Essays on prices, volumes, and policies in generic drug markets in high- and middle-income countries

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6th December 2018

A thesis submitted to the Department of Social Policy at the London School of Economics and Political Science for the degree of Doctor of Philosophy (Ph.D.), London, December 2018

Declaration

I certify that the thesis I have presented for examination for the Ph.D. degree of the London School of Economics and Political Science is solely my own work other than where I have clearly indicated that it is the work of others (in which case the extent of any work carried out jointly by me and any other person is clearly identified in it).

I declare that my thesis consists of 58,473 words (excluding the bibliography and appendixes).

London, December 2018

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Statement of conjoint work

The first article (Chapter 2) was co-authored by Dr. Panos G. Kanavos (primary Ph.D. supervisor at the London School of Economics and Political Science) and Prof. Martin McKee (London School of Hygiene and Tropical Medicine). The article was published in *The Milbank Quarterly* (© 2017 The Authors, CC BY license 4.0). The article was recognized by *The Milbank Quarterly* as the most read peer-reviewed article in the journal in 2017 (see https://www.milbank.org/news/milbank-quarterlys-top-5-articles-op-eds-2017/; last accessed 5 Dec. 2018).

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Author contributions: OJW conceived the study. OJW analysed the data and interpreted the findings. OJW drafted the paper. PGK and MM provided guidance on the study design, the data analysis, and the interpretation of the findings. All authors revised subsequent drafts and agreed on the final version of the paper before submission. OJW is the guarantor.

The second article (Chapter 3) was co-authored by Dr. Panos G. Kanavos. It was published in *BMC Health Services Research* (© 2017 The Authors, CC BY license 4.0).

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The third article (Chapter 4) was co-authored by Ms. Dale M. Sandberg, Dr. Anban Pillay, and Dr. Panos G. Kanavos. It was published in *Social Science & Medicine* (© 2018 The Authors, CC BY license 4.0). The chapter presented in this thesis is the submitted version of the paper. Some of the results and text were updated or re-analysed during the peer review process. At the time of writing, Ms. Sandberg was the Deputy Director for Sector Wide Procurement at the National Department of Health (NDoH) of South Africa. Dr. Pillay is the Deputy Director General for Health Regulation and Compliance at the NDoH. Ms. Sandberg and Dr. Pillay provided the data for the analysis. Ms. Sandberg drafted parts of the conceptual framework, discussion, and conclusion sections of the paper while a research assistant at the London School of Economics and Political Science in 2012; some of that text contributed to her master's thesis. Ms. Bernadette Stevens (NDoH) and Mr. Marc Parsons (London School of Economics and Political Science) assisted with cleaning the dataset.

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The fourth article (Chapter 5) was single authored by the Ph.D. candidate. The article is being prepared for submission to a peer-reviewed journal.

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The fifth article (Chapter 6) was co-authored by Dr. Panos G. Kanavos and was published in the *Bulletin of the World Health Organization* (© 2015 The Authors, CC BY license 3.0 IGO; licensee the World Health Organization).

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Some of the text in the Conclusion (Chapter 7) was published in an article in *Global Policy* (© 2017 University of Durham and John Wiley & Sons, Ltd). The article was co-authored by Prof. Martin McKee.

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I have lightly edited the text in some of the chapters to fit the narrative and flow of the thesis. Thus, some of the wording and ordering of paragraphs in this thesis differs slightly from what is found in the published articles. None of the empirical content or results differ, with the exception of some of the results in Chapter 4 that were updated or re-analysed during the peer review process. The results presented in Chapter 5 have not yet undergone peer review at a journal.

This statement is to confirm I contributed a minimum of 70% to Chapters 2, 3, 4, 6, and 7 as agreed to by the undersigned.

Panos G. Kanavos *Martin McKee* *Anban Pillay* *Dale M. Sandberg*

Other relevant work

During my Ph.D. studies, I co-authored peer-reviewed articles, reports, and book chapters on drug regulation, policies, and financing. These documents (listed below in reverse order of publication), while not contributing directly to my thesis, are relevant to the work presented in this book.

- Naci H, Wouters OJ, Gupta R, Ioannidis JPA (2017). Timing and characteristics of cumulative evidence available on novel therapeutic agents receiving Food and Drug Administration accelerated approval. *The Milbank Quarterly*, **95**(2): 261-290.
- Panteli D, Arickx F, Cleemput I, Dedet G, Eckhardt H, Fogarty E, Gerkens S, Henschke C, Hislop J, Jommi C, Kaitelidou D, Kawalec P, Keskimäki I, Kroneman M, López Bastida J, Pita Barros P, Ramsberg J, Schneider P, Spillane S, Vogler S, Vuorenkoski L, Wallach Kildemoes H, Wouters OJ, Busse R (2016). Pharmaceutical regulation in 15 European countries: Review. *Health Systems in Transition*, **18**(5): 1-118. (*Note*: Authors other than the first and last are listed in alphabetical order.)
- Wouters OJ, Cylus J, Yang W, Thomson S, McKee M (2016). Medical savings accounts: Assessing their impact on efficiency, equity, and financial protection in health care. *Health Economics, Policy and Law*, **11**(3): 321-335.
- Naci H, Lehman R, Wouters OJ, Goldacre B, Yudkin JS (2015). Rethinking the appraisal and approval of drugs for type 2 diabetes. *BMJ*, **351**: h5260.
- Wouters OJ, O'Donoghue DJ, Ritchie J, Kanavos PG, Narva AS (2015). Early chronic kidney disease: Diagnosis, management, and models of care. *Nature Reviews Nephrology*, **11**(8): 491-502.
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- Kanavos P, Wouters OJ (2014). Pharmaceutical parallel trade: Legal, policy, and economic issues. In: Culyer AJ (ed.), *Encyclopedia of Health Economics*, Vol. 3. Elsevier: Oxford, UK. 20-28 pp.

- Kanavos P, Wouters OJ (2014). Pharmaceutical policies in Cyprus: A review of the current system and future options. World Health Organization Regional Office for Europe: Copenhagen, Denmark. 1-64 pp. Available at: http://www.moh.gov.cy.

Contents

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Data disclaimer

The statements, findings, conclusions, views, and opinions contained and expressed in Chapters 2 and 3 were based in part on data obtained under license from the following IMS Health information services: Pricing Insights database (January - December 2013) and Midas database (January 1998 - December 2009). All rights reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Inc or any of its affiliated or subsidiary entities. The data that support the findings of these chapters are available from IMS Health but restrictions apply to the availability of these data, which were used under license for these studies, and so are not publicly available. Data are however available from the author on reasonable request and with permission of IMS Health.

With the exception of the procurement data (i.e., Republic of South Africa Pharmaceutical Database), the data used in Chapters 4 and 5 are in the public domain. The procurement data are not publicly available, and restrictions apply to the availability of these data. They are however available from the author on reasonable request and with permission from the South African National Department of Health.

The datasets generated during and/or analysed during the study presented in Chapter 6 are not publicly available, and restrictions apply to the availability of these data. They are however available from the author on reasonable request and with permission from the interviewees and the Cypriot Ministry of Health.

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I received ethics approval from the London School of Economics and Political Science (Research Ethics Committee application no. 404-2015) for the work conducted in Chapters 4 and 5, at the request of the South African National Department of Health (National Health Research Database application no. WC/2015RP28/838).

No conflicts of interest were reported by the co-authors of the studies presented in this thesis, based on the criteria set out in the International Committee of Medical Journal Editors (ICMJE) Forms for Disclosure of Potential Conflicts of Interest.

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Thesis production

I typeset this thesis using the TEX typesetting system, developed by Prof. Donald Knuth, on a computer running Arch GNU/Linux. I used the TEX Live distribution for processing the document, vim for text editing, and git for version control. I thank Dr. Edward Pinchbeck (LSE) for sharing some of his LATEX code.

All statistical analyses were conducted in Stata version 15 (StataCorp, College Station, Texas, USA), unless otherwise stated. The qualitative analysis in Chapter 6 was done in NVivo version 10 (QSR International, Melbourne, Australia).

Abstract

Background and importance: Rising drug prices are putting pressure on health care budgets. Policymakers are assessing how they can save money through generic drugs.

Objective: The aim of this Ph.D. was to explore issues relating to the prices and usage of generic medicines in high- and middle-income countries in five articles. This was done using quantitative and qualitative methods, including price and Herfindahl-Hirschman indexes, difference-in-differences regression analyses, semi-structured stakeholder interviews, and literature reviews. As a Ph.D. "thesis by papers", each of the five articles should be read as a stand-alone piece. However, the thesis presents an overarching narrative, outlined at the end of Chapter 1.

Novelty and empirical contribution: My original contributions to knowledge are: (i) updated analyses of generic drug policies, prices, and usage rates in high-income countries, based on a large, representative sample of generic medicines from 2013 (Chapters 2 and 3); (ii) evidence on the impact of a pharmaceutical tendering system on medicines prices, demand, and competition over a 15-year period (Chapter 4); (iii) quantitative data on the impact of therapeutic tendering on drug spending and prices (Chapter 5); and (iv) qualitative data on how a country can move from a fragmented health-care system to a single-payer one, using tendering as the basis for a comprehensive drug-benefit plan (Chapter 6).

Key findings: The prices and market shares of generics varied widely across Europe. For example, prices charged by manufacturers in Switzerland were, on average, more than 2.5 times those in Germany and more than 6 times those in the United Kingdom, based on the results of a commonly used price index. However, the results varied depending on the choice of index, base country, unit of volume, method of currency conversion, and therapeutic category. The results also differed depending on whether one looked at the prices charged by manufacturers or those charged by pharmacists. The proportion of prescriptions filled with generics ranged from 17% in Switzerland to 83% in the United Kingdom. The results of the first two studies indicated that the countries which used tender or tender-like systems to set generic drug prices in retail

pharmacies (ie, Denmark, Germany, the Netherlands, and Sweden) had among the lowest prices among the countries included in the studies.

Tendering can be an effective policy to procure essential medicines at low prices, based on analysis of data from South Africa and Cyprus. For instance, the average prices of antiretroviral therapies, anti-infective medicines, small-volume parenterals, drops and inhalers, solid-dose medicines, and family-planning agents dropped by roughly 40% or more between 2003 and 2016 in South Africa. Many tender contracts in South Africa remained competitive over time, based on the Herfindahl-Hirschman results, with some notable exceptions. However, the number of different firms winning contracts decreased over time in most tender categories. Also, there were large discrepancies between the drug quantities the health ministry estimated it would need to meet patient demand and the quantities the ministry went on to procure during tender periods. In South Africa, the introduction of therapeutic tendering was associated with an estimated 33% to 44% reduction in the prices of solid-dose drugs in 2014. National governments in countries aiming to introduce national health systems (eg, Cyprus and South Africa) will need to adapt their tendering systems and other pharmaceutical policies during transition periods.

