in the model building process. Non-parametric population pharmacokinetic modeling was performed

using the Pmetrics package (version 1.5; Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA) using R (version 3.2.2) that uses the algebraic model solver and NonParametric Adaptive Grid algorithm (NPAG) (19). In NPAG, 4 different structural base models were compared, i.e. a 1- and a 2-compartment model with an absorption constant, both with or without an absorption lag time. For these comparisons, parameters to be estimated were absorption constant (Ka, rate, unit per hour), absorption lag time (Tlag, hours), volume of distribution (V, liter), elimination constant (Ke, rate, unit per hour), transfer rate from central to peripheral compartment (KCP, rate, unit per hour) and peripheral to central (KPC, rate, unit per hour). Boundaries for the parameter estimates were determined based on gabapentin knowledge, estimated values and for KCP/ KPC on expected inter-compartmental clearance and volume of central and peripheral compartments. Upper parameter boundaries were 1.25 h-1 (Ka), 200 L (V), 0.008 h.ml-1 (Ke), 1.5 h (Tlag), 2.0 h-1 (KCP) and 2.0 h-1 for KPC.

Information with regard to the formulation was incorporated in the structural model by constructing models able to separately estimate 4 different parameter values for each subject, based on the administered formulation. A model was constructed to estimate 4 Ka values per subject, 4 Tlag values per subject, or 4 different values for all estimated parameters. The latter was achieved by dividing subjects' separate sampling visits into 'pseudo' subjects for this analysis, 4 per true subject, thus 96 in total.

The applied error model per observation ($1/error^2$) is a polynomial equation for the SD = .02 + .0075*(concentration), and error = (SD^2 + $Lambda^2$)0.5. The Lambda value is a fitted term to capture extra process noise on the observed values.

Selection of the optimal structural model was based on minimization of bias (mean predication error) and imprecision (mean square prediction error) and assessed using Visual Predictive Check (VPC) and the reduction of the Akaike Information Criterion (AIC) (20). The AIC is defined as (2 × k) – 2 × ln(L), with k for the number of parameters and L the likelihood. Scatterplot VPCs with prediction intervals (quantiles 0.05, 0.5 and 0.95) from simulation (n=1000). Selection of covariates (available covariates in the dataset were serum creatinine (both at pre-dose screening and at follow-up), age, sex, race, weight and height) to be included in the model was based on linear regression of each subject's covariates versus the Bayesian posterior parameter values. Inclusion of these covariates in the final model was based on the same selection criteria as the structural model selection.

Model evaluation

Internal validation was tested by residual error plots and the D'Agostino-Pearson test (21) for normality in distribution of the residuals, as implemented in Pmetrics. Non-compartmental analysis derived pharmacokinetic parameters C_{max} AUC_{0-t}, AUC_{0-inf}, T_{max} and $T_{1/2}$ (computed by the 'makeNCA' function in Pmtetrics) from both the observed concentrations and from individual Bayesian posterior predicted time-observation profile where compared.

External validation of the model was performed using a data set from an independent pharmacokinetic study as filed during registration at the MEB for another generic formulation of gabapentin. In this study, subjects received a single oral formulation of 800 mg and plasma gabapentin concentrations were determined pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 26, 48, 60 hours post dose. This external validation was performed using 352 concentration time points. A total of 22 subjects were included in the analysis, of which 14 males and 8 females. The mean age was 35 years (range: 23–47 years), and their mean body mass index was 23.3 kg/m2 (range: 19.2–26.9 kg/m2).

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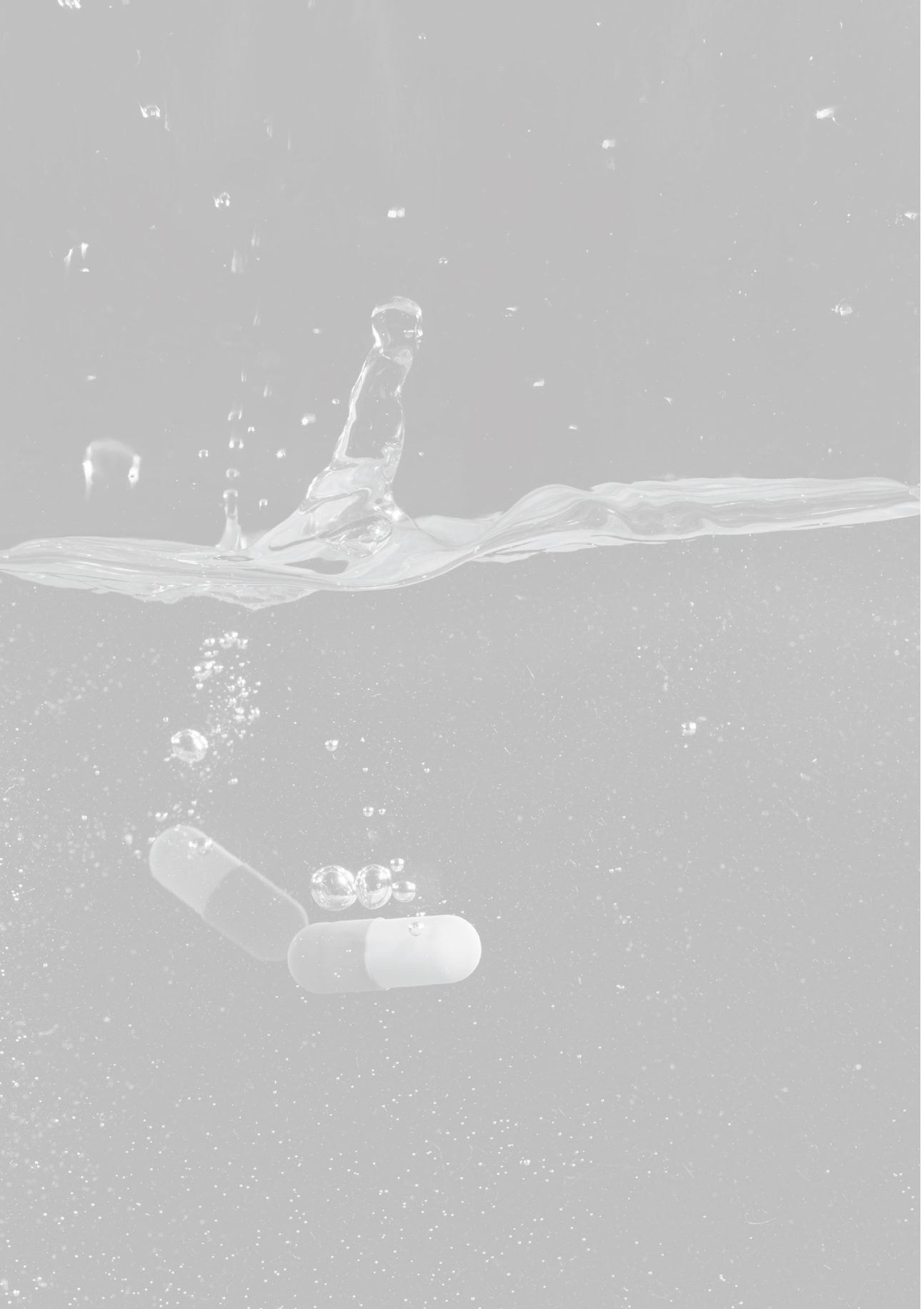

Chapter **3.2**

Interchangeability of generic drugs for subpopulations: bioequivalence simulation from a non-parametric PK model of gabapentin generic drugs

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Abstract

Patients are often switched between generic formulations of the same drug, but in some cases generic interchangeability is questioned. For generic drugs to be approved, bioequivalence with the innovator drug should be demonstrated; however, evidence of bioequivalence is not required in the intended patient population or relative to other approved generics.

We aim to identify pathophysiological pharmacokinetic subpopulations for whom there is a difference in comparative bioavailability, compared to a healthy population.

Methods

We used simulated exposures from a non-parametric model of multiple generics and the originator gabapentin. Exposure was simulated for virtual populations with pharmacokinetic characteristics beyond those of the healthy subjects, with regard to rate of absorption, volume of distribution and reduced renal function. Virtual parallel design bioequivalence studies were performed using a random sample of 24 simulated subjects, with standard acceptance criteria.

Results

Results indicate increased pharmacokinetic variability for patient populations with a lower rate of absorption or a reduced renal function, but no change of the average comparable bioavailability ratio. This increased variability results in a reduced likelihood of demonstrating bioequivalence. Observations were similar for comparisons between all different formulations, as well as between subjects who received the identical formulation in a repeated fashion. No relevant effect was observed for simulations with increased volume of distribution.

Conclusion

Our simulations indicate that the reduced likelihood of demonstrating bioequivalence for subjects with altered pharmacokinetics is not influenced by a formulation switch, nor does the average comparable bioavailability ratio change. Therefore, these results support generic interchangeability and current approval requirements for generics.

Introduction

A generic medicinal product, or 'generic', is defined in Directive 2001/83/EC of the European Commission to contain the same active substance and be the same pharmaceutical form as the originator (1). Generics are approved when identical quality and comparable bioavailability to the originator have been demonstrated. The efficacy and safety of generics do not need to be demonstrated with expensive clinical or non-clinical studies; hence, generics cost less, and price competition is present. Therefore, in clinical practice, originators are often substituted for generics, and generics are switched to other generics of the same active substance (2). However, in some cases, patients experience adverse drug reactions (ADRs) following a generic drug substitution or drug switch (3). These ADRs are unexpected, as comparable bioavailability is expected, and investigation of their origin is important. First, the outcomes of such an analysis may assist health care professionals to prevent patients from experiencing ADRs. Second, they may aid in testing the robustness of the current approval process of generic medicines. In the current analysis, we focus on a possible pharmacokinetic (PK) explanation for the reported ADRs.

Comparable bioavailability, as a key requirement for generics, should be demonstrated by so-called bioequivalence studies, the appropriate design of which is described in guidelines by, for instance, the European and United States regulators (4, 5). Bioequivalence studies are typically performed with healthy volunteers, often have a two-period, sequence-randomized, and single-dose crossover design. Primary parameters to be analysed are the area under the concentration-time curve (AUC) and the peak concentration (C_{max}). For both AUC and C_{max}, the 90% confidence interval (CI) for the geometric mean ratio (GMR) of the generic and originator should be within the acceptance interval of 0.80–1.25.

There are three main concerns with the demonstrated bioequivalence of generics. The first is 'drifting', which is described as a drift away from the original comparison: generics which are bioequivalent to the originator are not necessarily bioequivalent to one another. Second, it has often been suggested that BE in healthy volunteers does not necessarily warrant BE in the patient population, predominantly in paediatric populations (6, 7) and for immunosuppressive transplant drugs (8, 9). Third, bioequivalence is based on population

averages, and it may not be achieved for all individual patients when switching between formulations (10, 11). This could be the result of intraindividual variation, also known as inter-occasion variability (IOV).

The aim of this study is to challenge the concept of bioequivalence by addressing the aforementioned concerns. We aim to identify pathophysiological PK subpopulations for whom there is a difference in comparative bioavailability, compared to a healthy population, by use of modelling and simulation. To mimic possible patient populations, simulations are performed for virtual subjects with altered renal function, volume of distribution and absorption characteristics. These PK parameters can be subject to change, for instance during the condition of critical illness. Further, to mimic conditions under which drifting could occur, we simulate exposure from different generics in these virtual patient populations.

For this purpose, we use a non-parametric modelling and simulation approach, which has successfully been applied in the past in the detection of outliers and subpopulations (12). The model drug is gabapentin and the source PK data derives from a previously conducted bioequivalence study with the originator formulation and three generics, all approved in Europe (13). This study provided densely sampled exposure data. The model parameters have separately been estimated per formulation, and by the non-parametric nature of the model would allow identification of differences between formulations. The model construction and validation has been described in a previous study (14).

Methods

Simulations of gabapentin exposure data were performed using the integrated semi-parametric Monte Carlo simulator of the Pmetrics package (version 1.9.7; Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA) for R (version 4.0.4). The algebraic model solver and non-parametric adaptive grid algorithm (NPAG) have previously been applied to establish the gabapentin model (14). For the simulations, each point of the non-parametric joint density model (i.e. NPAG output) is a vector of values for the parameters in the model, with a probability or weight based upon the likelihood of those parameter values given the data in the model-building population.

The existing gabapentin model is based on PK data from a four-way crossover comparative bioavailability study with 24 subjects, each of whom received four different formulations (13). The optimal model has two compartments with absorption constant, an absorption lag time, and clearance adjusted for renal function, in which each model parameter was separately estimated per administered formulation. For the simulations, the non-parametric joint density of the model was split into four separate non-parametric joint densities – one per formulation (A, B, C or D). This split was achieved by four separate one-cycle NPAG runs, only including the data for formulation A, B, C or D.

Each of the four non-parametric joint densities was used to simulate single dose PK profiles for all of the 24 subjects, 100 per subject (2400 per joint density, total n = 9,600). For each scenario, a different seed for the random number generator was specified, to simulate from a different set of random parameters, i.e. a different subject. All comparisons in this study are therefore between subjects and not within subject. The non-parametric joint density for Formulation A was used twice, to allow for a comparison of two different subjects receiving the same originator formulation.

Simulations were performed for virtual populations with reduced renal function, increased volume of distribution (V) or altered absorption rate (Ka). Renal function is a covariate in the model and relates to gabapentin clearance by a multiplicative function of renal function on the elimination constant. Different populations were created through separate simulations retaining original parameter/covariate covariances but redefining the mean and standard deviation (SD) of renal function, which was estimated from the serum creatinine concentration, by using the Cockcroft–Gault equation. Renal function groups were simulated in accordance with European Medicines Agency (EMA) guidance with respect to renal function categorization: normal, >90 ml/min (mean 120, SD 30, limits 90–180); mildly decreased, >60 to <90 ml/min (mean 75, SD 15, limits 60–90); moderately decreased, >30 to <60 ml/min (mean 45, SD 15, limits 30–60); severely decreased, >15 to <30 ml/min (mean 22.5, SD 7.5, limits 15–30); and end stage, <15 ml/min (mean 7.5, SD 7.5, limits 1–15) (15).