Future research directions: More research is needed to better understand the drivers of differences in generic drug prices between countries. It is also important to examine why there are large differences in the prices of drugs in various therapeutic areas, both within and between countries. Also, data from more countries, especially low- and middle-income ones, are needed to determine which features of tendering systems are associated with lower prices. Future studies should re-examine the South African therapeutic tendering system once data from more post-intervention periods are available, possibly using other research designs like interrupted time-series models (ie, segmented regression analysis).

Policy implications: Price indexes are useful statistical approaches for comparing drug prices across countries, but policymakers should interpret price indexes with caution given their limitations. This thesis offers useful data for policymakers using, or planning to introduce, tendering systems, especially in countries aiming for universal health coverage, like Cyprus (Chapter 6) and South Africa (Chapters 4 and 5).

Abbreviations

AIDS	acquired immune deficiency syndrome
AMA	American Medical Association
APhA	American Pharmacists Association
ATC	anatomical therapeutic chemical (classification system)
CBO	Congressional Budget Office (United States)
DDD	defined daily dose
DERP	Drug Effectiveness Review Project (United States)
DiD	difference-in-differences
DNDi	Drugs for Neglected Diseases initiative
DTI	Department of Trade and Industry (South Africa)
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
FTC	Federal Trade Commission (United States)
GDP	gross domestic product
HHI	Herfindahl-Hirschman index
HIV	human immunodeficiency virus
HMO	health maintenance organization
INN	international non-proprietary name
IRP	internal reference pricing
MSF	Médecins Sans Frontières (Doctors Without Borders)
MSH	Management Sciences for Health
NDoH	National Department of Health (South Africa)
NGO	non-governmental organisation
NHI	national health insurance
NPC	National Pharmaceutical Council (United States)
OECD	Organisation for Economic Co-operation and Development
PBM	pharmacy benefit manager
PPP	purchasing power parity

PRISMA	preferred reporting items for systematic reviews and meta-analyses
R&D	research and development
SEP	single exit price
SUTVA	stable unit treatment value assumption
TB	tuberculosis
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UHC	universal health coverage
UK	United Kingdom
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
US	United States
WHO	World Health Organization
WTO	World Trade Organization
ZAR	South African rand

List of Tables

List of Figures

Introduction

"Begin at the beginning," the King said, gravely, "and go on till you come to an end; then stop."

– Lewis Carroll, *Alice in Wonderland*

MEDICINES are integral to modern health care. In the past half-century, the discovery of transformative new drugs revolutionized medicine. [1] The approval of the blood-pressure-reducing drug captopril and the cholesterol-lowering medicine lovastatin in the 1980s by US regulators ushered in a new era in cardiovascular care. The antidepressant fluoxetine, first marketed in the US in 1986, helped reshape psychiatric treatment. The chemotherapy imatinib, approved by the US Food and Drug Administration (FDA) in the early 2000s, radically improved the treatment of leukemia and other types of cancer. The discovery of protease inhibitors, a class of antiretroviral drugs, turned human immunodeficiency virus (HIV) into a manageable chronic illness. And the recent advent of immunotherapy promises to transform cancer therapy. Yet despite these advances, many patients worldwide lack access to medicines, with drugs often unaffordable or unavailable. [2–21]

I Access to medicines

The World Health Organization (WHO) views "equitable access to safe and affordable medicines as vital to the attainment of the highest possible standard of health by all". [23] This public health imperative falls under the umbrella term "access to medicines", which encompasses the accessibility (eg, physical location of pharmacies), availability, affordability, and acceptability (eg, quality) of medicines. [23] Access to essential medicines, as part of a broader right to health, was enshrined in international law by the WHO in its constitution (1946) and by the United Nations General Assembly in the International Covenant on Economic, Social and Cultural Rights (1966). [2,7,22,24–29] Right-to-health principles are written into many national constitutions. [25,26]

Access to affordable, high-quality, essential medicines is a matter of global concern. In 2015, the United Nations set up a high-level panel on access to medicines to "review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies". [30] In 2017, a commission convened by the medical journal *The Lancet* published a report on access to essential medicines for universal health coverage. [2] Organisations like the Access Campaign of Médecins Sans Frontières (Doctors Without Borders) and Drugs for Neglected Diseases initiative (DNDi) have for decades been promoting drug innovation and development in neglected disease areas and better access to health technologies for all. [31]

The availability of low-cost generic medicines is a key part of any national or international strategy to guarantee access to essential medicines for patients. [2] Generic medicines are bioequivalent replicas of brand name drugs, containing the same active ingredients and with identical quality, safety, and efficacy profiles. Generics can be sold

for much less than their brand name counterparts as they are relatively inexpensive to bring to market. Greater use of generic medicines instead of more expensive brand name ones can improve health-care efficiency and generate savings without stifling drug innovation. [9] In countries where patients lack insurance against prescription drug costs, the availability of generic drugs can promote equitable access to medicines.

The next section describes the life cycle of a new medicine, from its initial marketing after successful clinical trials in humans to the availability of generic versions of the medicine.

II Life cycle of a pharmaceutical product

Manufacturers of on-patent drugs, referred to as brand name or originator firms throughout this thesis, hold monopoly positions due to patents and other market exclusivities awarded during research and development. To the extent possible under the law, these firms charge the highest price the market will bear to maximize profits. [32] This is represented by stages 1 and 2 in **Figure 1**, which shows the life-cycle stages and typical price trend for a new pharmaceutical product.

If drugs with different active ingredients target the same condition and offer comparable therapeutic benefits, the situation could, in theory, resemble an oligopolistic market (stage 3 in **Figure 1**). In reality, there is often little price competition between therapeutic substitutes—also called "me-too" drugs or drug analogues [34]—as shown in previous studies, many of which looked at the US drug market. [35–45] For instance, the U.S. Congressional Budget Office (CBO) found, based on data for medicines in five therapeutic classes, that the prices of the breakthrough drugs—ie, the first active ingredients in each class to use a therapeutic mechanism—often continued to rise in the US at a rate faster than inflation after me-too competitors entered the market. [37] Similarly, Hostenkamp found no evidence of price competition between therapeutic substitutes sold in Danish hospital pharmacies. [36] Lu and Comanor reported that the average price of brand name drugs in their sample rose faster than inflation in the US after the introduction of therapeutic substitutes, although they found that the rate of increase was lower in therapeutic classes with more competitors, all else equal. [38] They also found that the prices of some me-too drugs which offered little or no therapeutic benefit over the first-in-class product were typically sold at a lower initial price than the first-in-class product—presumably in an attempt to gain market share—but that the prices were sharply raised for many of the products once they become more widely used. [38]

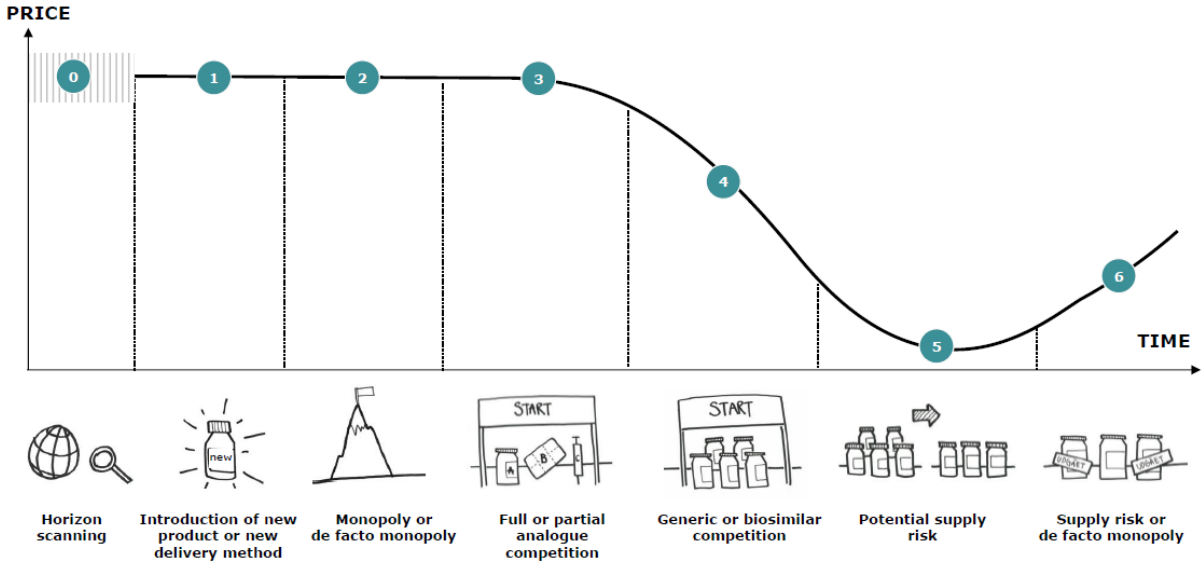


Figure 1: Pharmaceutical life-cycle stages and generalized price development for a specific disease area or condition.

Source: Reproduced from WHO (2016, p. 5), with permission. [33]

It is difficult to draw causal, and universally applicable, conclusions about the nature and extent of price competition between me-too products. Results are likely to differ from country to country, since price regulations and incentives for consumers to choose the least expensive me-too drugs vary widely across settings. For example, some countries, like France and Sweden, require regulatory approval for a drug to be reimbursed by the state and generally prohibit price changes once a product has been brought to market. Other countries, like the US, generally allow free pricing of products. [46] Such differences influence the pricing strategies of drug manufacturers. Drug substitution and internal reference pricing policies also differ across and within countries, as outlined in Chapter 2, and both types of policies can impact price competition between therapeutic substitutes. [46]

Still, several factors may explain the observed lack of price competition in many of these studies. Importantly, first-in-class medicines have the advantage that physicians become accustomed to prescribing those medicines and may be hesitant to switch patients to me-too drugs later on if there is no clear clinical rationale for doing so, especially since physicians often lack data on the comparative costs of treatments. [37, 47] The prescribing habits of clinicians may also be shaped by the promotional activities of drug firms and their sales representatives, who often try to differentiate their products from those of competitors. [47, 48] These firms sometimes engage in aggressive "switch" campaigns, in which doctors are encouraged to switch their patients to a me-too product. [49] As Kessler and colleagues describe, companies "rely on the widely

held notion—not always true—that what is newer is better and is therefore worth more. Aggressive advertising campaigns and lack of information among prescribing physicians about comparative costs can facilitate the higher pricing of 'me-too' drugs". [47] In the past, pharmaceutical companies have regularly made "false and misleading claims" about the superiority of their products over others in promotional materials and activities. [47] There are also rampant conflicts of interest in the medical-industrial complex, [47, 50] with many physicians receiving payments or research grants from drug firms, which may influence prescribing patterns. [51–53]

Moreover, for there to be strong price competition between therapeutic substitutes, consumers would need to be sensitive to differences in quality and price between such products. [35] (Here consumer refers, in most cases, to physicians or pharmacists who select treatment regimens for their patients. [54]) Yet there are usually major imperfections in consumer behavior in health care markets. [35, 55] Many clinicians are unaware about the comparative costs of treatments, and many prescribe based on habit rather than up-to-date clinical evidence. [56] Imperfections in consumer behavior may limit or even prohibit price competition between therapeutic substitutes.