V and Ka are primary variables in the gabapentin model, for which non-parametric joint densities were estimated by Pmetrics. Different populations were created by separate simulations in which the mean values for V and Ka in the non-parametric joint densities and covariances were adjusted, retaining point probability. For V, populations were created with one to five times the original

model-estimated Vs. For Ka, populations were created with one-third to three times the original model estimated Kas.

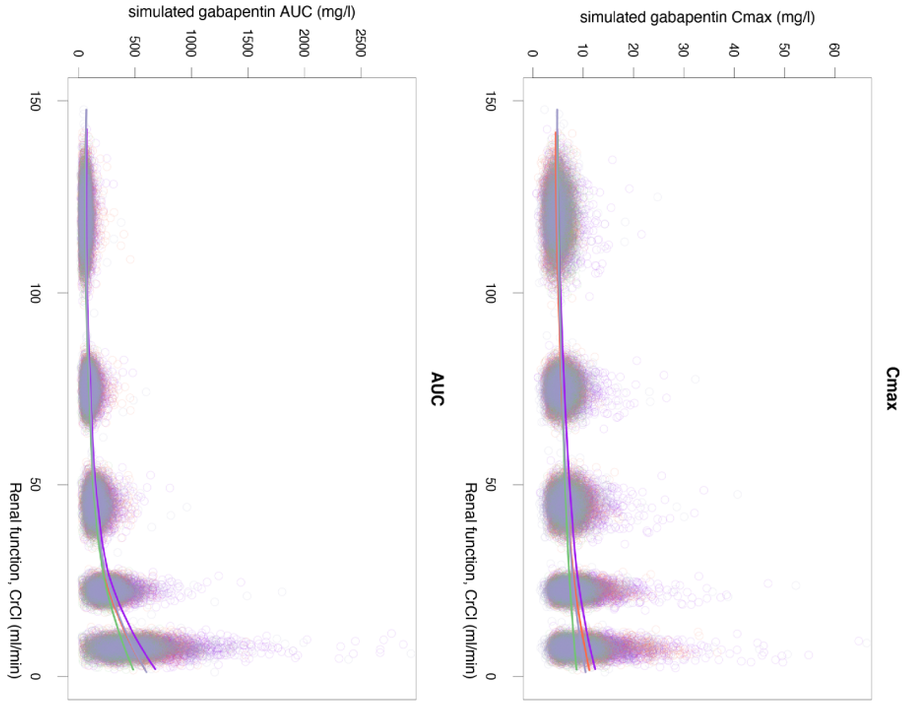
The AUC up to 72 hours was estimated using trapezoidal approximation of the 'makeAUC' function of Pmetrics, and C_{max} denoted the maximum simulated concentration of each simulated PK profile. Virtual parallel design bioequivalence studies (n = 300) were performed, per group using a random sample of 24 from the 2,400 simulated PK profiles. The AUC and C_{max} 90% CI for the GMR of test and reference products were to be within the acceptance interval of 0.80–1.25. All data analyses were performed using R.

Results

For each formulation, gabapentin PK profiles were simulated from a corresponding non-parametric joint density, i.e. four densities for the four formulations. Visual predictive check plots confirm suitability of the model and densities with similar distributions of simulated profiles and observed values for each formulation (fig. S1).

Renal impairment

As expected, simulated impaired renal function increased gabapentin concentrations (fig. S2) for all four formulations (fig. 1). Nonetheless, minor differences were noted between formulations. A slightly higher gabapentin exposure (both AUC and C_{max}) was predicted for Formulation A, and slightly lower for Formulation C. As illustrated in the violin plot, higher variability was predicted for gabapentin concentrations of Formulations A and D. However, the predictions demonstrated neither large differences nor the emergence of a subgroup of subjects with a notably different PK response for any of the formulations.



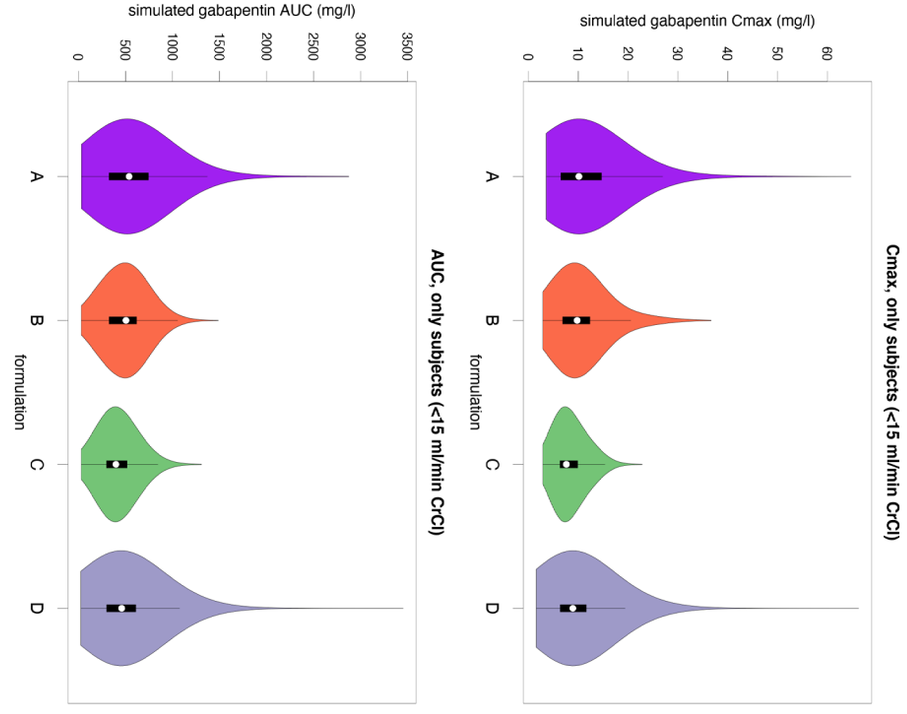


Figure 1: (right page, turn 90 degrees clockwise) Gabapentin concentration was estimated to increase for all 4 formulations, for subjects with reduced renal function. Left side: all individual values of AUC and C_{max} (open circles) and mean (lines), versus renal function. Different colors represent predictions for the different formulations (A, purple; B, red; C, green; D, light purple). Right side: violin plots for both AUC and C_{max}, per formulation, boxplot (median, interquartile box length and 1.5 range whiskers) with kernel density plot. These depict the distribution of AUC and C_{max}, only for subjects with a creatinine clearance below 15 ml/min.

To assess the influence of renal impairment on the likelihood of demonstrating bioequivalence, studies were simulated using random samples of 24 subjects. The percentage of simulated studies with 90% CIs within the 0.80–1.25 acceptance range of bioequivalence for both AUC and C_{max} declined with reduced renal function (fig. 2). This reduction was observed for all formulation comparisons, namely AB, AC, AD, BC, BD and CD. Importantly, this reduction was also observed to an analogous degree for the simulated bioequivalence studies comparing the simulations of different subjects receiving the same Formulation A twice ('AR').

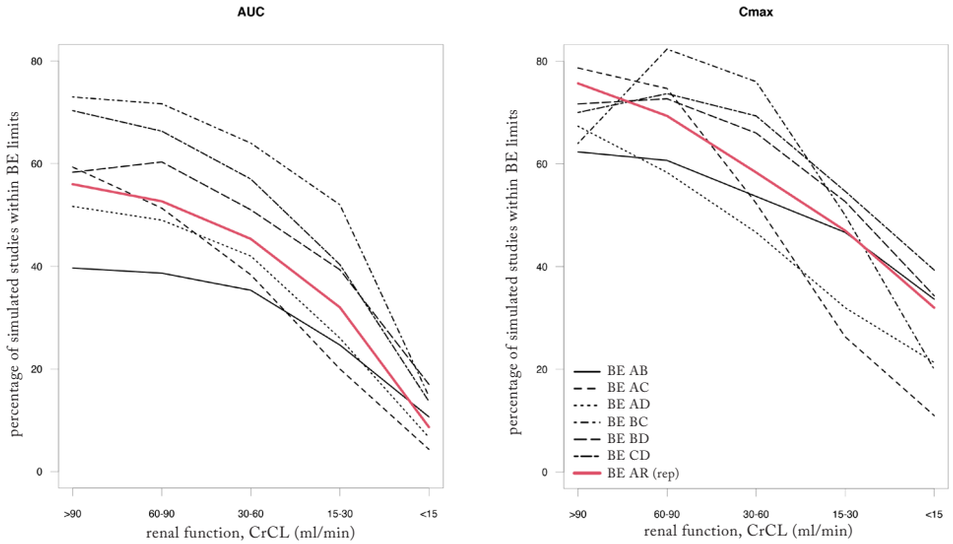
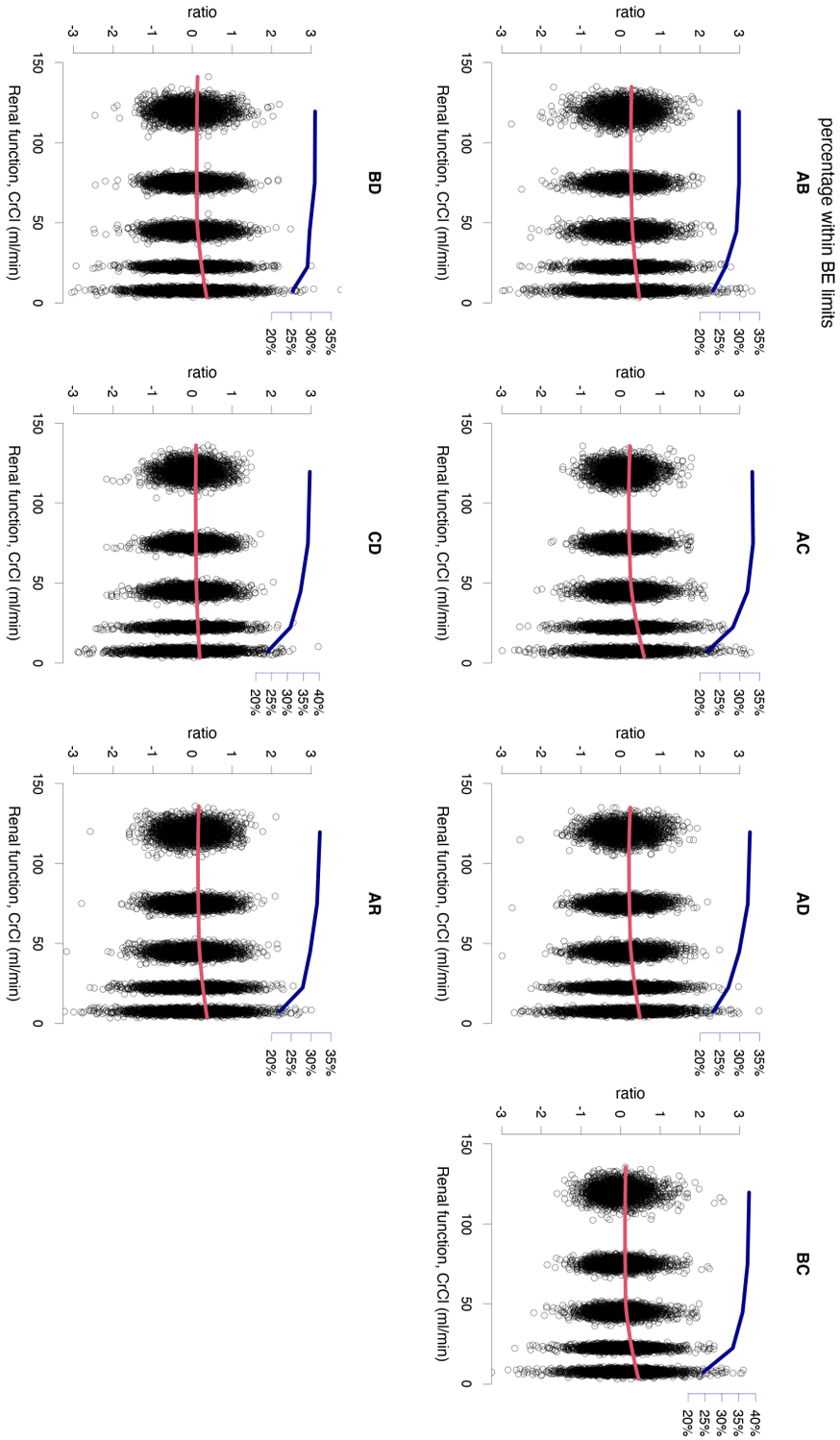


Figure 2: The percentage of simulated studies, of which the 90% CIs for both AUC and C_{max} are within the acceptance range of bioequivalence, declines with reduced renal function, for all formulation comparisons. The percentage of virtual bioequivalence studies with a 90% CI within the acceptance limits for bioequivalence is plotted per formulation comparison and renal function.

Figure 3: (right page, turn 90 degrees clockwise) Individuals with reduced renal function demonstrate higher variability of the ratio of the AUC, but the mean ratio is not different. For each individual, the ratio for AUC between each different combination of formulations is plotted against renal function (open circles). The red line is the regression line of all individual ratios. The blue line is the percentage of individual ratios within the acceptance criteria.



The individual ratio of the exposure for each virtual subject (n = 2,400) is depicted in fig. 3. The mean bioavailability ratio was not different for subjects with reduced renal function, but subjects with reduced renal function demonstrated higher variability of the ratio of the AUC, and C_{max} (fig. S3). This was observed both for the ratio of each individual combination of formulations and in the comparison of different subjects receiving Formulation A twice. Combining information on all switches, the percentage of individuals with a ratio for AUC or C_{max} within the bioequivalence range was 29.8–41.0% for subjects with a normal renal function (CrCl >90/ml), and it lowered to a range of 21.8–30.5% for subjects with a severely reduced renal function (<15 ml/min). The effect is comparable between the different formulation comparisons, and there are no subpopulations identified from these plots, which would demonstrate an aberrant ratio and true deviation from bioequivalence.

Volume of distribution

In patients with an increased distribution volume, a lower exposure for gabapentin is expected, with a more pronounced reduction of C_{max} than AUC. A reduction of both C_{max} and AUC was indeed predicted by simulations for subjects with an increased V, and this effect is comparable for all four formulations (fig. 4, fig. S4).

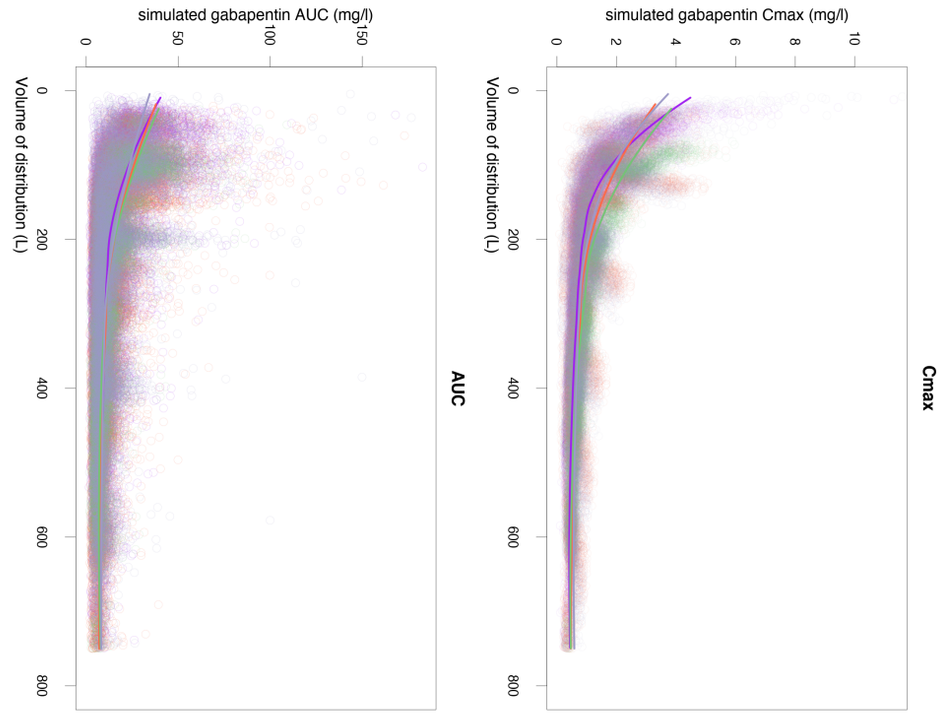


Figure 4: (right page, turn clockwise) A reduction of both C_{max} and AUC is indeed predicted for subjects with an increased Volume of Distribution and this effect is comparable for all 4 formulations. Left side: all individual values of AUC and C_{max} (open circles) and mean (lines), versus Volume of Distribution. Different colors represent predictions for the different formulations (A, purple; B, red; C, green; D, light purple). Right side: violin plots for both AUC and C_{max}, per formulation, boxplot (median, interquartile box length and 1.5 range whiskers) with kernel density plot. These depict the distribution of AUC and C_{max}, only for subjects with a Volume of Distribution 5 times the original model estimated values.

Bioequivalence studies using random samples of 24 subjects do not demonstrate a structural change in the percentage of studies with 90% CIs within the acceptance range of bioequivalence for both AUC and C_{max}, with an increased V (fig. S5).

The predictions for the individual ratios for AUC did not yield significant differences either, as a result of an increased V (fig. 5). There was no significant curvature of the regression line of the ratio. Variability of the individual exposure ratios appears to be lower only for subjects with a simulated V of more than 500 liters. Similar results were observed for C_{max} (fig. S6). Finally, no subpopulations with an aberrant ratio between formulations were identified from these plots. The absence of a relevant effect of the simulated increased V on the exposure ratios was noted for all formulation comparisons.

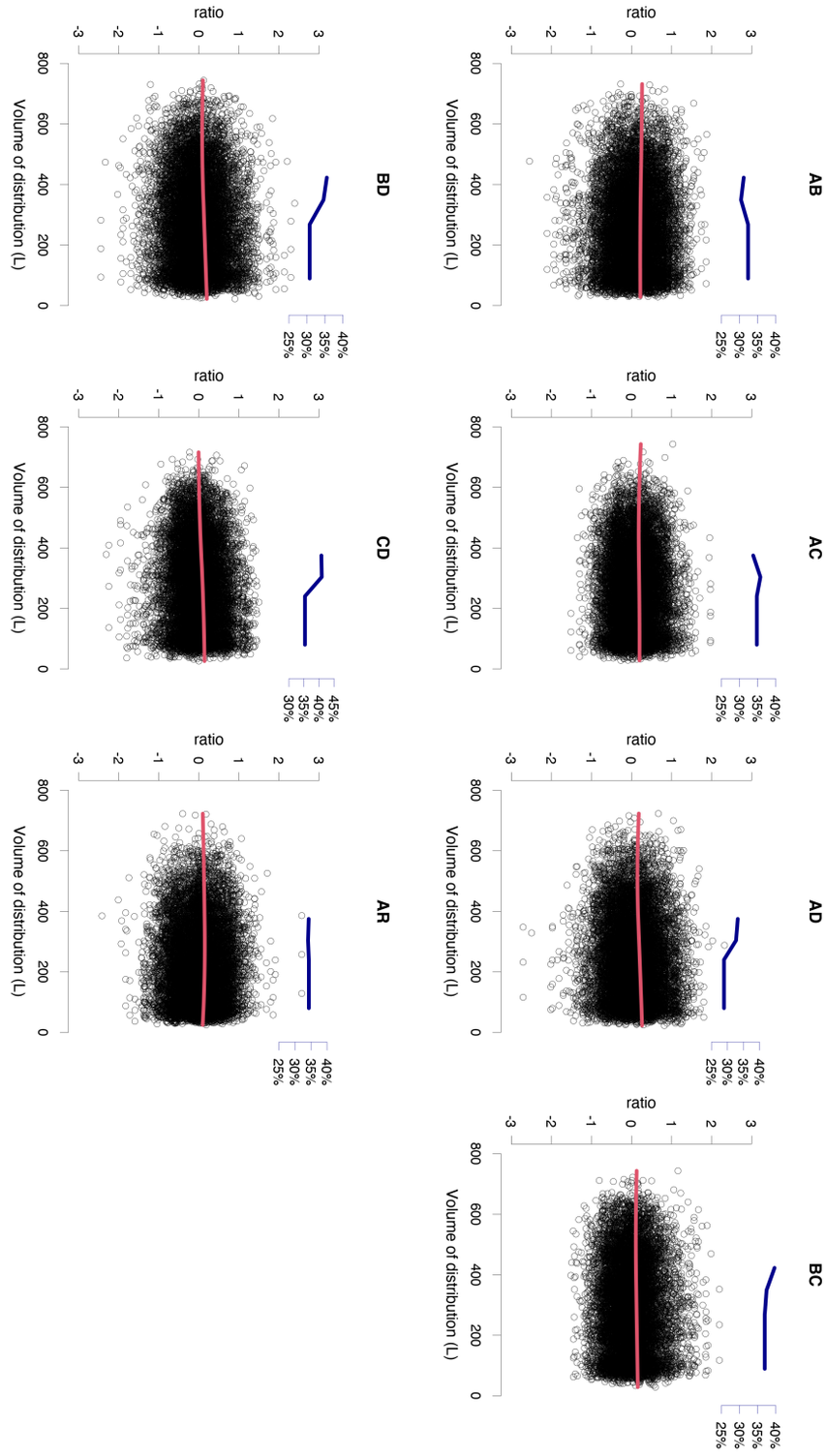


Figure 5: (right page, turn 90 degrees clockwise) The predictions for the individual ratios for AUC do not demonstrate significant differences as a result of an increased V. For each individual, the ratio for AUC between each different combination of formulations is plotted versus Volume of Distribution (open circles). The red line is the regression line of all individual ratios. The blue line is the percentage of individual ratios within the acceptance criteria.

Absorption rate constant

It is expected that in patients with an altered rate of absorption, that C_{max} is influenced significantly, and AUC to a lesser extent. Moreover, a higher rate of absorption is expected to lead to an increased C_{max}. Indeed, in the simulations, higher C_{max} values were predicted for higher Ka rates, but only up to a Ka of approximately 0.75 h^{-1} (fig. 6, fig. S7). The influence of Ka on the predicted AUC was limited. These effects are comparable for the different formulations. However, a higher variability was predicted for the highest Ka populations for Formulations A and D (C_{max}) and B and D (AUC).

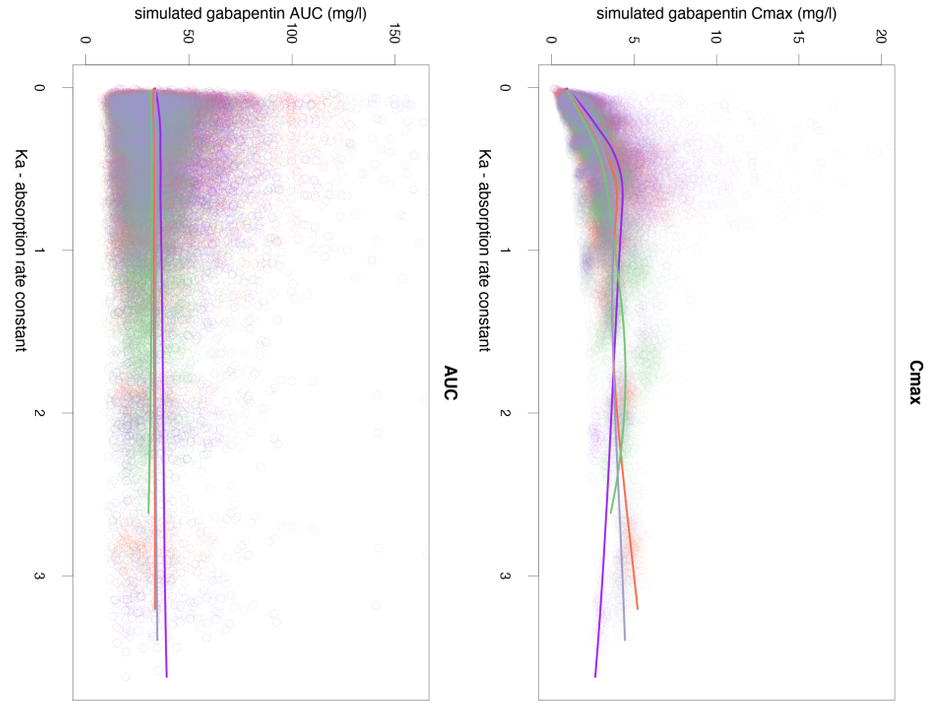


Figure 6: (right page, turn 90 degrees clockwise) An altered rate of absorption is predicted to influence C_{max} significantly, but only up to about a Ka of 0.75 h-1. AUC is influenced to a lesser extent. Left side: all individual values of AUC and C_{max} (open circles) and mean (lines), versus rate of absorption. Different colors represent predictions for the different formulations (A, purple; B, red; C, green; D, light purple). Right side: violin plots for both AUC and C_{max}, per formulation, boxplot (median, interquartile box length and 1.5 range whiskers) with kernel density plot. These depict the distribution of AUC and C_{max}, only for subjects with a rate of absorption 3 times the original model estimated values.

In simulated bioequivalence studies (fig. S8), it was predicted that, for all formulation comparisons, the percentage of studies with 90% CIs within limits for the ratio of C_{max} would increase with a higher Ka. Simulated individual exposure ratios predicted a large variability with a lower Ka, but did not demonstrate a significant effect of Ka on the mean of the bioavailability ratios (fig. 7. The difference in the variability of individual exposure ratios with a lower Ka was most pronounced for C_{max} and less so for AUC (fig. S9). In the individual ratio plots, we observed no distinct subpopulations for which a deviating ratio was predicted. In addition to renal impairment, volume of distribution, and the absorption constant, simulations were also performed for patients with a delay of the absorption lag time, but no effect on the exposure ratios was observed (data not shown).