Once the market exclusivity of a drug expires—at which time the brand name company is expected to have recouped its sunk research and development (R&D) costs[1]—any firm can legally sell a generic copy of the drug (stages 4 through 6 in **Figure 1**), subject to bioequivalence standards and good manufacturing practices. [62][2] Generic medicines are bioequivalent replicas of on-patent drugs: they contain the same active ingredients and have identical quality, safety, and efficacy profiles. [64, 65] Only the non-active ingredients, known as excipients, can differ between originator and generic drugs. For example, generics may contain different colouring, flavouring, and stabilising agents. [64] (Throughout this thesis, I use the term brand name or originator drugs to refer to patent-protected medicines and generic drugs to refer to bioequivalent replicas of originator products.[3])

Generic drugs are important for two reasons. First, as generic firms generally incur

[1] Some health policy experts argue that the high prices charged by brand name firms are not commensurate with the industry's R&D outlays. [57–59] By one estimate, US taxpayers, patients, and private industry alone pay roughly "1.7 times the global R&D expenses of major pharmaceutical corporations as a result of paying more than these corporations charge European countries for the same products — an excess amounting to US$ 40 billion in 2015, about 10 percent of total spending the US on pharmaceuticals". [60, 61] Topics around the pricing and patenting of new medicines are outside the scope of thesis. Instead, I assume that when an originator firm loses its market exclusivity for a brand name product, the firm has recovered its R&D costs. Regulators, payers, policymakers, and other stakeholders should then strive to make high-quality generic drugs available sustainably as soon as possible at affordable prices—all while encouraging patients to switch to generic drugs from their brand name counterparts.

[2] These standards are not always met in low- and middle-income countries, often due to inadequate regulatory capacity, leading to variable quality. [63] The WHO operates a pre-qualification scheme for suppliers to try to guarantee the quality, efficacy, and safety of generic medicines in these countries. [62]

[3] There are branded generic products, but the distinction between branded and unbranded generics is not essential for this thesis.

fewer research, development, and advertising costs, generics can be priced considerably lower than on-patent drugs. [8, 48] In this way, generic drugs can generate sizable savings for payers. Here payer refers to "any groups, other than patients, that are responsible for funding or reimbursing the cost of health care. ... Depending on the country, the term 'payer' might refer to private or public insurers, employers, or other third-party payers". [66] In countries where patients bear most or all of the cost of drugs, lower generic prices can improve the affordability of treatment. Second, the availability of generic drugs could stimulate innovation, as it should encourage originator firms to invest in research and development to regain their monopoly positions. Payers can also use the savings from generics to buy on-patent drugs, which may promote innovation. However, it is important that savings from generics are used to pay for new medicines which have been shown, preferably in high-quality, head-to-head randomized clinical trials, to be better than older, cheaper alternatives. [67] Otherwise, the savings from generic medicine may contribute to the proliferation of me-too drugs, ie, drugs which provide little or no added therapeutic benefit over existing treatment options. [67]

Payers thus aim to minimize generic drug prices and to maximize the volume market shares of generic drugs. The latter has increased steadily over the last two decades in most high- and middle-income countries. In 2014, around 9 out of 10 prescriptions were filled generically in the US, representing roughly one-third of drug spending. [68] The US Association for Accessible Medicines, a trade association for generic drug manufacturers and distributors, estimated that the use of low-cost generic medicines saved the US health care system roughly US$ 1.7 trillion between 2006 and 2016, including US$ 115 billion in savings for Medicare and Medicaid in 2016 alone. [69] In Europe, generics account for about half of drug consumption, but only 18% of spending. [70]

Yet a recent US study estimated that the underuse of cheaper generics leads to nearly US$ 6 billion in unrealised savings per year. [71] An earlier study approximated that US drug expenditure would decrease by about 11% if generics were substituted for all originator drugs that are dispensed despite generics being available. [72] Another study estimated that the cost of treating hypertensive patients would drop by 25% in the US if physicians followed clinical guidelines more closely and prescribed generics when appropriate. [73] Studies from Canada, China, EU member states, Japan, Latin American countries, and the US have also highlighted significant shortcomings in generic drug markets in each of these countries or regions. [8, 10, 14–21] There is growing concern that, over time, as prices drop, generic markets may experience a steep decline in competition and drug shortages (stages 5 and 6 of **Figure 1**), as witnessed in the US and other countries in recent years. [74–77] This is discussed further in Chapter 2.

Many blockbuster drugs—drugs with over US$ 1 billion in annual sales—will lose their patents in the coming years. It is therefore timely to study drug market function

to improve generic drug policies (incl. competition between therapeutic substitutes), ie, stages 3-6 in **Figure 1**. This is especially critical in periods of economic recession when available resources are further constrained. Access to cheap, effective, safe, high-quality generic medicines is critical if health systems worldwide are to address the rising costs of health and pharmaceutical care. [78–81] The aim of this Ph.D. was to explore issues relating to the prices and usage of generic medicines in selected high- and middle-income countries in five related articles, as described further in the next chapter.

In this thesis, I only analysed generic drug markets (ie, bioequivalent new molecular entities), not markets for biosimilar products. As described earlier, generic drugs are bioequivalent, chemically-derived copies of brand-name pharmaceutical products. Biological, biopharmaceutical, and biosimilar products, which are derived from human or animal materials, follow different approval and regulatory pathways. [82–91]

III Thesis requirements

This thesis adheres to the London School of Economics and Political Science (LSE) guidelines for a "thesis by publishable papers", which should (i) "consist of at least three papers, an introduction, conclusion, and any other linking chapters that might be appropriate" and (ii) "have a minimum of 50,000 words and a maximum of 100,000 words including figures and tables in the overall count".

The LSE Department of Social Policy guidelines further state: "The papers should ... have been published in high-quality refereed journals, be submitted for publication to such a journal, or be of a quality to be published in such a journal. The large majority of the work for the papers concerned should have begun after the student's initial registration for M.Phil./Ph.D. At least one paper should be single authored, and any other papers should be primarily authored by the student. If there are any co-authored papers, the thesis should be accompanied by specific detailed statements on the contribution of the co-authors".

The full requirements for LSE doctoral theses can be found in the university's "Regulations for Research Degrees", available at `https://www.lse.ac.uk/`.

IV Structure of the thesis

Chapter 1 reviews literature relevant to this thesis, including data on the supply- and demand-side policies used in generic drug markets, as well as the pricing and usage of generic medicines in high- and middle-income countries. Chapter 1 also outlines gaps in the literature and the research questions posed in each thesis paper.

Chapters 2 through 6 present the empirical results of each study. As a Ph.D. thesis by papers, each of the five articles should be read as a stand-alone piece. However, the thesis presents an overarching narrative, outlined at the end of Chapter 1.

Chapter 7 summarises the main contributions of this thesis, offers ideas for future research, discusses possible policy implications of my findings, and outlines limitations of this research.

1

Literature review

"There is no such thing as truth. People who really know what happened aren't talking. And the people who don't have a clue, you can't shut them up."

– Tom Waits, *Interview in Pitchfork magazine (Nov. 2006)*

Key messages

- There are gaps in our understanding of off-patent drug markets.
- There are few published comparisons of generic drug prices and usage rates in high-income countries using large, representative samples of medicines.
- There is little evidence on the impact of pharmaceutical tenders on competition and drug prices over time.
- Little is known about the impact of tendering for medicines by therapeutic class on prices and spending.

THE World Trade Organization (WTO) agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) outlines minimum standards of intellectual property rights. All WTO member states must incorporate these standards into national legislation, although the TRIPS agreement contains "provisions that allow a degree of flexibility and sufficient room for countries to accommodate their own patent and intellectual property systems and developmental needs". [92][1]

In accordance with the TRIPS agreement, new pharmaceutical products or manufacturing processes are patented for a minimum of 20 years in WTO member states to reward innovation and incentivise research and development.[2] In some countries, including European Union (EU) member states and the United States (US), patent terms can be prolonged to ensure returns on investment for firms; [10, 93] other forms of market exclusivity may also apply. [93]

While patent protection is meant to stimulate innovation, it is important to protect payers from excessive drug costs. Between 2000 and 2015, drug spending per person (adjusted for inflation) increased dramatically in many member states of the Organisation for Economic Co-operation and Development (OECD) (**Figure** 1.1). [94] In 2015, drug spending as a proportion of GDP among these countries ranged from 0.5% in Luxembourg to 2.2% in Greece (median: 1.4%), while drug spending as a proportion of total health spending ranged from 6.8% in Denmark to 29.2% in Hungary (median: 15.1%). Drug spending per capita (median among OECD countries in 2015: US$ 511.6) is likely to continue to rise, in real terms, due to ageing populations, growing income levels, and increasing costs of new drugs, among other factors. [78–81]

In off-patent markets, the key entry barriers, namely intellectual property protection and high research and development costs, are removed. Once the market exclusivity of a brand name drug expires, generic drug firms with marketing approval can start selling copycat versions of the originator drug. In theory, an infinite number of generic substitutes could become available shortly after the loss of market exclusivity.[3] Although this should lead to a competitive environment, market imperfections will likely remain. Importantly, the market for medicines is characterized by a tiered demand system, in which physicians and pharmacists make treatment decisions for

[1] For instance, the Doha Declaration affirmed the right of developing countries to issue compulsory licenses, enable pharmaceutical parallel trade, and take other steps to "ensure access to medicines in the interests of public health". Critics argue, however, that governments in low- and middle-income countries have not taken adequate advantage of these provisions to guarantee access to essential medicines for patients. [92]

[2] A patent is usually enforced from when the application is filed, which, for medicines, is typically around the time of discovery. [92] Thus, the 'effective' patent length following clinical trials and marketing approval is shorter than the 20-year 'nominal' length. [93] Products can also enjoy a period of data exclusivity (for safety, quality, and efficacy data produced during clinical trials) to "protect undisclosed test data, submitted to drug regulatory authorities for the purposes of obtaining marketing approval, against unfair commercial use". [92] The period of data exclusivity may extend beyond the date of patent expiry. [10]

[3] Some patients may experience side-effects to the inactive ingredients of generics.

patients, who are often price insensitive if covered by comprehensive insurance. [62] Physicians and pharmacists, in turn, may not be aware of all generic medicines or still prefer originator products. [95] Patients may also exhibit brand loyalty to originator drugs. [96] In fact, a number of recent studies and systematic reviews have found that many physicians, pharmacists, and patients hold unfavorable views of generic drugs which are not evidence based. [51,95–104]

Even if a perfectly competitive off-patent market is unattainable, generic drug policies may help decrease prices and encourage patients to switch from originator to generic drugs. To expedite generic entry, most high-income countries streamline the approval process. [105–108] In the US, for instance, Roche-Bolar provisions[4] allow generic firms to submit "abbreviated new drug applications" prior to patent expiry. In these applications, generic firms can refer to the data generated by originator firms and do not have to re-conduct all the clinical tests. [105,107,109] Similar exemptions exist in the EU and other countries. [106][5]

To understand the functioning of generic drug markets, it is important to examine the supply- and demand-side factors influencing the availability, prices, and market shares of generic drugs. To this end, I conducted two separate literature reviews to identify literature gaps and research questions which I addressed in each of the five thesis articles.