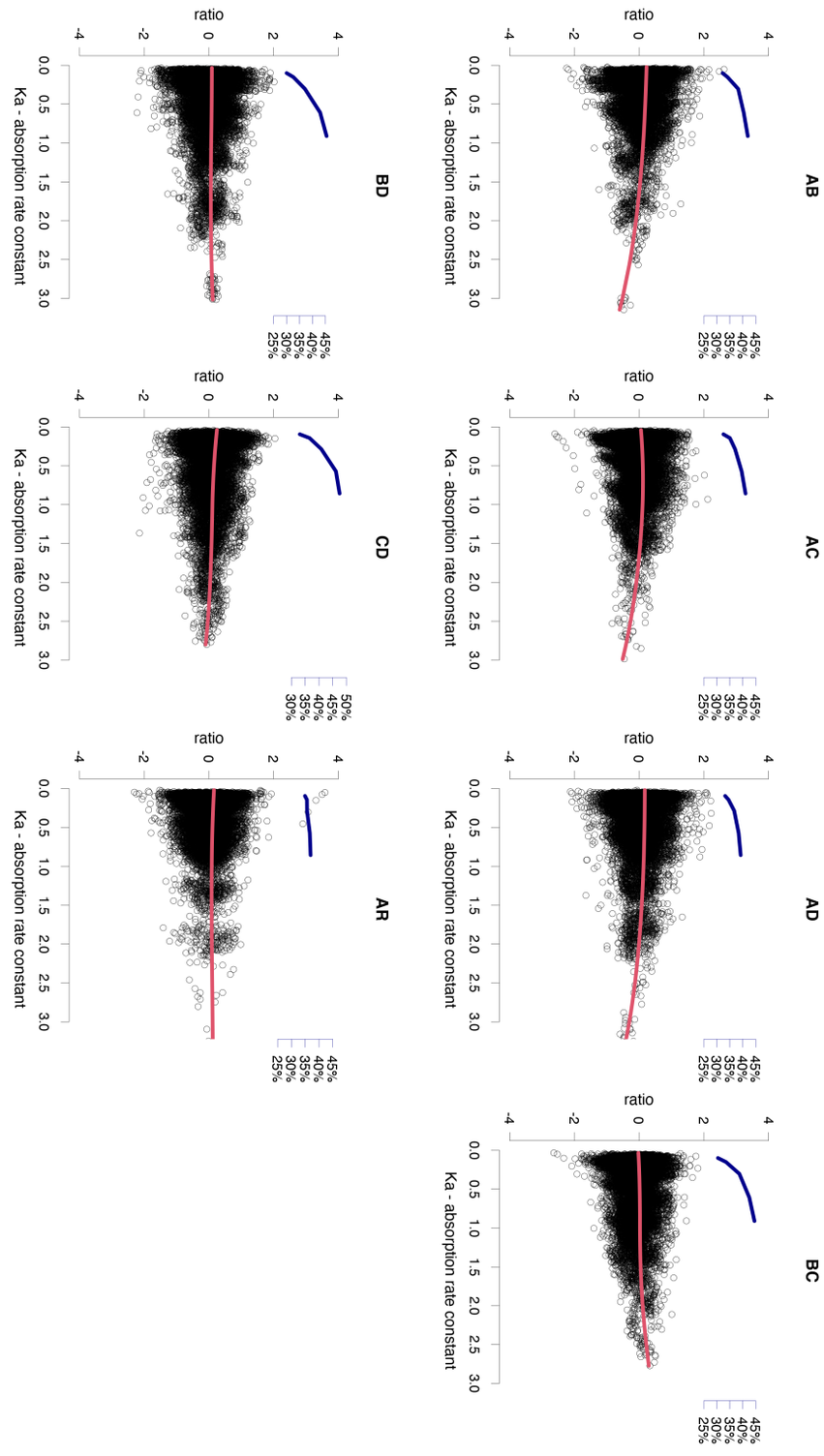


Figure 7: (right page, turn clockwise) Simulated individual C_{max} ratios predict a large variability with lower rate of absorption, but do not demonstrate a significant effect on the mean of the ratios. For each individual, the ratio for C_{max} between each different combination of formulations is plotted against rate of absorption (open circles). The red line is the regression line of all individual ratios. The blue line is the percentage of individual ratios within the acceptance criteria.

Discussion

In this study, simulations were performed to identify possible subpopulations for whom comparable bioavailability is less likely to occur upon generic switching. Results of the simulations do not indicate a relevant change of the PK as a result of an increased volume of distribution, but do indicate increased PK variability for patient populations with a lower rate of absorption or reduced renal function. Consequently, with this increased variability, the likelihood of demonstrating comparable bioavailability in the given populations is reduced.
However, the average comparable bioavailability ratio for these simulated patient populations does not change. In other words, bioequivalence can also be assumed in these subpopulations, although wider acceptance criteria or larger sample sizes would be required to demonstrate this according to the relevant requirements. These altered requirements were described in another simulation study and is the reason why both the FDA and EMA guidelines allow for widening of the bioequivalence acceptance criteria scaled to the intrasubject variability of the active substance (4, 5, 16).
Importantly, identical observations with respect to increased variability were made for different subjects who were simulated to receive the same formulation twice. Therefore, the simulations indicate that the reduced likelihood of demonstrating comparable bioavailability is not the result of the formulation switch, but of the altered PK parameters and PK variability in the population. In other words, a patient who receives a different but generic formulation of the same drug is as likely to demonstrate comparable bioavailability as a patient who receives the same formulation of the same drug, even for a patient with altered PK parameters.
No PK subpopulations with altered comparative bioavailability were identified, even though the model was constructed to allow such differences to emerge. This is congruent with the expectation that altered PK, particularly with regard to distribution, metabolism and elimination, will not affect the comparable bioavailability ratio between different formulations. These findings are also in line with previous research in more standardized populations with narrower distributions of PK profiles. A previous retrospective analysis of replicate design bioequivalence studies concluded that exposure differences originate predominantly from IOV and not from a formulation change (17). Prior research has

also explained that although a patient's PK may be different, it does not change the comparable bioavailability between formulations (18). These results support the idea that it is better to perform bioequivalence studies in healthy subjects than in the intended patient population, as variability unrelated to the formulation is lower, and sensitivity to detect true formulation differences is higher.
Further, no differences with respect to potential drifting were observed in the comparison between the generics and the originator or in comparisons of the different generics amongst themselves. This fits the current scientific view that drifting is merely a theoretical possibility and that in clinical practice, no evidence for the occurrence of drifting has been identified (19, 20).
Additionally, the simulated exposure and individual comparable bioavailability ratios were homogenously distributed for all subpopulations investigated in this study, and no outliers within those subpopulations were identified. Thus, based on this study, there is no evidence of a subpopulation of patients which would demonstrate a true deviation of bioequivalence, as demonstrated in another population.
An important restriction of this study is that validation of our experimental methodology is limited. Although there was good agreement between observed and predicted values for all models, a positive or negative control was lacking. However, the question remains as to whether such controls exist. It is unknown whether generics exist which demonstrate increased differences in bioavailability when patients with altered PK characteristics switch between formulations, which would be a positive control for this study. The next most suitable option would be to incorporate a proven bio-inequivalent formulation in the study. However, it remains to be seen whether, for this formulation, a decreased likelihood of demonstrating comparable bioavailability in certain subpopulations would be found.
Another limitation is that it is not possible to estimate the true IOV, as the original study (13) lacked an experimental arm in which subjects received repeated administration of one of the formulations. Therefore, we were not able to perform simulations for the same subject with a crossover repeated administration of the same formulation, and we were forced to perform simulations with a parallel design. However, this does not affect our study conclusions. Although variability was inflated, as between-subject variability was added for each comparison, this variability was added to all comparisons to the same

extent. Thus, comparisons can still be made between simulations of different formulations. The overestimated variability is perhaps also visible in the percentage of successful bioequivalence studies, which was lower than expected.
A further limitation was the use of data for only one active substance and the generalizability to other active substances. Gabapentin demonstrates relatively straightforward PK, as there is little or no metabolism and complete renal clearance. For active substances with more complex PK properties, these processes could interfere with the likelihood of achieving comparable bioavailability in subjects with altered PK. However, complexity could also only add to the variability, and the conclusions of this study could still stand.

To conclude, in our simulations, we found a reduced likelihood of demonstrating comparable bioavailability for subjects with altered PK behaviour for a given sample size, but this is not influenced by a formulation switch. Moreover, the average comparable bioavailability ratio for these simulated patient populations does not change. Further, we did not find evidence for the occurrence of drifting when comparing generic–generic switches. The outcome of this study could be strengthened through an analysis of other active substances, data for repeat administrations and data for bio-inequivalent formulations. Nonetheless, our study results strengthen the idea that aberrant PK profiles following a generic switch in specific subpopulations are more likely the result of intrasubject variability than the result of the formulation switch. These findings support generic interchangeability and the regulatory requirements for these drugs' approval.

Supplementary materials

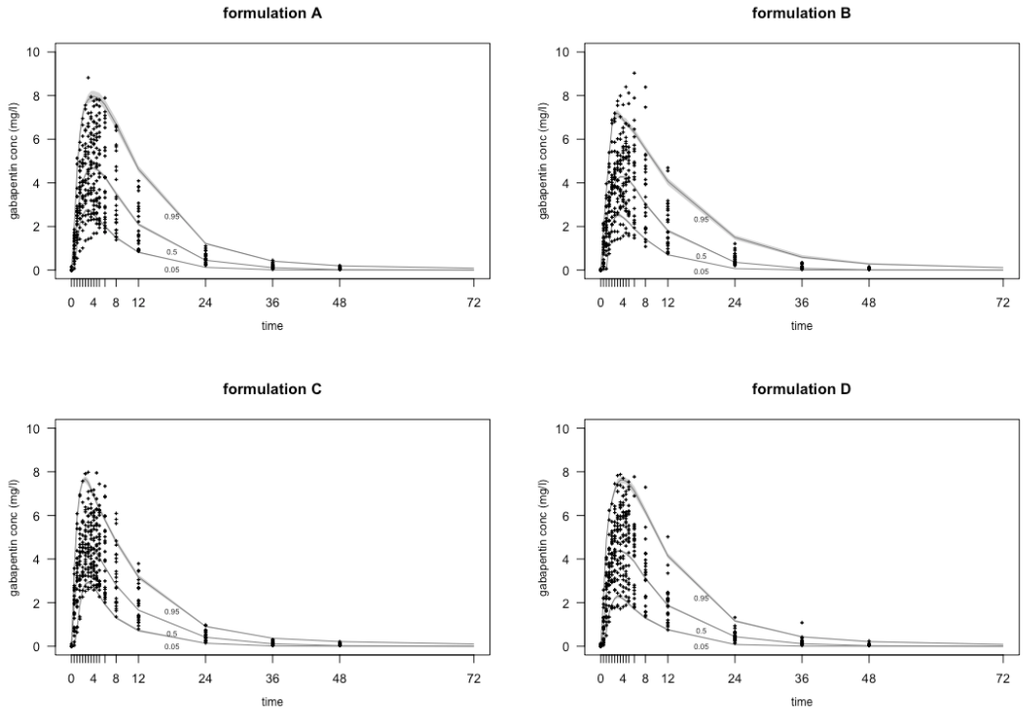


Figure S1 Visual Predictive Check plots demonstrate a good agreement between simulated and observed values for each formulation. Observed values (dots), and simulated values' median and 90% prediction interval lines with 90% CI bands around (n=2400).

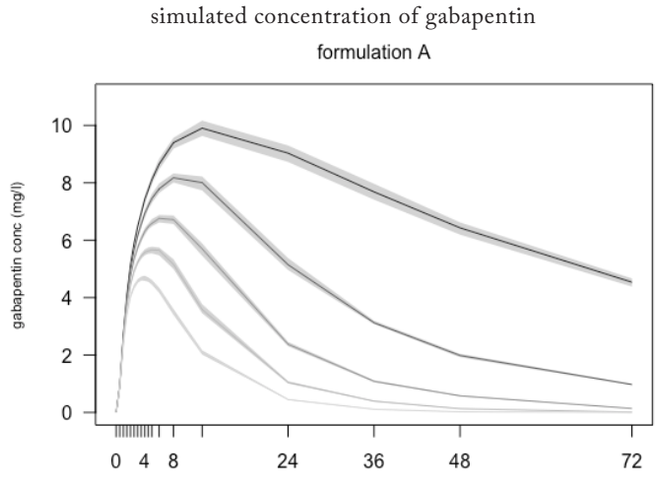


Figure S2: For patients with an impaired renal function, gabapentin plasma concentration will increase. Concentration time curve for the median simulated gabapentin concentration of formulation A, of subjects within different simulated renal function. Gray shade lines from dark to lighter ranked on renal function group, with 90% CI bands around. Darkest shade of gray: end stage, <15 ml/min, severely decreased, (>15 - <30 ml/min), moderately decreased (>30 - <60 ml/min), mildly decreased (>60 - <90 ml/min), lightest shade of gray: normal (>90 ml/min).

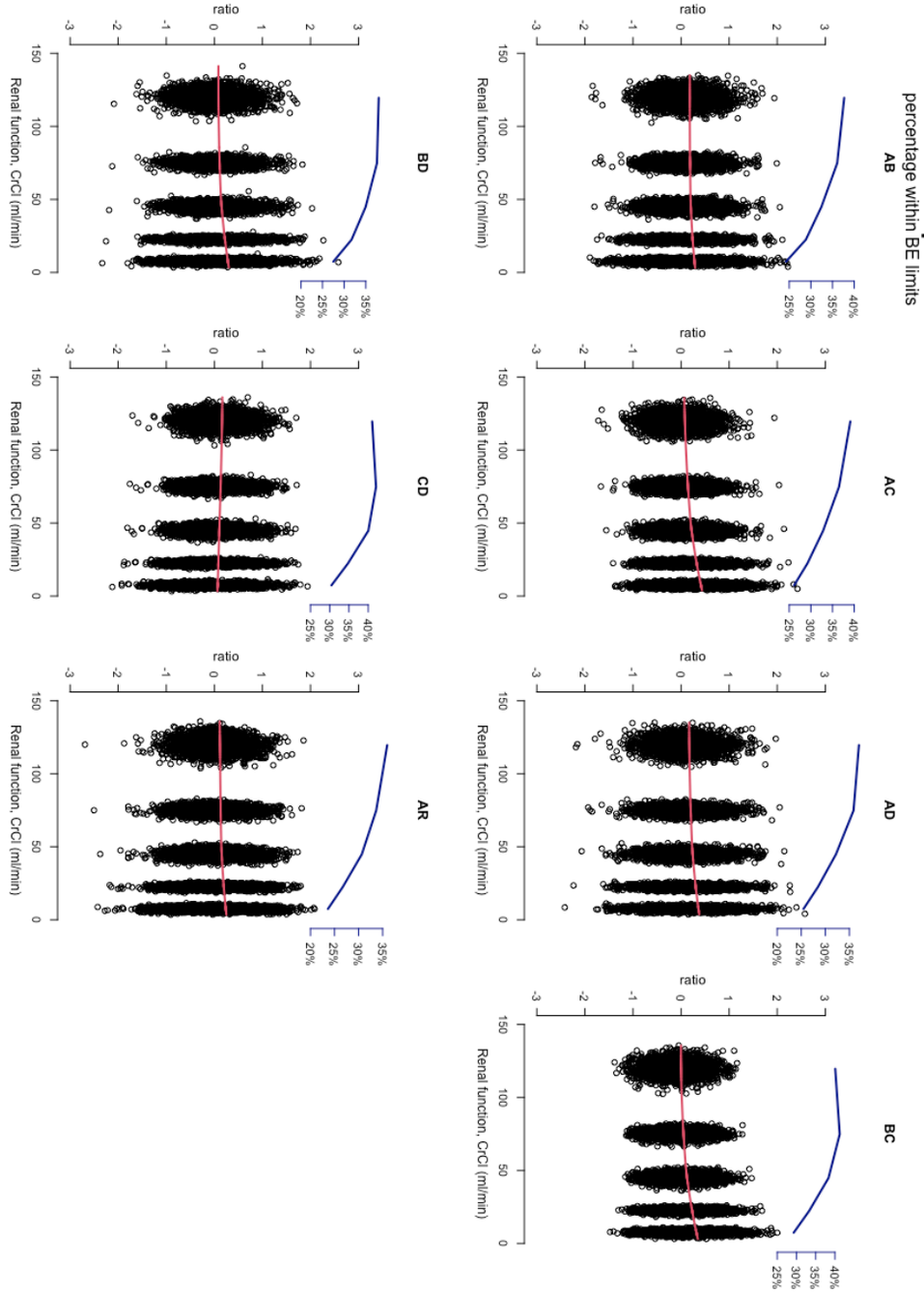


Figure S3: (right page, turn clockwise) Individuals with reduced renal function demonstrate higher variability of the ratio of the C_{max}, but the mean ratio is not different. For each individual, the ratio for C_{max} between each different combination of formulations is plotted against renal function (open circles). The red line is the regression line of all individual ratios. The blue line is the percentage of individual ratios within the acceptance criteria.

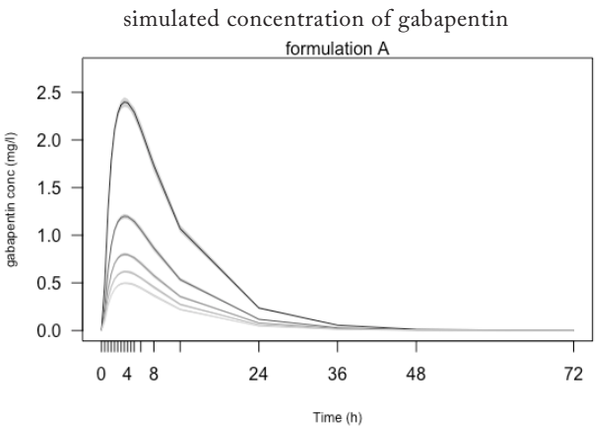


Figure S4: A reduction of both C_{max} and AUC was predicted by simulations for subjects with an increased Volume of Distribution. Concentration time curve for the median simulated gabapentin concentration of formulation A, of subjects with an up to five-time increased V. Gray shade lines from dark to lighter, with 90% CI bands around. Lighter grays are larger Vs.

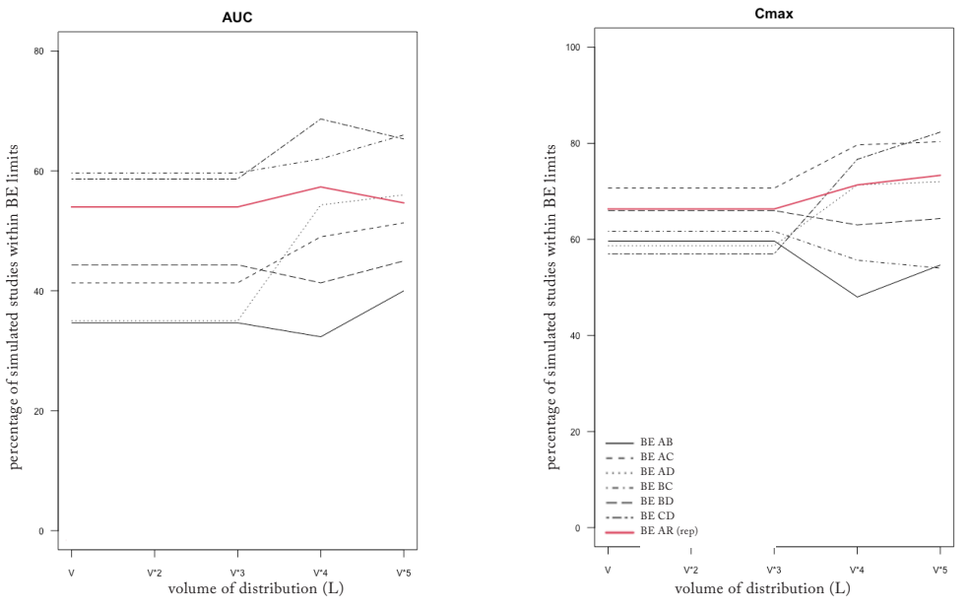


Figure S5: Bioequivalence studies using random samples of 24 subjects with in increased Volume of Distribution demonstrate a small increase of the percentage of acceptable bioequivalence. The percentage of virtual bioequivalence studies with a 90% CI within the acceptance limits for bioequivalence is plotted per formulation comparison and Volume of Distribution.

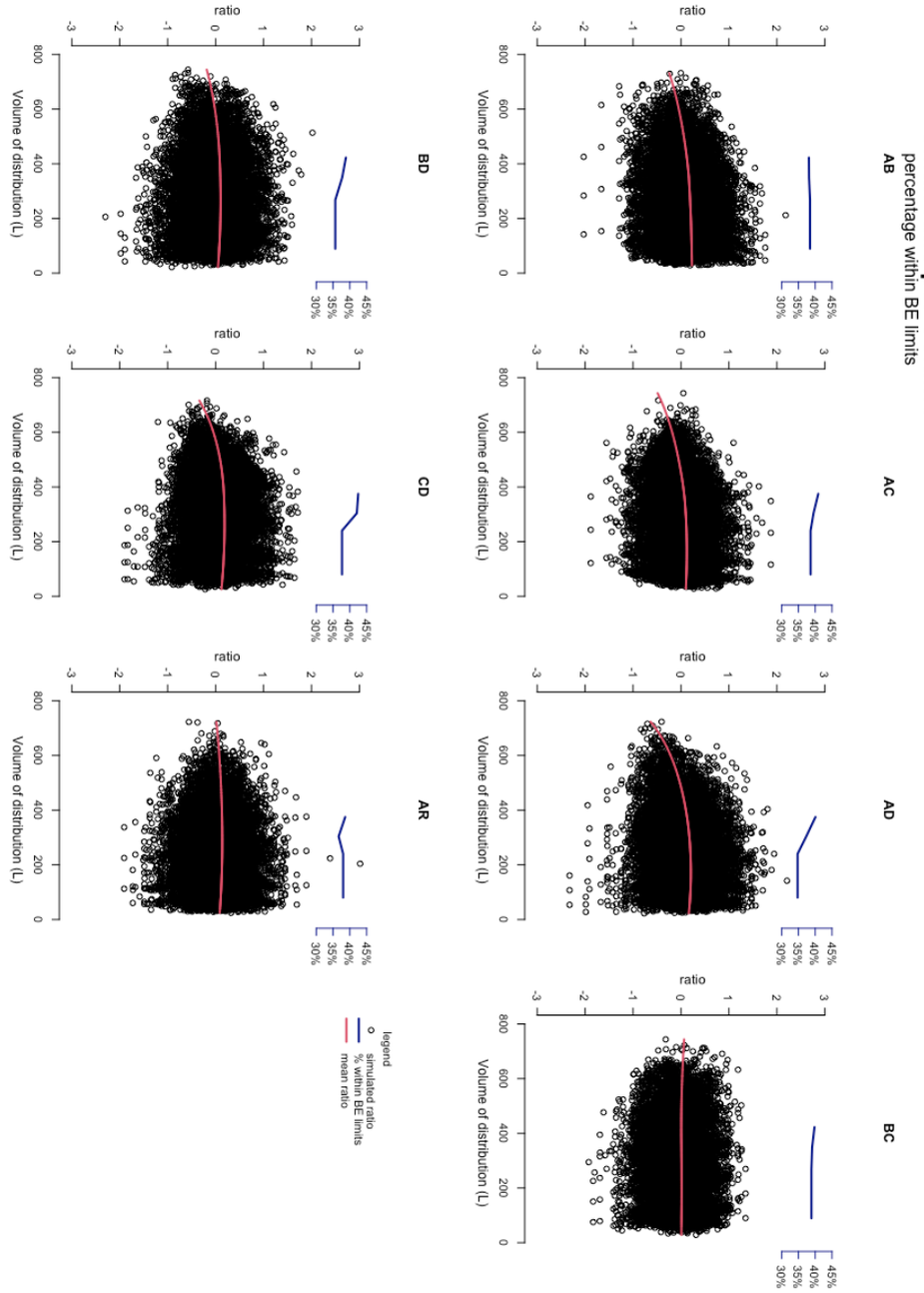


Figure S6: Variability of the individual exposure ratios appears to be lower only for subjects with a simulated V of more than 500 liters, but the mean ratio is not different. For each individual, the ratio for C_{max} between each different combination of formulations is plotted against Volume of Distribution (open circles). The red line is the regression line of all individual ratios. The blue line is the percentage of individual ratios within the acceptance criteria.

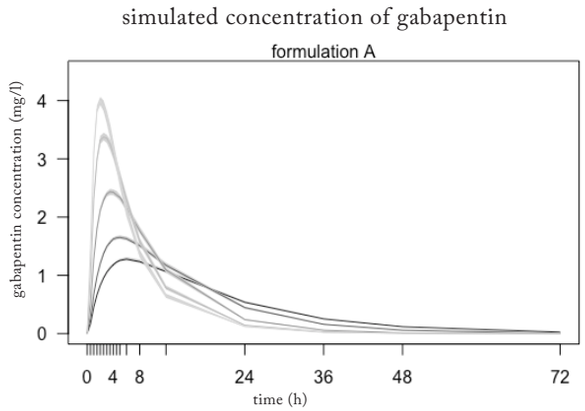


Figure S7: For patients with an altered rate of absorption, C_{max} is influenced, and AUC to a lesser extent. Moreover, a higher rate of absorption leads to an increased C_{max}. Concentration time curve for the median simulated gabapentin concentration of formulation A, of subjects with an up to three-time reduced and increased absorption constant. Gray shade lines from dark to lighter, with 90% CI bands around. Lighter grays are higher Kas.

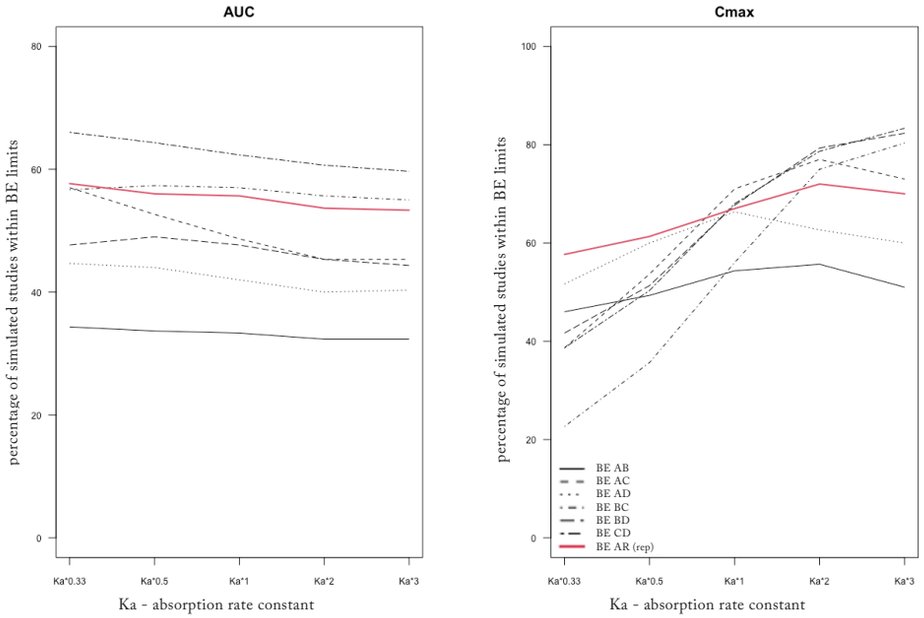


Figure S8: The percentage of simulated bioequivalence studies, of which the 90% CIs for C_{max} are within the acceptance range of bioequivalence, increases with higher rate of absorption, for all formulation comparisons. The percentage of virtual bioequivalence studies with a 90% CI within the acceptance limits for bioequivalence is plotted per formulation comparison and absorption constant.