In the rest of this chapter, I discuss: (i) the methods followed for both literature reviews, (ii) the key supply- and demand-side policies used in generic drug markets in high- and middle-income countries to encourage price competition among generic drug companies and promote generic drug use, (iii) the available evidence on which factors influence the availability, prices, and market shares of generic drugs in high- and middle-income countries, (iv) the gaps in the literature on generic drug markets addressed in this thesis, and (v) the research questions posed in each thesis paper.

[4]The name comes from a 1984 patent dispute in a US court case between Roche Products, Inc., an originator firm, and Bolar Pharmaceutical Co., Inc., a generic firm.

[5]The US also provides six-month marketing exclusivity to generic drug companies that successfully challenge brand-name patents. This is usually called a "Paragraph IV challenge" after the relevant clause in the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. [109] However, this clause is controversial since it results in a duopoly between the off-patent originator drug and first generic entrant. [109] The first generic entrant is then able to price its product just below the price of the off-patent originator, since it cannot legally face any further competition. [110] This limits the potential savings for payers, which may explain why such clauses are rarely adopted in other countries. [108]

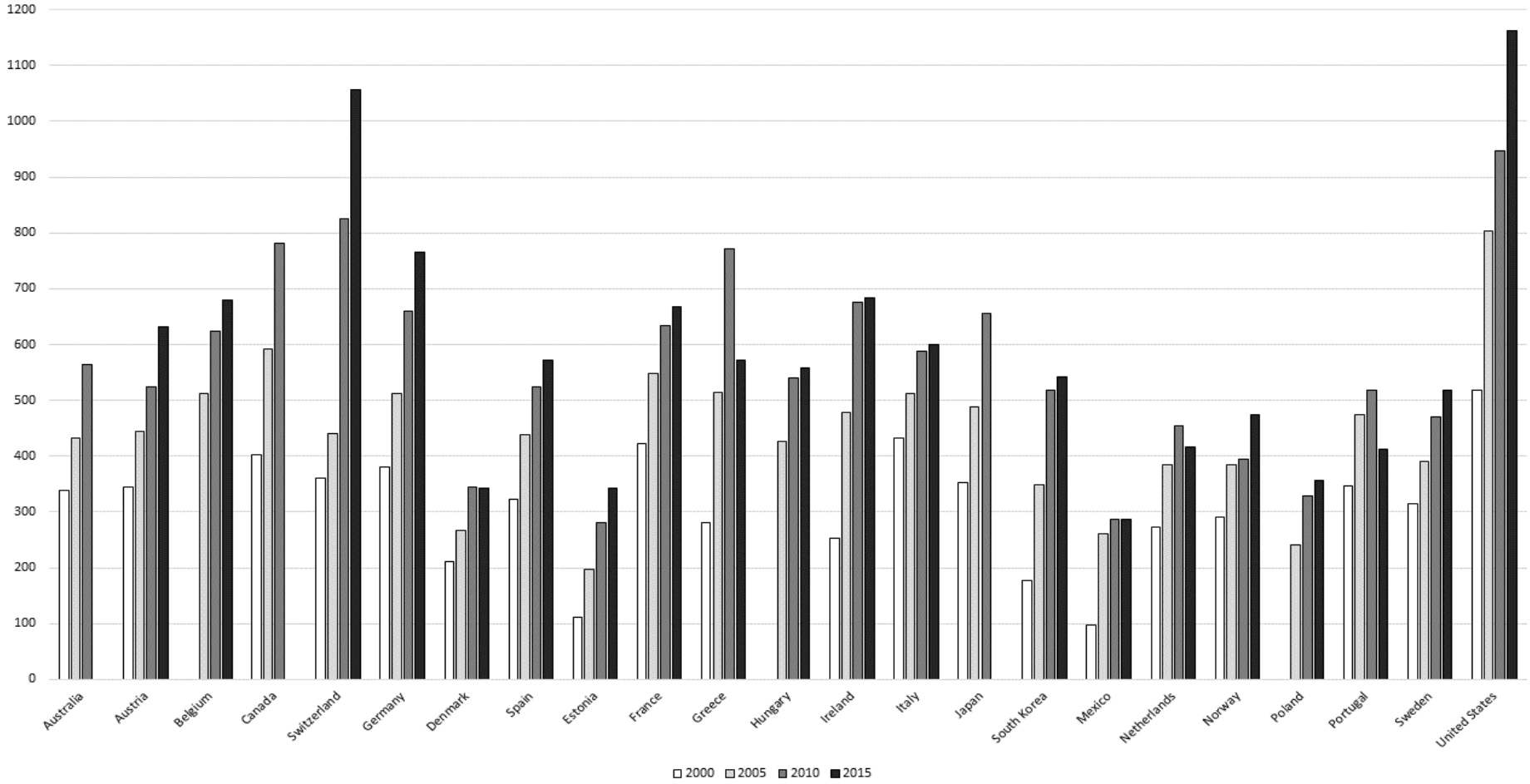


Figure 1.1: Total pharmaceutical expenditure (US$ per capita) in 23 OECD countries (2000-2015).

Note: 2000 data were unavailable for Belgium, Hungary, and Poland; 2015 data were unavailable for Australia, Canada, and Japan.

Source: Reproduced from OECD data. [94]

1.1 Methods

1.1.1 Scoping literature review: Generic drug policies

I reviewed the generic drug policies in the ten largest generic drug markets in Europe in 2013, which—listed in order—were: Germany, France, the UK, Spain, Italy, Poland, Switzerland, the Netherlands, Portugal, and Belgium.[6] These countries were selected since they are also covered in Chapters 2 and 3.

I focused on high-income countries due to availability of information and data. A recent literature review [111] summarized pharmaceutical pricing and purchasing policies used in low- and middle-income countries. The generic drug policies identified in that review mirrored those used in the ten countries above, with the exception of cost-plus pricing (**Table 1.1**). At the end of each section, I give examples of low- and middle-income countries which use each policy. [111]

To categorize pharmaceutical policies, I followed the conceptual framework outlined by Kanavos (2014), [8] which distinguishes between supply- and demand-side policies. Supply-side measures target prices and reimbursement rates, while demand-side measures target quantities (**Table 1.1**). Supply-side measures include policies aimed at controlling distribution chain costs, such as regulation of mark-ups and discounts. I did not examine measures used to speed up generic market entry, like allowing generic drug firms to file so-called abbreviated new drug applications prior to patent expiry. Supply- and demand-side policies play complementary roles in fostering strong generic drug markets.

To identify the generic drug policies applied in each country in 2013 for reimbursed medicines, I followed a four-step approach. First, I used previously-compiled lists of policies in each country (2000-2010) as a baseline; [8, 108] these lists included all the study countries except Belgium and Switzerland. For Switzerland I used a 2007 country report published by the OECD as the baseline, [112] while for Belgium I relied on a published article from 2005 on the country's generic drug policies. [113]

Second, I searched MEDLINE for peer-reviewed literature published between 1 January 2011 and 11 August 2015 (search date) with up-to-date information for each country; **Appendix A** provides a summary of the search strategy, search dates, and results. The references were handled in EndNote X7 (Thomson Reuters, Toronto, Canada). I also searched the websites of the respective health ministries—if these pages were available in English or French—for information about generic drug policies. When there were discrepancies between sources, I relied on the most recently-published information. **Figure 1.2** and **Box 1.1** summarise the search strategy and results, respectively.

[6] The sizes of the European generic drug markets were determined based on IMS Health data on sales in euros in 2013; all foreign currencies were converted to euros based on yearly average exchange rates. The dataset is described in greater detail in Chapter 2.

Third, I compared our findings with internal IMS Health guides on the pharmaceutical sectors in the study countries in 2013. These documents outlined the generic drug policies in each country. When there were discrepancies between the data identified in the first two steps and the IMS Health guides, I relied on the information in the guides.

Finally, I contacted at least one pharmaceutical policy researcher or health ministry official from each country to verify the identified policies (**Appendix A**). The policy summaries are meant to provide an overview of the approaches used in each country to regulate generic drug markets, but exceptions may apply to some products. Also, to contextualize the policy summaries below and provide evidence on their effectiveness, I added references to relevant studies where appropriate.

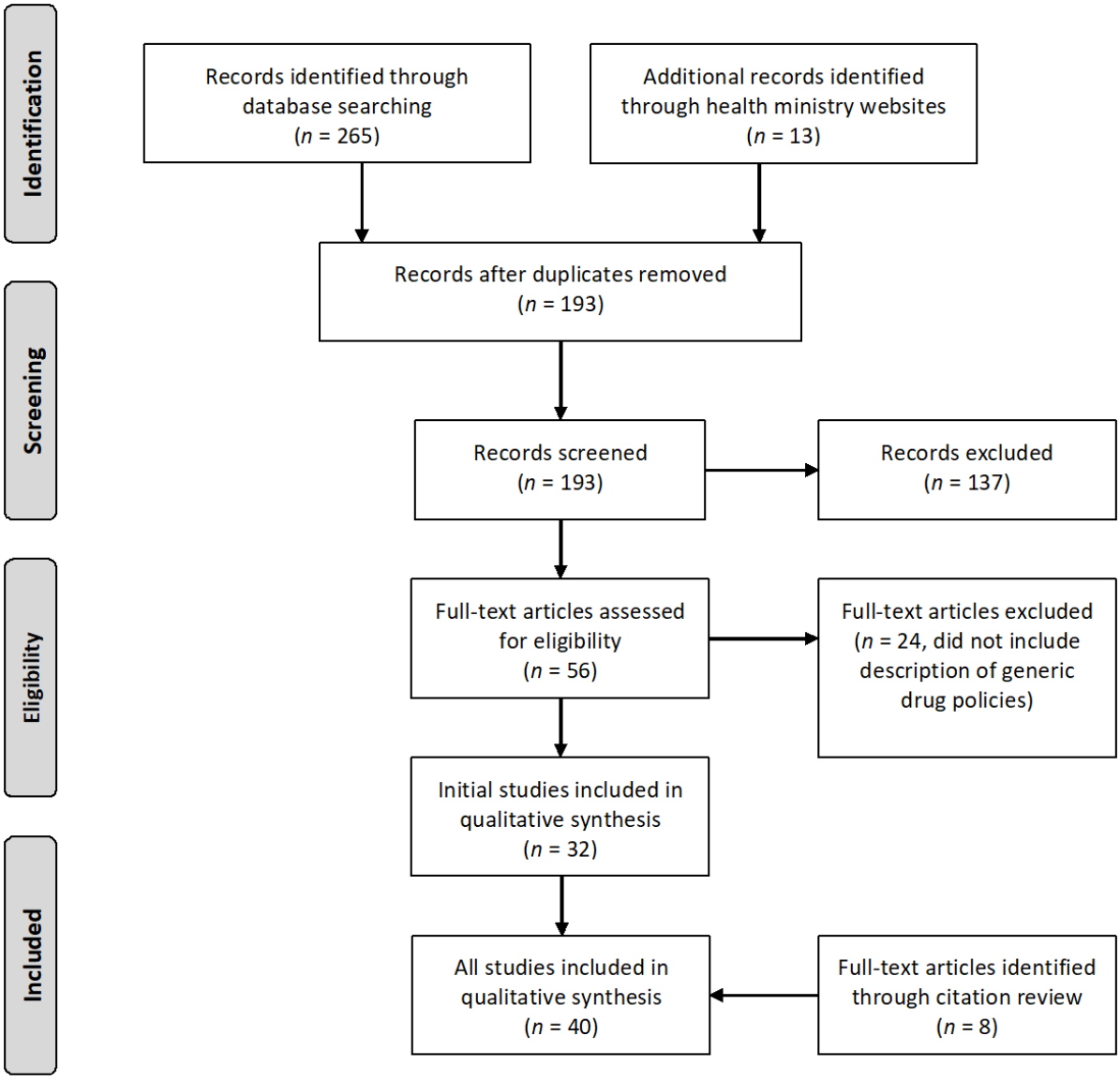


Figure 1.2: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart.

Note: The PRISMA flow chart was developed by [114].

Box 1.1: Search strategy and selection criteria.

The aim of the literature review was to identify which generic drug policies were used in 2013 in the retail drug markets in Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, and the UK.

I searched the MEDLINE database (PubMed portal, title/abstract) for English- and French-language peer-reviewed studies published between 1 January 2011 and 11 August 2015 (search date). I excluded conference abstracts and used the following keywords:

1. (generic or off-patent)
2. (drug* or medicine* or pharmaceutical*)
3. (Belgium or England or France or Germany or Italy or Netherlands or Northern Ireland or Poland or Portugal or Scotland or Spain or Switzerland or UK or U.K. or United Kingdom or Wales)

An asterisk truncated the search word (eg, drug* = drug, drugs, etc.). I carried out the search for each country separately, so line 3 only included one country at a time. For the UK search, I also included the terms England, Northern Ireland, Scotland, and Wales.

I included an article if it contained at least one section describing the supply-side or demand-side generic drug policies in the study country. This could include a comprehensive overview of such policies in the background/introduction section of an article, as determined by the author. The reference lists of identified articles were screened and relevant articles were included. These citation checks sometimes revealed articles which were relevant for other study countries.

1.1.2 Narrative literature review: Generic drug markets

Next, I surveyed peer-reviewed studies, grey literature, and books published since 2000 to identify factors associated with: (i) generic market entry, (ii) originator drug prices and market shares (following loss of market exclusivity), and (iii) generic drug prices and market shares. I also included highly referenced older publications. I summarised the qualitative data as a narrative review. Much of the evidence on competition and

market structures in generic drug sectors comes from Europe and the United States.

These studies were identified through unstructured searches of EconLit, Embase, MEDLINE (PubMed), Scopus, ISI Web of Science, and Google Scholar over the course of my Ph.D. studies. The searches included terms like "generic medicine", "generic drug", "market entry", "market share", "originator drug", "originator medicine", "policy", "price", "pricing", "reimbursement", and common synonyms; I used asterisks (*) where appropriate to truncate search terms. I searched "article title, abstract, and keywords" (or the closest equivalent in each database), as well as MEDLINE and Embase subject headings (MeSH and Emtree, respectively). The reference lists of identified articles were screened; relevant articles suggested by experts were also included. The references were handled in EndNote X7 (Thomson Reuters, Toronto, Canada) or Mendeley (Elsevier, Amsterdam, Netherlands).

1.2 Supply-side generic drug policies

Supply-side policies can be broadly categorised into two groups: market mechanisms and procurement strategies. [108] Market mechanisms are regulations which affect the prices and reimbursement rates of medicines. Three of the most common ones are price capping, free pricing, and internal reference pricing. Procurement strategies, which are non-market mechanisms, refer to the centralised purchasing of a particular quantity of generics at an agreed-upon price. Tendering is the only procurement strategy used for generic drugs. Supply-side measures also included policies aimed at controlling the distribution chain.

These policies were applicable for reimbursed prescription medicines, and the policies were usually set and enforced by government officials in the national health ministry or medicines agency, depending on the country. In some countries, like Spain, individual payers can set different reimbursement rules. Some pricing authorities (eg, Italy) also reserve the right to enact across-the-board price cuts at their discretion, while others (eg, Belgium and Portugal) require manufacturers to repay part of their turnover on reimbursed drugs each year if total public spending exceeds a predetermined level.

1.2.1 Free pricing

Belgium, Germany, and the UK are the only countries among the ten to generally allow generic drug firms to set their own prices, presumably in the hopes that this will encourage generic entry and price competition. [115, 116] In Germany, however, manufacturers bringing new generic products to market must offer a rebate (10%) to sickness funds unless the products are priced at least 30% below the reference price

(see section below on internal reference pricing); additional rebates apply to products that are not subject to internal reference pricing.

Free pricing can be coupled with internal reference pricing and demand-side policies, which are discussed in subsequent sections. Some studies suggest that prices are lower over time, on average, in countries which allow free pricing than in those which enforce price caps (see next sub-section). [10, 43, 46, 108, 116, 117] However, it is difficult to disentangle the effects of multiple drug policies operating concurrently.

1.2.2 Price capping

The national governments of the other seven countries cap the ex-manufacturer prices of generic drugs (ie, impose maximum allowable prices). The caps specify the minimum amount by which generic drug manufacturers must drop their prices in relation to those of the originator drugs. [111, 116, 118–120]

These reductions are fixed in France (60%), Poland (25%), Portugal (50%), and Spain (40%); Portugal is the only country where the cap applies to wholesale prices. In Italy (30-75%) and Switzerland (10-60%), the caps are calculated on a sliding scale based on the average annual turnover of the originator product in the years preceding loss of market exclusivity. The caps are larger for generic versions of drugs with higher turnovers during the periods of patent protection. In the Netherlands, the cap for a given medicine is calculated based on the ex-manufacturer prices of the same drug in selected EU countries.

Price-cap regulation is prevalent in Europe, where it is seen as easy to implement and is politically popular. It is unclear, though, whether price caps contain drug costs effectively, as they limit the first-mover advantage for generic firms. [116, 121] In the absence of a price cap, the first generic entrant might only offer a limited price reduction to maximise profits. This could encourage other generic firms to enter the market and stimulate price competition. [115] Medicines for Europe, a trade organization for generic drug firms which was previously called the European Generic Medicines Association, argues that price-cap regulation partly removes this incentive and may lessen savings. [122]

Policymakers in some low- and middle-income countries set maximum retail prices (eg, China, India, Philippines, South Africa [private sector], and Sri Lanka), maximum wholesale prices (eg, Sri Lanka), and maximum ex-manufacturer prices (eg, Bulgaria, Sri Lanka, Turkey, and Vietnam) for generic medicines. [111]

1.2.3 Internal reference pricing

Internal reference pricing sets a maximum reimbursement rate for generic drugs. [13, 123, 124] There are two main types of internal reference pricing: molecular and therapeutic. Molecular reference pricing—also called chemical or generic reference pricing [116, 123]—sets a reference price for drugs with the same active ingredient (ie, the off-patent originator drug and any available generic versions of that drug). Therapeutic reference pricing sets a reference price for all drugs considered therapeutic equivalents (ie, the off-patent originator drug, any available generic versions of that drug, and other brand name or generic drugs that treat the same condition). A key aim of the latter is to curb spending on "me-too drugs" which offer limited therapeutic benefit over existing ones. [125–128]

If a product is priced above the reference price, the patient usually has to pay the difference out-of-pocket. For example, if three generics of a drug are priced at €10, €15, and €20 per 30-day supply, a payer may be willing to reimburse up to the average price (€15) and force patients to pay a €5 surcharge if they select the most expensive option.

Eight of the countries set maximum reimbursement rates for generic medicines through internal reference pricing. In most of the countries, medicines are grouped by active ingredient—that is, a basket consists of the originator drug and the available generic versions of this drug—and then a reimbursement cap is set for each of these baskets. Often, the reference price is the lowest retail price among the medicines in a basket. In Germany and Poland, the groups can also include medicines considered to be therapeutically equivalent, which may be on- or off-patent drugs with different active ingredients. If the price of a generic medicine exceeds the molecular or therapeutic reference price, the patient must pay the difference in all of the countries except Spain, where products priced above the reference price are not reimbursed at all.

Internal reference pricing is meant to spur competition between drug firms by making patients more price sensitive. [125] The evidence suggests the prices of more expensive drugs tend to drop to the reference level, while the prices of cheaper products often increase to the reference level. In other words, internal reference pricing seems to incite one-off reductions in spending, but may not encourage further price competition. [116, 123, 125, 126, 128] Reference pricing systems may operate more efficiently if the reference prices are revised periodically, as this could prevent the reference price from acting as a price floor. [115] However, there are few date on the long-term impact of reference pricing on generic drug prices and spending. [123]

Internal reference pricing is also used in low- and middle-income countries, including Bulgaria, the Philippines, Thailand, and Turkey. [111]

1.2.4 Tendering

In a tender, a drug purchaser puts out a request for a quantity of a medicine and asks for bids from domestic or international manufacturers with the right to sell the product in the country. Usually, the purchaser then asks the manufacturer which offered the lowest price to supply the market for the duration of the contract.