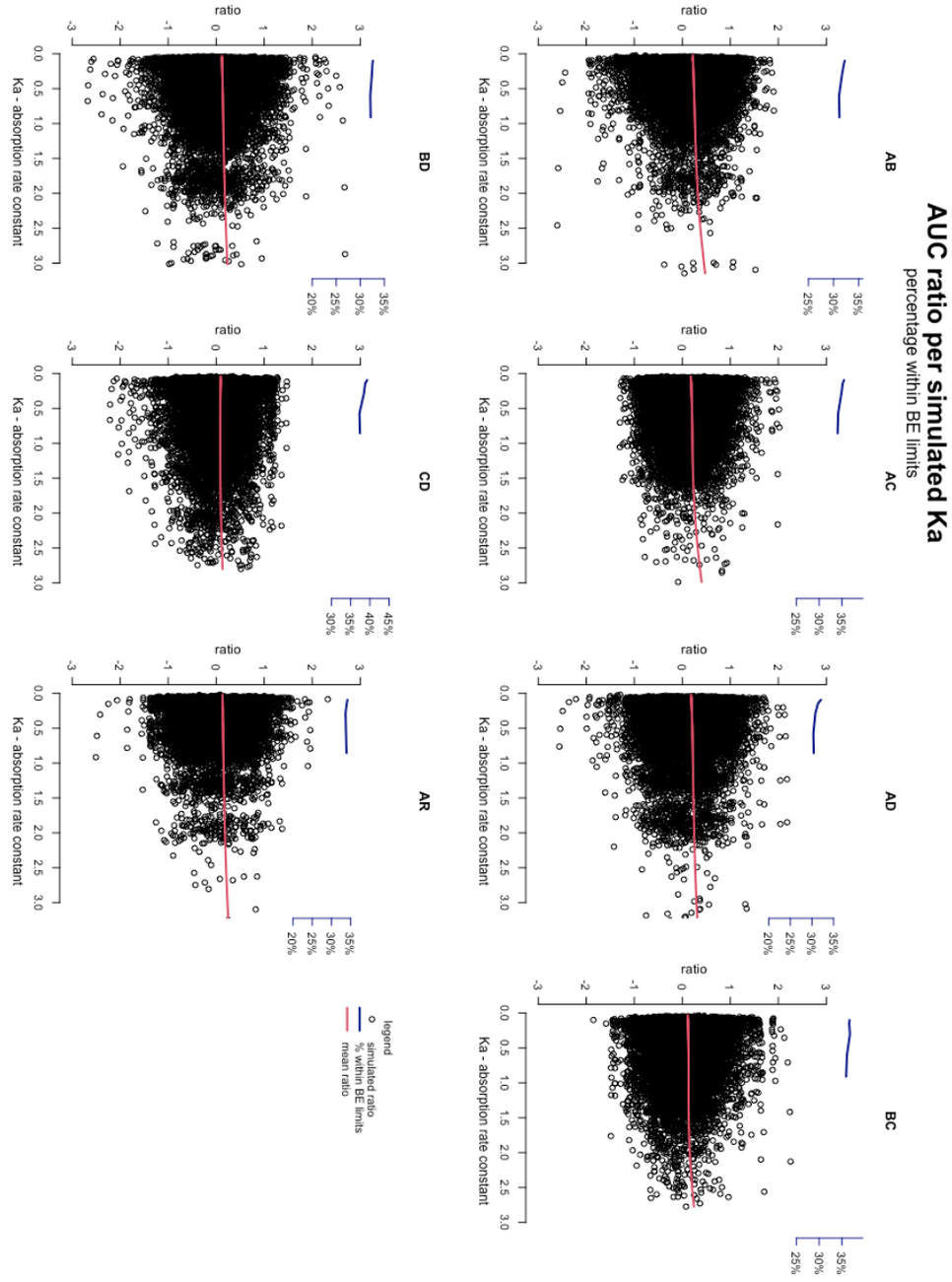


Figure S9: Simulated individual AUC ratios predict a larger variability with lower rate of absorption, but do not demonstrate a significant effect on the mean of the ratios. For each individual, the ratio for AUC between each different combination of formulations is plotted against rate of absorption (open circles). The red line is the regression line of all individual ratios. The blue line is the percentage of individual ratios within the acceptance criteria.

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Chapter 4

General Discussion

Since the emergence of the modern generic drug industry, the discussion on generic drugs has been ongoing, and the quality and interchangeability of generic drugs with the same active substances have been fiercely debated in the literature. In this chapter, we provide an integrated discussion on findings from the individual articles included in this thesis.

Integrated Summary

Information used to discredit generic drugs has mostly relied on anecdotal evidence from case reports. However, scientific scrutiny is lacking to draw conclusions from this information, and a systemic approach is key in the evaluation of generic drugs. Therefore, the first part of this thesis analyzed data on generic drug use and generic drug interchangeability from the best available systematic sources.

The Netherlands Pharmacovigilance Centre Lareb regularly receives reports on adverse drug reactions (ADRs) related to a generic drug switch (1). These reports of clinical discomfort for the patient are unwanted, unexpected, and likely avoidable. Therefore, the etiology of these reports must be studied. The reported ADRs also allow the extent of generic interchangeability to be studied; the number of patients who switch generic drugs and experience an ADR can be determined. However, two major barriers to these studies must be overcome before inferences can be made from reported ADRs. First, these reports are generated by a spontaneous reporting system, and the number of reported ADRs compared to the true number of experienced ADRs is unknown. Second, the number of reported ADRs is a floating numerator—that is, the at-risk population is unknown. In other words, the number of patients who reported an ADR related to a generic drug switch is known, but the number of patients switching between generic drugs is not.

Data on the number of patients who switch between generic drugs are not publicly available in the Netherlands, nor have the reasons for these switches been identified. Therefore, the aim of the study discussed in chapter 2.1 was to determine the frequency of generic drug switches in the Netherlands. For this, we utilized the database of the Dutch Healthcare Institute (ZiNL), which contains insurance claims data regarding 96% of the Dutch patient population. Due to the computational intensity of the data extraction, we limited the study period from June 2009 to December 2016 and chose 20 active substances for which the greatest number of ADRs related to switching were reported to Lareb. Our study included a total of 23.8 million generic drug switches, and based on our analysis, we concluded that generic drug switching is common, that many products are involved, and that most switches (80%) occur between two generic versions of the same drug. Additionally, we observed an increase in the switch rate between January and March each year, likely attributable to the Dutch "preference policy." This policy facilitates yearly renewal of contracts regarding the drug products eligible for reimbursement.

The findings presented in chapter 2.1 sparked our interest in the rationale for the occurrence of drug switches, since this is relevant to policymakers who want to reduce the number of drug switches, mainly to promote patient convenience. Therefore, we performed a pilot study identifying reasons for patients' generic drug switches, as described in chapter 2.3. We documented the reasons for drug switches at 16 Dutch pharmacies and found that the majority of drug switches were either the result of a shortage of the drug product on a national level (32%), the Dutch preference policy (23%), or deals between pharmacists and wholesalers (12%).

In chapter 2.2, we described our study of the relative number of reported ADRs when corrected by the number of drug switches in the Netherlands. We retrospectively analyzed a period of 7.5 years, in which 2,602 such ADRs were reported. Of those ADRs, 1,348 were for one of the included 20 active substances we studied (chapter 2.1). Furthermore, we found an average reporting rate of 5.7 ADRs per 100,000 drug switches for those active substances. A different set of active substances was identified as having an above-average ADR reporting rate based on the absolute number of reported ADRs following adjustment for the number of drug switches. Thus, the number of drug switches should be incorporated in the analysis of these ADRs. Additionally, we found that the number of drug users was an acceptable replacement for the number of drug switches in the analysis since these data are more readily available for routine pharmacovigilance analyses.

The second part of this thesis focused on bioequivalence, which must be demonstrated using the best available methodology as it plays a central role in the approval of generic drugs. We challenged the robustness of bioequivalence using modeling and simulation in chapter 3.1 and chapter 3.2.

Bioequivalence is statistically confirmed comparable bioavailability, for comparable drug products. Current guidance dictates that bioequivalence should be demonstrated using so-called "average bioequivalence." When comparing blood concentrations obtained after administration of two comparable drug products, the 90% confidence intervals (CI) of the geometric mean ratio for both the area under the curve (AUC) and peak concentration (C_{max}) should be within prespecified limits, which are usually 80.00–125.00% (2-4). This criterion should ensure comparable bioavailability of the two drug products. However, this approach only ensures comparability of the average ratios; it does not account for the range of individual ratios. These individual ratios can be well outside the 90% CI limits. This has been observed in participants in bioequivalence studies and is thus likely occurring in real-world patients who switch between generic drugs.

Bioequivalence studies are usually performed with healthy volunteers, and for generic approval, bioequivalence must only be demonstrated to the originator drug. Public and scientific literature has often criticized this approach, arguing that bioequivalence in healthy volunteers cannot be extrapolated to the patient population, who have comorbidities and altered pharmacokinetics. It has also been challenged that the demonstrated bioequivalence of a generic to the originator does not necessarily ensure bioequivalence between different generics of the same active substance. As demonstrated in chapter 2.1, in clinical practice, most patients switch between two generic drugs, not between the originator drug and a generic drug. Using modeling and simulation as described in the second part of this thesis, we investigated these critiques described above, aiming to identify a patient population who displayed a reduced likelihood of demonstrating bioequivalence when switching to, or between, generic drugs.

In chapter 3.1, we described the development and validation of a non-parametric pharmacokinetic model for gabapentin based on data from a previously conducted comparative bioavailability study between the gabapentin originator and three generic drug products. We found that the optimal model was a two-compartment model with an absorption constant, an absorption lag-time, and elimination adjusted for renal function, in which each model parameter was separately estimated per drug product. Optimal fit of the model was confirmed by both internal and external validation.

In chapter 3.2, we described the simulations performed with this model. We simulated a large number of pharmacokinetic profiles for virtual subject populations with pharmacokinetic characteristics mimicking patient populations. Compared to the healthy volunteers originally included in the clinical study, our virtual patient populations had an increased volume of distribution, altered absorption constant, or renal impairment. For each virtual population, we analyzed the individual exposure ratios between different drug products and performed bioequivalence studies on 24 subjects. The results indicated a higher variability for the individual exposure ratio for subjects with a lower rate of absorption, a smaller volume of distribution, and reduced renal function. Additionally, the likelihood of demonstrating bioequivalence was reduced for these subjects. However, the average ratio did not change for the subject populations. Further, no differences were observed between the comparisons of the originator with the generic drugs, or between different generic drugs. Similar results were observed when two administrations of the originator drug product were compared. Thus, the reduced likelihood of comparable bioavailability for a subject is not driven by the specific drug product switch but is rather the result of intra-subject variability of the active substance.

Integrated Discussion

In chapter 1.2, we described the current scientific debate on generic interchangeability. From a regulatory perspective, no compelling evidence has been provided that would warrant change to the regulation of generic drug approval. To understand the discussion on generic interchangeability and the bioequivalence criteria, prescribability and switchability must be distinguished. These two notions of interchangeability were first described by Anderson and Hauck (5, 6). The term prescribability refers to a situation in which a patient is naïve to a drug and for whom there is a choice between two drug products. In this case, knowing that both products will achieve similar concentrations of the active substance, which are within the same therapeutic window of safety and efficacy, is sufficient to justify a product change. The term switchability refers to a patient who is already on continued drug treatment, but for whom a switch to another drug product is considered. In this case, more clinical information is available, namely that a specific drug product, dose, and corresponding concentration of the active substance are efficacious and sufficiently safe for this patient. This additional information aids the prescriber in preventing unnecessary harm to

the patient in the form of ineffective or toxic dosing. Therefore, switchability should be established; the prescriber should be sufficiently sure that similar blood concentrations will be achieved for this patient with the new drug product of the same dose.

Anderson and Hauck argue that establishing population bioequivalence is sufficient for prescribability. Population bioequivalence is comparable to average bioequivalence, as the average bioavailability of two drug products should be comparable. However, for population bioequivalence, there should also be a comparable population distribution regarding the bioavailability of the two drug products. Anderson and Hauck also argue that an additional level of evidence is required for switchability beyond population bioequivalence, in the form of "individual bioequivalence." This should be achieved by some sort of confirmation that "most individuals have similar bioavailabilities" (5).

On population bioequivalence, particularly as proof of generic prescribability, no active debate exists in the scientific literature. More attention has been given to the debate on individual bioequivalence as a necessary regulatory requirement for ensuring switchability.

The FDA added to this debate, by providing criteria for individual bioequivalence in 1997 guidance on in vivo bioequivalence studies, as well as a multi-year research program into the individual bioequivalence criterion (7, 8).

Pivotal in the approach to individual bioequivalence is characterization of a subject-by-formulation interaction, which is the extent to which individual bioavailability ratios of two drug products differ between subjects. Demonstration of the absence of such an interaction would lead to increased confidence in the switchability of the drug products, as it is often believed that distinct subpopulations exist for which demonstration of average bioequivalence in healthy volunteers is insufficient. Other advantages of the individual bioequivalence approach include scaling of acceptance criteria based on the within-subject variability of the reference product and an incentive for both originator and generic drug makers to develop drugs with a reduced variability. However, the 2002 FDA bioequivalence guidelines, the first to follow the 1997 guidelines, did not mention individual bioequivalence (9). Implementation of this requirement was not pursued for a number of reasons. First, several statistical issues existed for the proposed measures of individual bioequivalence, including determining and justifying the cut-off for a clinically relevant subject-by-formulation term.

Second, no clear understanding of any mechanistic basis, or clinical relevance of a subject-by-formulation interaction, was reached. Third, replicate design studies are needed to demonstrate individual bioequivalence, but these would increase the burden on resources.

Therefore, implementing a requirement for individual bioequivalence was not justified, particularly in the absence of any clearly demonstrated problems with interchangeability in clinical practice. During a meeting of the FDA Advisory Committee for Pharmaceutical Science on the subject of individual bioequivalence, Dr. L. Benet summarized his position as follows: "…individual bioequivalence still remains a theoretical solution to solve a theoretical clinical problem. We have no evidence that we have a clinical problem, either a safety or an efficacy issue, and we have no evidence that if we have the problem, that individual bioequivalence will solve the problem" (10).

Regulatory requirements for bioequivalence have since been discussed on several occasions, most recently by Concordet et al., as was described in chapter 1.2 (11, 12). However, no compelling evidence has been presented that would warrant a change to the requirement of average bioequivalence. The results from this thesis described in chapter 2.1 and chapter 2.2 support the absence of clearly demonstrated interchangeability problems (i.e., reduced safety or efficacy). In chapter 2.1, we demonstrated the relatively high frequency of drug switches in clinical practice in the Netherlands. With such high rates of drug switches, any true generic interchangeability problem should have surfaced, especially because we demonstrated that most of these switches are between two generic versions of the drug, which are regarded the worst case of switching, due to the theoretical possibility of drifting.

In chapter 2.2, we proposed a new approach to the analysis of ADRs related to generic switches, with an increased likelihood of identifying relevant switch-related ADRs. However, even with the improved method, drawing a conclusion on the presence of interchangeability issues is difficult, as the pharmacovigilance system is based on spontaneous reporting of ADRs. Spontaneous reporting is known for underreporting (13), and fluctuations in the number of ADR reports could merely be fluctuations of the reporting rate. Thus, although we may have found a relative difference of switch-adjusted ADR reporting rates between some active substances in our study, drawing a conclusion on the presence of interchangeability issues was not possible.

The results described in chapter 3.1 and chapter 3.2 support the position that no compelling evidence exists that would warrant a change to regulatory requirements. Issues with the subject-by-formulation interaction halted the FDA from further pursuing individual bioequivalence requirements in the late 1990s. This interaction is not only difficult to prove but also difficult to interpret, as no mechanistic understanding of any subject-by-formulation interaction exists. In chapter 3.1 and chapter 3.2, we used modeling and simulation to identify pharmacokinetic subpopulations for whom comparable bioavailability is less likely to occur when a switch between two drug products is made. If we had identified such a subpopulation, it would have indicated a mechanistic understanding of a subject-by-formulation interaction. However, we did not identify such a subpopulation in the simulation study. Thus, we did not identify any indication of a subject-by-formulation interaction for those populations.

An additional consideration for not implementing individual bioequivalence requirements in the absence of compelling evidence to do so is given by the "learn and confirm" paradigm of L. Sheiner (14). According to this view, learning and confirming in all phases of drug development must be distinguished, particularly for the design of the study. A bioequivalence study is a confirmatory study, as it should confirm the absence of a relevant difference between the bioavailability of two drug products. According to Sheiner, the conclusion is clear and unequivocal for a confirmatory study with a simple design and a sharp null-hypothesis that is rejected. From a regulatory perspective on the assessment of generic drugs, a clear and unequivocal conclusion is key, to come to the yes or no decision for market approval. This need for a clear conclusion is reflected in the study design of bioequivalence studies, for instance, in the choice of a homogenous study population. Any additional variability from a heterogenous study population would reduce the study's power to identify differences related to the studied drug products. Increased inter-subject variability would not be an issue per se, as each subject is its own control in a bioequivalence study with a crossover design (15). However, a more heterogenous population would likely introduce additional intrasubject variability, which does reduce study power. The latter was observed in our simulations for virtual subjects with pharmacokinetic characteristics mimicking patient populations, as described in chapter 3.2.

Regarding the generic interchangeability of prescribability and switchability, as proposed by Anderson and Hauck, there is no reason to doubt the prescribability of generic drugs. Demonstration of average bioequivalence provides sufficient evidence that a patient who is prescribed a generic drug will reach sufficiently similar concentrations of the active substance and thus experience sufficiently similar safety and efficacy as the originator drug. This position is indirectly supported by an absence of an active debate on this subject in the scientific literature.

To draw a conclusion on the switchability of generic drugs, however, is not as straightforward. Conceptually, a higher level of evidence is required to ensure switchability than is required for prescribability. As described above, the implementation of individual bioequivalence, suggested to be necessary to ensure switchability, was not adopted by the FDA for several reasons. The results from this thesis support the reasons for which implementation of these requirements was not further pursued.

Whether any specific measure for switchability can be established, or is required, has yet to be determined. The same arguments for not implementing the individual bioequivalence requirement by the FDA can be applied more generally to the original claim of Anderson and Hack: for switchability, a confirmation that "most individuals have similar bioavailabilities" is necessary. The same points for discussion arise—what metric to apply and how to determine its acceptance limits, what conclusions can be drawn without a mechanical understanding of the underlying issue, and whether an additional burden on resources is justified without a clearly demonstrated issue in clinical practice. The current average bioequivalence requirements, even in absence of a direct measure of individual exposure ratios, provide sufficient confirmation that individuals will likely achieve similar exposure over time.

However, even in the absence of clearly demonstrated interchangeability issues identified from clinical practice, ADRs related to generic drug switching are reported, and patients are thus experiencing clinical discomfort. Whether clinical pharmacology is the main cause of this clinical discomfort is questionable. The clinical discomfort may be the result of a significant difference of exposure to the active substance, before and after a drug switch. Such differences exist, but as we described in chapter 3.2, they are likely attributable to intrasubject pharmacokinetic variability, rather than the drug switch. Consequently, the intrasubject variability of exposure to the active substance is present not only during a drug switch but also during continued use of a single drug product.

Still, the ADR reports we presented in chapter 2.2 were explicitly related to the drug switch. Thus, similar ADRs were either not present, not consciously experienced, or not reported during continued use. Reporting the ADRs only related to a drug switch has been suggested as the placebo, or nocebo, effect of generic drug switches (16).

However, a patient who has experienced issues with a generic drug switch would not agree with this view on the etiology of the ADRs, nor would prescribers and physicians who have experience with such issues, or researchers who presented studies or case reports that discredit generic drugs. However, with a systematic approach, as we performed, and with other unbiased large-scale investigations, no presence of true interchangeability issues causally related to generic drug switches has been demonstrated.

Nonetheless, the perspective of the individual patient must be considered, as experienced clinical discomfort can have a significant impact on patients' quality of life. Although the causal relationship between reported ADRs and drug switches is unclear, reducing the number of drug switches is beneficial for patients for several reasons. First, our conclusions may be incorrect, and ADRs may indeed be causally related to generic drug switches. In chapter 2.1 and chapter 2.2, we were not able to conclude on the presence of interchangeability issues, but we did not demonstrate the absolute absence of interchangeability issues either. Second, as reasoned above, a drug switch may influence the way a patient experiences clinical discomfort more consciously compared to the experience of the same clinical discomfort during continued drug use. Third, although we have concluded the absence of identified interchangeability issues and identified subject-by-formulation interactions, this conclusion is not necessarily true for all future and perhaps more technologically complex drug products. Fourth, drug switches may confuse patients and result in drug intake errors. This confusion could stem from the different name, packaging, shape, or color of the generic drug. Intake errors are of particular relevance since drug switching is frequent in the Netherlands, as described in chapter 2.1. Additionally, as the results from our pilot study presented in chapter 2.3 suggest, a large percentage of the drug switches in the Netherlands have an economical incentive. This is logical, as the existence of generic drugs is based on price reduction, but when patients do not directly benefit from something and are instead burdened by it, the frequency of switching that is acceptable should be reconsidered.

Indeed, reconsidering an acceptable frequency of switching is an example of why the concept of generic interchangeability falls between science and regulation and is thus an example of regulatory science. From a purely scientific point of view, we were not able to identify interchangeability issues for generic drugs; thus, the high frequency of generic switching we observed is scientifically of no interest. However, as with all aspects of drug regulation, a healthy balance of benefit versus risk must be maintained. In this case, the financial benefits of generic drug use and generic switches should be weighed against the burden of frequent switches for the individual patient.

Interchangeability as a concept of both science and regulation is demonstrated in the requirements of generic drug approval. From a scientific view, higher-level evidence is required to ensure switchability rather than prescribability, as more information on the patient is available. However, from a regulatory perspective, any additional burden on requirements for drug development and bioequivalence studies should be justifiable and in proportion to the extent of the problem. Since a clinical switchability problem was not identified, the same level of evidence is sufficient for switchability as for prescribability. Additionally, clear and unequivocal conclusions for granting or not granting market access are necessary within regulation. This is reflected in the acceptance interval of 90% CI for the mean ratio in a bioequivalence study: 80.00–125.00%. These limits should not be exceeded "when rounded to two decimal places" (2), but the basis for these limits is an arbitrarily set 20% difference, which medical experts have "determined to be significant" (17). Here, science meets regulation.

Future Perspectives

In this thesis, we add to the current understanding that generic interchangeability can generally be assumed and that no changes to the system of generic drug approval are required. We did not identify clinical interchangeability issues with generic drugs or subpopulations for whom a subject-by-formulation interaction could exist. However, we were not able to exclude the existence of these clinical issues or subpopulations either. Therefore, quality research, both retrospective and prospective, must continue to be performed.

Pivotal to our conclusion of interchangeability is the absence of any know subject-by-formulation interaction and demonstrated interchangeability issues

from clinical practice. Thus, these two subjects should remain topics of research, as they are essential to maintaining the conclusion that the reported ADRs are the result of intrasubject variability.

Research into the subject-by-formulation interaction should focus on the link between patient and drug product characteristics, and it should investigate whether acceptable differences between two drug products could result in an altered absorption of the two drug products. Modeling and simulation, such as physiologically based pharmacokinetic modeling and simulation (PBPK), could aid in understanding the absorption phase.

For the second research topic, the absence of interchangeability issues in clinical practice, sufficient pharmacovigilance on generic interchangeability must be maintained, as pharmacovigilance is the gatekeeper of any clinically problematic drug product on the market. However, any signal of interchangeability issues, even with the improved system proposed in chapter 2.2, can only be hypothesis-generating; further investigation is required. Large randomized clinical trials that test interchangeability will likely not be performed. Therefore, other sources of data of a systemic nature, or other forms of data collection, should be explored to come to a firm conclusion.

Not only should generic interchangeability be established, but patients', prescribers', and physicians' trust in generic interchangeability must be increased. Patients should be confident that they will receive the best available drug treatment and product, and prescribers and physicians play an important role in increasing patients' confidence. Increased trust in generic interchangeability will not only benefit the treatment of a patient, through reduction of the nocebo effect, but will also reduce the resource constraints of prescribers and physicians. For this reason, specific reasons for generic drug mistrust must be elucidated to design actions that could increase trust in generic interchangeability.

Furthermore, the number of drug switches must be reduced. This is a difficult task, mainly due to the large number of stakeholders involved. Nonetheless, chapter 2.3 provided a basis for further research into achieving a reduction of drug switches in the Netherlands. This chapter also provided direction on increasing trust in generic interchangeability. For instance, a large portion of the drug switches in the Netherlands is economically motivated, without direct benefit to the patient; often, reimbursement drives the choice of the specific drug product, and the patient has no level of control. Thus, regained control over the chosen drug product might mitigate patients' distrust in generic drugs and their interchangeability. Choice of a specific drug product may increase the costs of pharmaceutical health care. Thus, economic viability of additional patient control could be achieved by an out-of-pocket payment by the patient toward the difference of the price of the chosen product compared to the reimbursed price. In the Netherlands, patients are currently required to pay the full price for a non-reimbursed drug product preferred by the patient. Payment of the difference would at least provide the patient with a reasonable alternative compared to a forced switch.

Greater changes to the system must also be explored. Drugs are generally known by their international nonproprietary names (INN), but originator drugs are distinguished from generic drugs by use of a brand name. Additionally, generic drug products often have a different color, shape, or size compared to the originator drug and other generic drug products. Legal protection of these unique characteristics is based on intellectual property and mainly serves the purpose of differentiating between drugs and brand awareness (18). However, these differences can confuse patients and lead to inappropriate use of the drug. For example, a recent patient survey suggested strong reliance on drug product appearance for correct intake of the drug. About 5% of the patients for whom the drug product appearance changed with a drug switch stopped taking their drug (19). Thus, the change in name and appearance does not contribute to trust in generic interchangeability. Although reforming the system would be an enormous legal challenge, uniform naming and identical product appearance would be in the best interest of the patient.

Overall, by continuing to perform high-quality research into generic interchangeability, specifically subject-by-formulation interaction and clinical interchangeability, the prescribability and switchability of generic drugs should continue to be confirmed. Additionally, by reducing the number of drug switches and building trust in generic interchangeability, generic drugs will play a prominent role in the pharmaceutical landscape, reducing pharmaceutical health care expenditure without compromising patient well-being.

Conclusion

We presented the results of a number of studies challenging the position of generic interchangeability. First, we demonstrated a high number of generic switches in the Netherlands and proposed an improved methodology for the pharmacovigilance of drug switches. Second, through pharmacokinetic modeling and simulation, we did not identify possible patient subpopulations for whom aberrant pharmacokinetic profiles were more likely to occur as a result of a drug switch. However, the simulations did indicate increased pharmacokinetic intrasubject variability, which was not related to the drug switch.
Results of these studies support generic interchangeability—both prescribability and switchability—that is sufficiently ensured with the current regulatory requirements for approval of generic drugs. Nonetheless, to increase patients' well-being, reducing the number of generic drug switches would still be of great benefit to the patient.