Tendering schemes, also called reverse auctions, can differ across jurisdictions in several ways. Importantly, schemes vary with regard to the price criteria (eg, lowest price or any price within 5% of lowest), the number of winners, and the length of the tender period. [129] Tenders can be issued by public or private payers. [129] Often, payers award the contract based on several criteria, including price, firm's country of origin (ie, local vs. foreign), quality, delivery date, and after-sales service (eg, respond to drug-related queries). [129]

Of the ten countries included in this review, only Germany, the Netherlands, and Spain tender for generic drugs.[7] In all three countries, a purchaser—a sickness fund in Germany, a private health insurer in the Netherlands, or the Andalusian Health Service in Spain—can only tender for drugs with the same active ingredients. In Germany, some sickness funds split contracts between as many as four firms if the price bids are similar.

Tendering is used in many low- and middle-income countries in Africa (eg, Angola, Botswana, Democratic Republic of the Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, and South Africa), the Western Pacific (eg, China, Fiji, Lao People's Democratic Republic, Malaysia, and Vietnam), and Latin America. [111] In China, for instance, where tenders are issued at provincial level, the national government supports a tendering system consisting of two stages: in the first round, suppliers are asked to submit documentation showing that they satisfy quality and performance standards, after which government official evaluate the commercial bids of applicants who passed the first round. [130]

1.2.5 Distribution regulation

In all the countries except Germany and Poland, the governments enforce regressive margins for wholesalers and pharmacies: the percentage mark-ups decrease on a sliding scale as drug prices increase. Even if a mark-up is regressive, however, pharmacists might earn more in absolute term by prescribing more expensive, branded medicines.

Some of the countries also allow pharmacists to charge a dispensing fee. Pharmacists in Belgium, for example, receive an extra fee (€1.26) for dispensing a medicine included in the reference price system. These fees can differ based on the length of a prescription

[7] Only the Spanish autonomous community of Andalusia issues tenders for drugs sold in retail pharmacies.

and the amount of subsidies given to pharmacies in less-populous areas. In Poland, the wholesaler mark-ups are fixed at 6%, although the pharmacy mark-ups are regressive. In Germany, the distribution-chain mark-ups are fixed percentages. In the Netherlands, Switzerland, and the UK, the margins are unregulated, probably with the aim of encouraging price competition. With the exception of Germany, all of the countries have eliminated or reduced the value-added taxes on prescription medicines.

Manufacturers and wholesalers can offer confidential discounts in all countries except Italy and Poland. This is done to incentivise pharmacies to dispense their drugs by offering discounts; the level and scope of the discounts are usually confidential. [116, 131, 132] Generic manufacturers often give discounts to wholesalers on bulk orders to incentivize wholesalers to buy medicines from them instead of their competitors, while wholesalers often give discounts to pharmacies for the same reason. Some countries cap the permissible level of discounts. In France, for example, the maximum permitted discounts offered by wholesalers to pharmacists for generic products is 17%, while in Spain it is 10%. All the countries that allow discounts, except Portugal, require wholesalers and pharmacies to repay a defined amount of their profits from such discounts; this is known as a "clawback". Italy, which forbids discounting for reimbursed medicines, still requires pharmacies to repay some of their profits each year based on annual turnover rates.

Margin levels and discounting practices are regulated in many low- and middle-income countries, including Bangladesh, Bulgaria, China, India, South Africa, Sri Lanka, Turkey, and Vietnam. [111]

1.2.6 Supply-side lessons

There are differences in the features and mix of supply-side policies employed in high- and middle-income countries, despite often shared health and industrial policy goals.

As shown in **Table 1.2**, regulators and payers sometimes follow markedly different strategies to decrease prices. For example, while some countries, like France, force generic drug firms to decrease prices through price caps, others, like the UK, allow free pricing. This may be due to a weak understanding of which measures are most effective. In particular, there is disagreement over whether market forces or centralised procurement are most appropriate to support a strong generic market. It is important to disentangle the effects of these policies on generic prices to promote evidence-based practices.

The available evidence on the impact of different generic drug policies on prices is of variable quality. Several studies have found that generic drug prices tend to be lower over time in countries with less regulation of generic drug prices, after controlling for relevant factors like population size (ie, a proxy for market size), demand-side policies

(eg, compulsory generic substitution), and time since market entry. [10, 46, 108, 116, 117, 133] Meanwhile, systematic reviews have consistently found that internal reference pricing can lead to immediate savings through reductions in drug prices, although the long-term effects of the policy are unclear. [116, 123, 125]

There is growing interest in the use of tenders to obtain price reductions on generic drugs. Tendering has been commonly used for inpatient drugs and other medical technologies, such as vaccines, [134–139] but tendering for outpatient medicines is still in its infancy. Studies have documented early experiences with tendering in Germany, the Netherlands, and other European countries. [129, 140–143] The limited available evidence suggests that generic prices can decrease by more than 90% following a tender. [129, 144] There is little published data on whether price reductions are sustained over time.[8]

Overall, the supply side of generic markets is complex and poorly understood. There is a need for more evidence on the comparative effectiveness of supply-side policies, especially tendering for which there is currently little published data.

1.3 Demand-side generic drug policies

The revenue of generic firms is largely volume-driven, as they incur few research and development costs and can accept low prices. [122] Payers apply demand-side policies to influence patient choices, physician prescribing, and pharmacist dispensing.

1.3.1 Physicians

Generic prescribing is the prescription of drugs by international non-proprietary name, rather than brand name (eg, atorvastatin instead of Lipitor). It can be mandatory (eg, Portugal), voluntary (eg, the UK), or forbidden.[9] The recent introduction of mandatory generic prescribing in Spain is expected to save the country € 2 billion per year. [149]

Some health ministries and health insurers use electronic prescribing systems to monitor and influence prescribing habits (eg, encourage or enforce generic prescribing). For example, electronic prescribing is compulsory in the UK, and the electronic system automatically changes brand names to generic names in prescriptions, although clinicians can manually reverse this change.

[8] The European Parliament, [145] Management Sciences for Health (MSH), [146] OECD, [147] and WHO [148] have published legal principles or recommendations on good procurement practices. **Appendix B** summarizes the recommendations of MSH and WHO.

[9] In 2013, generic prescribing was not forbidden in any of the ten countries included in this literature review. However, it was forbidden in other European countries, like Austria and Greece.

Table 1.1: Key supply- and demand-side policies in off-patent drug markets.

Supply-side policies		
Pricing	Free pricing	Generic drug firms are allowed to set their own prices.
	Cost-plus pricing	The price is set as function of the basic production costs, R&D expenditure, and a negotiated premium, usually based on supplier-submitted data.
	Price capping	Payers set maximum generic drug prices, which are usually linked to the originator price (eg, mandated 30% reduction).
	Tendering	Payers purchase generic drugs from the firm that offers the best bid based on the tender specifications.
Reimbursement	Internal reference pricing	Payers establish a reimbursement cap for a drug based on the prices of comparator products.
Supply chain	Discounts	Wholesalers or manufacturers incentivise pharmacies to dispense their drugs by offering discounts, which are usually confidential.
	Margin controls	Regulation of the margins charged by distributors (wholesalers and importers) and retailers (pharmacies, online sellers, supermarkets, and dispensing doctors).
Demand-side policies		
Prescribers	Clinical guidelines	Guidelines outline the appropriate care for a condition; they often express a preference for generic drugs.
	Financial incentives	Explicit (eg, physician remuneration or pay-for-performance) or implicit (eg, budget control).
	Formularies	Specify which drugs can be prescribed (or reimbursed) and often express a preference for generic drugs.
	Generic prescribing	Drugs are prescribed by international non-proprietary name instead of brand name (eg, atorvastatin instead of Lipitor).
	Prescription monitoring	Payers use information technology systems to review prescription patterns, also known as e-prescribing.
Pharmacists	Generic substitution	Payers encourage or require pharmacists to dispense the generic version of a drug, even if the off-patent originator is prescribed by the physician.
Patients	Cost sharing	Out-of-pocket expenses to increase price sensitivity and to encourage cost-effective purchasing.
	Education campaigns	Disseminate information to patients to encourage health literacy (eg, information on generic drugs) and promote active patient involvement in health care.

Source: Author's compilation from [111, 116, 121, 123, 140, 150–153].

Table 1.2: Pricing and reimbursement policies for generic medicines sold in the retail sector in the study countries (2013).

	Price capping	Free pricing	Reference pricing		Tendering	Dist. mark-ups			Discounting			Clawbacks	No or reduced VAT[a]
			Molecular	Therapeutic		R	Fx	U	C	U	F		
Belgium		✓[b]	✓[c]			✓				✓		✓	✓
France	✓[d]		✓[e]			✓			✓			✓	✓
Germany		✓		✓	✓		✓		✓			✓	
Italy	✓		✓				✓				✓		✓
Netherlands	✓		✓		✓			✓		✓		✓	✓
Poland	✓			✓		✓					✓		✓
Portugal	✓[f]		✓			✓				✓			✓
Spain	✓		✓		✓[g]	✓			✓			✓	✓
Switzerland	✓							✓		✓		✓	✓
United Kingdom		✓						✓		✓		✓	✓

Dist. = distribution; R/Fx/U = regressive, fixed, or unregulated; C/U/F = capped, unregulated, or forbidden

[a]For all prescription medicine, including generic ones.

[b]Mandatory price cuts apply for generic medicines with active ingredients that have been reimbursed for 12 years or longer.

[c]Reference prices are set at between 15.5% and 41% below the price of the off-patent originator, depending on the product, and these percentages are increased over time.

[d]In some cases, the required price reduction can be reduced if a generic manufacturer able to justify it, although the reduction can never be less than 10%; once a generic medicine is marketed, the price of the originator brand is automatically reduced by 20%.

[e]Internal reference pricing is only used when uptake of a particular generic medicines does not reach the desired level (ie, <60% 12 months after loss of market exclusivity; <65% after 18 months; <70% after 24 months; and <80% after 36 months).

[f]The cap is higher (75%) for generic versions of originator products priced below €10.

[g]Currently, only the autonomous community of Andalusia issues tenders in Spain.

Source: Author's compilation from various sources (see **Appendix A**)

Payers or national governments in some countries also apply financial incentives, such as target rates of generic prescribing, to encourage physicians to prescribe cost-effectively. In France, for instance, the national pay-for-performance scheme includes financial rewards for clinicians who meet generic prescribing targets, while clinicians in Belgium who fail to meet similar targets can face financial penalties.[10]

1.3.2 Pharmacists

If a clinician writes a prescription for a brand name drug when a generic version is available, pharmacists are sometimes allowed to dispense the generic; in most countries, patients and clinicians can block generic substitution. This policy, known as generic substitution, can be mandatory (eg, Sweden), voluntary (eg, France), or forbidden (eg, Belgium and the UK). In the UK, one of the two countries where it is forbidden, if a physician prescribes a brand-name drug, it usually reflects an explicit decision by the prescriber to forgo the generic option in the electronic prescription system; rates of generic prescribing by physicians are very high in the UK. In Poland, patients need to approve any prescription changes that are made by pharmacists.