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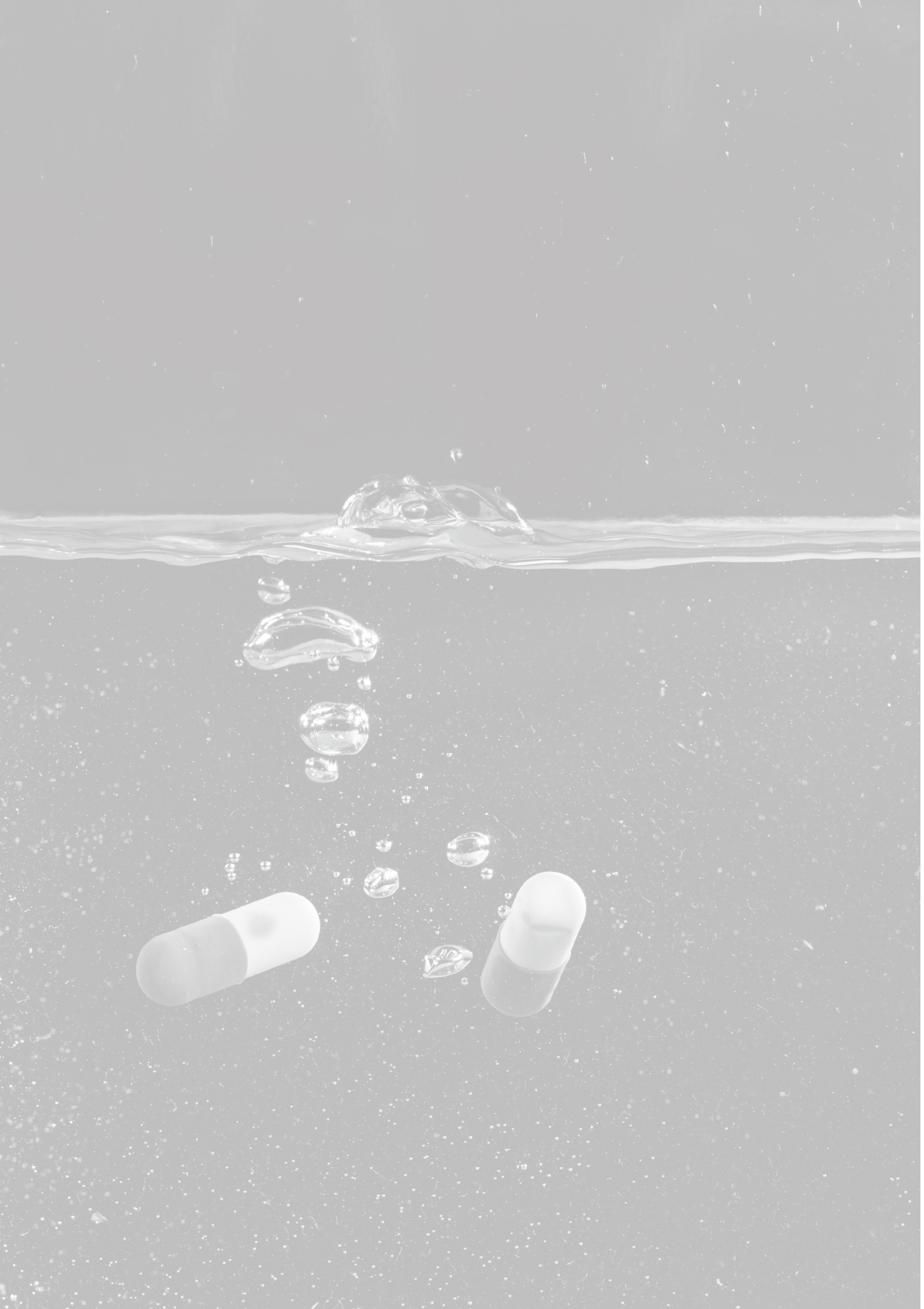

Chapter 5

Short summary | Nederlandse samenvatting

This thesis is about generic interchangeability. In **chapter 1.1** we discuss what generic drugs are, in a historical context, and why it is so important to study their interchangeability. In **chapter 1.2** we describe current requirements market approval of generic drugs and common issues for discussion, from the viewpoint of the regulator. In **chapter 2**, we describe our investigation into generic drug switching and clinical discomfort for the patient. We study the frequency of generic drug switches in the Netherlands, for a number of drugs (**chapter 2.1**) and analyze the number reported adverse drug reactions (ADRs) related to generic drug switches in relation to this number of generic drug switches (**chapter 2.2**). We demonstrate that generic drug switching is very common in the Netherlands, many different drug products are involved, and most switches (80%) are between 2 generic versions of the same active substance. For our selection of active substances, we found an average reporting rate of 5.7 ADRs per 100.000 drug switches and if the number of drug switches is used in the analysis of these ADRs, different active substances would be identified to have an above average reporting rate. In **chapter 2.3** we describe a pilot study into the reasons for generic drug switching in the Netherlands. We found that the majority of drug switches were either the result of the Dutch preference policy (23%), or a shortage of the drug product on a national level (32%).

In **chapter 3** we challenged the robustness of the methodology of bioequivalence by modeling and simulation. We investigated whether or not a conclusion of bioequivalence in a healthy population holds true for a vulnerable patient population with altered pharmacokinetic characteristics. In **chapter 3.1** we report the model validation and in **chapter 3.2** we describe the simulations with the model. The results of the simulations do not indicate a relevant change of the pharmacokinetics as a result of an increased volume of distribution, but do indicate increased pharmacokinetic variability for patient populations with a lower rate of absorption or reduced renal function. For these subjects, the likelihood of demonstrating bioequivalence was reduced, but the average ratio did not change. Further, no differences were observed between the comparisons of the originator and generic drugs, between the generic drugs, or between subjects who received the same drug product on two separate occasions. Therefore, we concluded that the reduced likelihood of comparable bioavailability for a subject is not influenced by the drug switch, but the result of intra subject variability of the active substance.

Dit proefschrift gaat over de uitwisselbaarheid van generieke medicijnen. In **hoofdstuk 1.1** beschrijven we van uit een historisch perspectief wat generieke medicijnen zijn en waarom het zo belangrijk is om het wisselen tussen verschillende generieke medicijnen van dezelfde werkzame stof te bestuderen. **Hoofdstuk 1.2** gaat over de toelatingseisen voor generieke medicijnen en discussiepunten daarover, vanuit het oogpunt van de toezichthouder.

In **hoofdstuk 2** beschrijven we het wisselen tussen generieke medicijnen in Nederland en de invloed daarvan op het welbevinden van patiënten. We bestudeerden de wisselingen tussen generieke medicijnen van twintig werkzame stoffen (**hoofdstuk 2.1**) en analyseerden het aantal gemelde bijwerkingen in verhouding tot het aantal wisselingen (**hoofdstuk 2.2**). We tonen aan dat er erg vaak gewisseld wordt, dat het om veel verschillende producten gaat en dat het grootste aantal wisselingen (80%) tussen twee generieke producten van dezelfde werkzame stof is. Voor onze selectie van werkzame stoffen werden er per 100.000 wisselingen gemiddeld 5,7 bijwerkingen gemeld. Wanneer we het aantal gemelde bijwerkingen in verhouding zetten tot het aantal wisselingen, identificeren we andere werkzame stoffen met een bovengemiddeld aantal meldingen. **Hoofdstuk 2.3** is ons verkennende onderzoek naar de oorzaken van de wisselingen in Nederland. We vonden dat de meerderheid van de wisselingen het gevolg is van het preferentiebeleid (23%), of een landelijk tekort van het generieke product (32%).

In **hoofdstuk 3** testten we de betrouwbaarheid van bioequivalentie, door middel van modellering en simulatie. Bioequivalentie is de bevestiging dat er voor een werkzame stof vergelijkbare bloedconcentraties zijn, wanneer de inname van twee producten met elkaar vergeleken wordt. We onderzochten of de conclusie van bioequivalentie bij gezonde vrijwilligers ook stand houdt in een groep patiënten met veranderde farmacokinetiek. In **hoofdstuk 3.1** beschrijven we de validatie van het model, in **hoofdstuk 3.2** beschrijven we de simulaties met het model. Met de simulaties laten we zien dat wanneer er gewisseld wordt, er geen relevante verandering van de bloedconcentraties te verwachten is voor een patiënt met een groter verdelingsvolume, maar wel toegenomen variatie van de bloedconcentraties voor een patiënt met een lagere opname snelheid of een verminderde nierfunctie. Voor deze patiënten is het minder waarschijnlijk dat bioequivalentie in een studie kan worden aangetoond, maar de gemiddelde bloedconcentratie ratio van twee producten blijft gelijk. Er zijn geen verschillen

waargenomen voor de vergelijkingen tussen de verschillende generieke producten of het innovator product, ook niet voor patiënten welke hetzelfde product op twee verschillende momenten kregen. Daarom komen wij in deze studie tot de conclusie dat de grotere variatie van de bloedconcentraties voor een patiënt niet wordt veroorzaakt door het wisselen tussen generieke medicijnen, maar door toegenomen intra-individuele variabiliteit van de werkzame stof.

Chapter 6

Societal and scientific impact

This chapter discusses the societal and scientific value of the research presented in this thesis. Generic interchangeability is a highly relevant topic for patients, prescribers, regulators, and scientists.

Patients should be able to trust the quality, safety, and efficacy of the drugs they use—in the case of this research, generics in particular. In the Netherlands, there are almost 11 million prescription drug users, and about 2/3 of all dispensed drugs are generic (1, 2). Thus, a large portion of patients use generic drugs and, as demonstrated in chapter 2.1, often switch between generic versions of the same drug.

When we combined data from the National Health Care Institute in the Netherlands with data from the Netherlands Pharmacovigilance Centre Lareb, as discussed in chapter 2.2, we estimated that 5.7 ADRs are reported per 100,000 drug switches on average. This reporting rate may be low, but the impact of these ADRs on individual patients is high, especially in the absence of any obvious personal benefit to the patient.

Therefore, patient organizations are fierce advocates of system reform, in which patients are switched between drugs less often and unavoidable switches are better guided by the physician and pharmacist. In April 2018, 14 patient organizations published a report on the unwanted effects of drug switches for patients (3, 4). This report was described by several Dutch newspapers with the following headline: “1 in 3 patients sicker after drug switch” (5).

In response, the Dutch Ministry of Health, Welfare, and Sport initiated a working group with representatives of patients, physicians, pharmacists, and health care insurers to come to a mutual agreement on how generic drug switching can be performed responsibly (6). The Ministry commissioned Vektis Intelligence to research the number of drug switches and Gupta Strategist to research the incentives for drug switching (7, 8). We collaborated with the researchers in both these investigations. Results from both these investigations aligned with the results we described in chapter 2.1 and chapter 2.3.

We also participated in the first discussions of the working group mentioned above. Additionally, we were involved in creating an overview of drugs for which drug intake mistakes caused by confusion of drug switches could result in serious clinical complications (9). These efforts led to publication of a guideline in which all stakeholders found common ground on how to reduce the number of drug switches and assure drug switching could be performed responsibly in Dutch pharmaceutical practice (10).

The societal and scientific value of the research presented in this thesis can also be found in the realm of science and drug regulation, that is, regulatory science. Regulatory science is defined by the European Medicines Agency as “a range of scientific disciplines that are applied to the quality, safety, and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. It encompasses basic and applied medicinal science and social sciences, and contributes to the development of regulatory standards and tools” (11). In chapter 3.1 and chapter 3.2, we described our efforts to challenge the robustness of bioequivalence, the most important regulatory requirement for generic drug approval. As shown in chapter 2.1, most (80%) of the drug switches occur between two generic drugs. Therefore, challenging the current regulation of demonstrating average bioequivalence only to the originator drug is of particular importance. As described in the corresponding chapters, our results (considering their limitations) support generic interchangeability and the regulatory requirements for generic drug approval.

Dissemination of our contribution to the scientific community was ensured by scientific publications, particularly by the opinion paper on the view of the regulator regarding generic interchangeability (chapter 1.2). A wider audience was also targeted by providing background information for a newspaper article (12) and a public information leaflet on generic medicines (13).

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Chapter 7

dankwoord | about the author

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was geweest als mij dit niet was gelukt. Dankjewel.

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Pieter Jelte Glerum was born on July 18, 1984 in Soest, the Netherlands. Both primary (Soest) and secondary (Zeist) education were followed in accordance with the method of Maria Montessori. Although initially aiming to study medicine, Pieter obtained a Bachelor's degree in Biomedical Sciences at Utrecht University. His bachelor thesis was on reasons for sports drop-out in youth, supervised by dr. S.L. Schmikli at the Department of Rehabilitation and Sports Medicine of the University Medical Center Utrecht (UMCU). During the master's program in Biomedical Sciences, two larger research internships were performed. The first was at the Laboratory of Experimental Cardiology of the UMCU, on mechanisms of human cardiomyocyte progenitor cell differentiation, in which experience was gained with cell culture, and several genomic and proteomic techniques under the supervision of dr. P. van Vliet. After this, the study portfolio gravitated towards medicine evaluation. The second master's internship was performed at the Medicines Evaluation Board (MEB), under the supervision of dr. C.C. Gispen - de Wied; in which the content of one of the decision-making bodies of the MEB was analyzed. Under the supervision of the chair of the MEB, prof. dr. H.G.M Leufkens, a master thesis was written on modernization of medicine evaluation. Since 2011, Pieter Glerum has worked as an assessor of clinical pharmacokinetics at the MEB in the Netherlands.

orandum est ut sit mens sana in corpore sano

- Juvenalis

all of this stuff in our veins is the same

- Guy Edward John Garvey

I need to hear my thoughts
turn the music up loud

- Calvin Cordozar Broadus Jr.