Payers increasingly intervene at the pharmacy level to diminish the importance of prescribing decisions. [155, 156] In an older study, Simeons and De Coster [115] estimated that for the 10 best-selling off-patent drugs in Europe, generic substitution would reduce public spending on these drugs by between 21% (Poland) and 48% (Denmark). The European Commission [10] has found that mandatory generic substitution is associated with quicker generic entry and lower prices.

Generic substitution is used in low- and middle-income countries, including China, Sri Lanka, Turkey, and Vietnam. [111]

1.3.3 Patients

Governments, payers, and generic firms sometimes launch public education campaigns to promote the cost-saving potential of generics, as well as the bioequivalence of generic and originator drugs. [150]

Cost sharing also affects patient drug consumption: patients are more likely to demand generic medicines if they are asked to pay more for brand-name ones. [108] Most countries apply cost sharing strategies to encourage patients to consume cheaper generic medicines, usually with limits on how much patients can be asked to pay for medicines annually. In Switzerland, for example, patients typically have to pay higher co-pays for originator branded medicines if cheaper generic drugs are available. As previously explained, in all the countries that use internal reference pricing, patients

[10] Roughly half of existing schemes in the US reward generic prescribing. [154]

pay more for products priced above the reference prices. In the UK, meanwhile, patients pay a flat fee of £7.85 per prescription item (€9.25), irrespective of the drug price. Some patients are exempted from this fee, and currently around 90% of prescription items are dispensed free of charge in the UK. In some countries, government agencies and health insurers launch public campaigns to educate patients—as well as clinicians and pharmacists—about the equivalent quality, safety, and efficacy profiles of generic and originator brand drugs.

Differential co-payments are used in Bulgaria, China, Malaysia, and Turkey. [111]

1.3.4 Demand-side lessons

In general, there is greater consensus about which demand-side policies are appropriate. [150, 157] As demand-side policies directly affect the behaviour of physicians, pharmacists, and patients, it is also easier to monitor policy performance and to correct issues than it is with supply-side policies.

On the demand-side, many countries encourage or require physicians to prescribe medicines by their generic names and pharmacists to substitute generic drugs for originator brand medicines (**Table 1.3**). Mandatory generic substitution can generate substantial savings for payers and is associated with quicker market entry of generic drugs. [10, 155, 156]

Overall, it is important to remember that there are different ways of achieving similar results, and that improvements in generic drug markets are not the only options for controlling pharmaceutical spending. **Box 1.2** highlights additional strategies to those discussed.

Table 1.3: Demand-side policies for generic medicines sold in the retail sector in the study countries (2013).

	Physicians				Pharmacists			Patients	
	Generic prescribing		Prescribing guidelines[a]	Financial incentives	Generic substitution			Cost sharing	Education campaigns[b]
	M	V			M	V	F		
Belgium		✓	✓	✓			✓[c]	✓	
France	✓[d]		✓	✓	✓[e]			✓[f]	✓
Germany		✓	✓	✓		✓		✓	
Italy	✓		✓	✓	✓			✓	✓
Netherlands		✓	✓	✓		✓		✓	
Poland		✓				✓[g]		✓	
Portugal	✓			✓		✓[g]		✓	✓
Spain	✓		✓	✓	✓			✓	✓
Switzerland		✓	✓			✓		✓	
United Kingdom		✓	✓	✓			✓		

M/V/F = mandatory, voluntary, or forbidden

[a]In most countries, guidelines are only available for selected illnesses with a high budget impact; the guidelines are usually not binding, but guideline adherence is increasingly monitored electronically or through claims data.

[b]I considered whether government agencies, payers, or generic drug firms periodically conducted education campaigns; such campaigns might not have occurred in 2013 specifically.

[c]Pharmacists must dispense one of the three cheapest options for prescriptions written with international non-proprietary names, as well as prescriptions for antibiotic and antifungal agents; if a patient refuses to be dispensed one of these options they must pay the full price of more expensive medicines.

[d]Clinicians can still write the brand name next to the international non-proprietary name, and they can prohibit generic substitution on the prescription.

[e]Unless otherwise specified by the physician. Also, not all medicines are included on the national generic substitution list; however, many of the omitted medicines are included in the generic prescribing targets of the national pay-for-performance scheme.

[f]A patient that refuses to be dispensed a generic drug has to pay upfront for the brand-name drug and be refunded later, whereas a patient that agrees to be dispensed the generic drug pays nothing at the point of service. Also, if insurance covers a fixed % of the drug price, then patients might pay more out-of-pocket for brand-name medicines due to their higher prices. However, most patients have supplementary private health insurance to cover such costs.

[g]Pharmacists are legally required to notify patients about the availability of cheaper generic options; patients can choose a generic version of a medicine if the prescribing physician has not forbidden substitution on the prescription.

Source: Author's compilation from various sources (see **Appendix A**)

Box 1.2: Complementary strategies to improve the quality and efficiency of prescribing.

1. Governments should improve health technology assessment methods to ensure payers and health care systems obtain good value for money. [158] Otherwise, increasing the use of generic drugs does not guarantee more efficient spending. For example, the savings from generic drugs might be used to pay for costly new medicines for which there is no evidence of superiority over older, less-expensive treatments. [67]

2. Physicians and pharmacists should encourage rational drug use to curb spending and optimise value for money. This means managing both over- and under-utilization of medicines, [159–161] taking into account the fact that prescription drugs may not always the best medical option. For instance, a recent study suggested that exercise might be as effective as, or even more effective than, statins at preventing type 2 diabetes mellitus, repeat heart attacks, and repeat strokes. [162] Clinicians should help shape patient expectations about the benefits of medicines.

3. Regulators should try to reduce or eliminate the use of obsolete drugs. [163] In mid-2009, for example, the European Medicines Agency recommended the gradual withdrawal of dextropropoxyphene-containing medicines across the EU, after concluding that "their risks, particularly the risk of potentially fatal overdose, are greater than their benefits". [164] Yet in 2014, there were more than 105,000 prescriptions filled in England for co-proxamol (paracetamol/dextropropoxyphene), accounting for over £3 million (US$ 4.4 million) in spending. [165] It is important to note that although weaning patients off obsolete treatments might be good value for money, it is not always cost saving. [163] Patients might be started on newer, more expensive drugs, which could increase drug spending.

1.4 Evidence on prices and market shares in generic drug markets

To date, much of the research on off-patent markets has focused on the determinants of: (i) generic market entry, (ii) originator drug prices and market shares (following loss of market exclusivity), and (iii) generic drug prices and market shares. The following sections summarise key studies in these three areas.

1.4.1 Generic market entry

The timing of generic entry is important, as delays reduce savings. The data suggest that the time from the loss of market exclusivity for the brand name drug to the availability of the first generic is influenced by the market size (ie, perceived profitability, which depends on population size and burden of disease), product characteristics, supply- and demand-side policies, therapeutic class, and country-specific factors. [9,21,107,166–174] These variables influence a firm's decision to launch a drug onto the market, which is presumably based on expected revenue.

In 2009, the European Commission concluded an 18-month inquiry into the pharmaceutical sector, with a focus on competition between generic and originator firms. [10] The 219 active ingredients included in the study sample accounted for roughly 70% of total drug spending in the European Union—based on sales in the year preceding loss of market exclusivity. The inquiry found that about half of originator drugs faced generic competition within a year of loss of market exclusivity. Generic market entry occurred, on average, seven months following loss of exclusivity. For the highest-selling originator drugs, the delay was, on average, only four months. The findings varied markedly across EU member states. The report conservatively estimated € 3 billion in savings forgone annually in the EU from delayed entry. It also outlined strategies that originator firms employ to hinder generic entry, such as strategic patenting (eg, patent clusters), paying generic firms not to enter the market, and launching frivolous patent infringement lawsuits. [10]

1.4.2 Originator drug prices and market shares

Several studies have analysed the impact of loss of market exclusivity on the prices of originator drugs. These studies have drawn opposing conclusions: some studies found that generic entry led to a decline in the prices of originator products, [45,175,176] while others observed that the originator drug prices remained constant or increased after the introduction of the first generic product. [166,177–181] The latter price response, sometimes referred to as the "generic competition paradox", may represent an attempt

by originator firms to capitalise on the brand-loyal patients who are unlikely to consume generic drugs. [182] Policies such as tendering and internal reference pricing, however, limit the ability of originator firms to freely set prices.

The effect of generic entry on the market shares of originator drugs is more intuitive. Studies have consistently found that originator volume shares decrease sharply after loss of market exclusivity. [108, 166, 175, 183] However, originator firms sometimes launch second-generation drugs prior to patent expiry and encourage physicians to switch their patients to these treatments to maintain profit levels. [10, 49]

1.4.3 Generic drug prices and market shares

The evidence indicates that generic prices are influenced by many of the same factors that influence generic entry, including supply- and demand-side policies, number of generic competitors, country size, product characteristics (eg, pack size), and time since loss of market exclusivity. [10, 21, 62, 108, 116, 133, 166, 172, 180, 184–186] Some studies suggest that competition is weaker in highly-regulated off-patent markets compared to unregulated or weakly-regulated ones. [10, 46, 116, 117]

Studies have found that the generic drug prices drop significantly as competitors enter the market. [37, 175, 187, 188, 188] This trend seems to continue until a threshold is reached and the market becomes saturated. For example, Wiggins and Mannes [45] studied price competition in the market for anti-infective medicines. They found that the average prices of generic drugs dropped by 83% when the number of firms increased from 1 to between 6 and 15. The prices dropped even further when over 40 sellers were present.

Compared to the originator prices at the time of loss of market exclusivity, the European Commission inquiry [10] found that, on average, generic prices decreased by 25% and 40% after one and two years, respectively. The average generic volume market shares were 30% and 45% after one and two years, respectively. Even a marginal increase in the market share or decrease in the prices would generate sizable savings.

A widely cited 2009 study found, for a basket of 15 widely-used off-patent medicines in low and middle-income countries, that the average availability of these medicines in public pharmacies ranged from 30% in Africa to 54% in the Americas. [4] The median government procurement prices of the cheapest generics were 3 times higher than international reference prices in the Americas, and 12 times higher in western Pacific countries. In all geographic regions, generic medicines were more often available in private pharmacies than in public ones, but usually at a much higher cost. The median prices of generic medicines in private pharmacies were 9 times higher than international reference prices in Europe, and 25 times higher in the Americas. [4] The average wholesale margins ranged from 2% to 380% in those countries for which cost

breakdowns were available; in these countries, the average retail margins ranged from 10% to 552%, while value-added taxes ranged from 4% to 15%. [4]

1.5 Literature gaps and research questions

There are knowledge gaps in the literature on generic drug markets, which are briefly summarised below. The introduction section of each article summarizes the relevant literature and knowledge gaps to motivate each study aim.[11] **Box 1.3** summarises the Ph.D. research topics.

Article 1

Although it is often claimed that generic prices vary across high-income countries, there are few peer-reviewed studies which compare generic drug prices. The existing comparisons are likely outdated, given how often pricing and reimbursement policies change. Moreover, the impact of distribution margins and taxes on generic drug prices has been underexplored, even though studies indicate that those costs can account for most of the retail price of a generic drug, ie, the price charged by pharmacists to patients or third-party payers. Nearly all studies have looked at ex-manufacturer prices, ie, those charged by manufacturers to wholesalers, which do not account for distribution costs. To address this gap, the first article (published in *The Milbank Quarterly*) provides an updated analysis of generic drug prices, utilization rates, and policies in 13 high-income countries to understand the nature and extent of any differences.

Article 2

Previous studies which have compared medicine prices across countries have often relied on different methods, making it difficult to compare findings. Most analyses have also had small sample sizes, which may have biased the results. In the second study (published in *BMC Health Services Research*), I compare the ex-manufacturer and retail prices of a large sample of generic drugs in seven European countries in 2013, using the same dataset as in Article 1; the data were provided freely by IMS Health under an academic license. I calculated all commonly used price indexes to outline the methodological challenges to comparing generic drug prices. It is critical that policymakers are aware of the advantages and limitations of these types of analyses, given that the results of price comparisons might be used to justify changes to pharmaceutical policies.

[11] Small parts of the text here, such as description of study objectives, reappear in the introduction sections of the respective chapters.

Articles 3, 4, and 5

The results of the first two studies indicate that countries which use tender or tender-like systems to set generic drug prices in retail pharmacies (ie, Denmark, Germany, the Netherlands, and Sweden) have among the lowest prices among the countries included in the studies. Pharmaceutical tendering refers to the bulk purchase of medicines from suppliers at agreed-upon prices over contracted periods. It is increasingly promoted as an effective measure to drive down the prices of generic medicines.

The short-term cost savings from tendering must be weighed against the potential adverse long-term effects on competition in generic drug markets. Proponents of tendering claim it will result in prices which more accurately reflect costs of production. Previous studies have documented early experiences with tendering in Germany, the Netherlands, and other European countries. These analyses generally found that the introduction of tenders was associated with large price decreases for generic medicines. In the Netherlands, for example, the prices of some generic drugs dropped by as much as 90% overnight in retail pharmacies when insurers first started issuing tenders, suggesting that tenders can scoop significant one-off savings from price competition. [129] However, such results cannot necessarily be generalized across therapeutic groups or medicine forms (tablets versus creams, for instance), and it is not clear whether subsequent tenders would sustain such low prices—or if prices would instead creep back up as manufacturers drop out of the market. Critics argue it will create product shortages, drive generic firms out of business, and lead to higher prices in the long-run, as manufacturers drop out of the market. Yet there is little empirical evidence on the effects of tendering on prices, competition, and supply security in the pharmaceutical sector.

The final three Ph.D. papers present evidence of the impact of tendering in South Africa and Cyprus. These countries were chosen as case studies for two reasons. First, the countries operate some of the longest-running tendering systems in the world, so they represent two of the few settings where the long-term effects of tendering can be analysed. The tendering systems in other European countries, like Germany and the Netherlands, were introduced more recently. Second, the health care systems in both countries are organized similarly. Both health care systems consist of a public and private sector. Most individuals are eligible for public-sector coverage, but only around four-fifths of the population in each country seeks care in the sector. The remaining 20% of individuals—most of them high earners—obtain care in the respective private sectors. Pharmaceutical tenders are only issued in the public sectors. Both national governments have announced plans to introduce national health insurance schemes, which will provide need-based universal access to high-quality care, free at the point of use, with funding from general tax revenues and employee contributions. Thus, there

were opportunities to draw shared policy lessons from the two case studies.

The third paper (published in *Social Science & Medicine*) outlines a conceptual framework for analysing the South African tendering system and presents evidence on the impact of the system on prices and competition over the past 15 years. In this paper, I calculated price and Herfindahl-Hirschman indexes to measure trends in prices and market concentration for tenders issued between 2003 and 2016, among other statistical analyses. To conduct this research, I spent roughly 1.5 years in South Africa as a Visiting Research Fellow at the University of Cape Town and the National Department of Health of South Africa (Essential Medicines Directorate, Pretoria, South Africa). During my field work, I filed a government data request under the Promotion of Access to Information Act (2000), received government data on medicine prices and quantities in the public and private sectors (2003-2016), and cleaned, organised, and analysed these datasets with input from local health ministry officials and academics.

The fourth paper, which is being prepared for submission to a peer-reviewed journal, evaluates the impact of therapeutic tendering on the prices of medicines. In 2014, to enhance price competition, the South African health ministry began tendering by therapeutic class for medicines which it considers interchangeable. For instance, the health ministry views the cholesterol-reducing drugs atorvastatin (10 mg), fluvastatin (40 mg), lovastatin (20 mg), rosuvastatin (5 mg), and simvastatin (10 mg) as therapeutically equivalent. Under the new policy, the health ministry started only buying the least expensive product in this group. It is expected that tendering by therapeutic class generates larger savings than tendering by individual products. The aim of this study is to estimate, using a difference-in-differences regression model, the effect of therapeutic tendering on (i) the prices of medicines subjected to the policy and (ii) the total spending on these products.

The fifth paper (published in the *Bulletin of the World Health Organization*) reviews the pharmaceutical sector in Cyprus in terms of the availability and affordability of medicines and analyses pharmaceutical policy options for the national health system finance reform which was expected to be introduced in 2017. The government needed to decide which drugs to cover in the forthcoming system, which pricing and reimbursement policies to apply, and how much patients would have to pay for medicines. The Cypriot Ministry of Health sought support from the World Health Organisation (WHO) Regional Office for Europe to decide on these issues. The WHO, in turn, asked researchers from LSE Health to provide technical assistance to the health ministry. Like South Africa, Cyprus uses tendering to procure medicines in the public health care sector. The paper explores how the public and private markets could be efficiently merged in the forthcoming national health system and assesses the key barriers to the implementation of the new system. To collect primary data, I conducted semi-structured interviews with seven key national stakeholders from groups that are directly or indirectly involved

in the tendering process. These interviews were conducted during a four-day study visit to Nicosia, Cyprus in April 2014. I also examined secondary data provided by the Cypriot Ministry of Health; these data included the prices and volumes of prescription medicines in 2013. The results of this study may be useful for policymakers in other countries aiming to establish a comprehensive drug-benefit plan under universal health coverage, like South Africa.

Box 1.3: Ph.D. research question and subsidiary topics.

Research question:

What are features of an efficient generic drug market?

Subsidiary topics:

1. How do generic drug prices, policies, and utilization rates compare across selected high-income countries? (*Article 1*)
2. What are the methodological challenges to comparing generic drug prices across countries? (*Article 2*)
3. What is the effect of pharmaceutical tendering on prices and competition over a 15-year period? Evidence from South Africa. (*Article 3*)
4. What is the price impact of tendering for medicines by therapeutic class? A difference-in-differences estimation based on data from South Africa. (*Article 4*)
5. What are features of a sustainable tendering system for generic drugs under universal health coverage? Evidence from Cyprus. (*Article 5*)

Appendix A: Search strategy for the generic drug policies employed in each country in 2013

Step 1: Literature search

Description

In 2013, which generic drug policies were used in the retail drug markets in Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, and the UK?

Box A: Exclusion/inclusion criteria.

Publication Years: January 1, 2011 - August 11, 2015 (search date)
Languages: English or French
Publication Types: Excluded "Conference Abstracts"

I included an article if it contained at least one section describing the supply-side or demand-side generic drug policies in the study country. This could include a comprehensive overview of such policies in the background/introduction section of an article, as determined by the author.

The reference lists of identified articles were screened and relevant articles were included. These citation checks sometimes revealed articles which were relevant for other study countries.

Search words

I conducted an advanced search in PubMed (MEDLINE) of "title/abstract"; an asterisk truncated the search word (eg, drug* = drug, drugs, etc.).

- (generic or off-patent)
- (drug* or medicine* or pharmaceutical*)
- (Belgium or France or Germany or Italy or Netherlands or Poland or Portugal or Spain or Switzerland or UK or U.K. or United Kingdom)
- 1 and 2 and 3

I carried out the search for each country separately, so line 3 only included one country at a time. For the UK search, I also included the terms England, Northern Ireland, Scotland and Wales.

Search results (references are listed in alphabetical order)

Belgium

Box B: Belgium search results.

Initial search results: 24
Excluded from title/abstract review: 18
Excluded from full article review: 1
Included results (initial): 5
Articles from citation review: 3
Included Results (total): 8

References identified through the search:

- Dylst P, Vulto A, Simoens S (2014). "Does increased use of generic medicine by elders in Belgium help to contain escalating health care budgets?" *Journal of Aging & Social Policy*, **26**:266-280.
- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- Fraeyman J, Van Hal G, Godman B, Beutels P (2013). "The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium." *Expert Reviews of Pharmacoeconomics and Outcomes Research*, **13**(1):141-151.
- Fraeyman J, Van Hal G, De Loof H, Remmen R, De Meyer GRY, Beutel P (2012). "Potential impact of policy regulation and generic competition on sales of cholesterol lowering medication, antidepressants and acid blocking agents in Belgium." *Acta Clinica Belgica*, **67**(3):160-171.
- Fraeyman J, Verbelen M, Hens N, Van Hal G, De Loof H, Beutels P (2013). "Evolutions in both co-payment and generic market share for common medication in the Belgian Reference Pricing System." *Applied Health Economics and Health Policy*, **11**(5):543-52.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.
- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

France

Box C: France search results.

Initial search results: 35
Excluded from title/abstract review: 28
Excluded from full article review: 2
Included results (initial): 5
Articles from citation review: 3
Included Results (total): 8

References identified through the search:

- Anonymous (2013). "Generics: keep a balanced view." Rev Prescrire, 33(361):854-861.
- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- Dylst P, Vulto A, Simoens S (2014). "Analysis of French generic medicines retail market: why the use of generic medicines is limited." *Expert Rev Pharmacoecon Outcomes Res*, **14**(6):795-803.
- Pichetti S, Sermet C, Godman B, Campbell SM, Gustafsson LL (2013). "Multilevel analysis of the influence of patients' and practitioners' characteristics on patented versus multiple-source statin prescribing in France." *Applied Health Econ Health Policy*, **11**:205-218.

- von der Schulenburg F, Vandoros S, Kanavos P (2011). "The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors." *Health Economics Review*, **1**:18.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.
- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

Germany

Box D: Germany search results.

Initial search results: 32
Excluded from title/abstract review: 28
Excluded from full article review: 2
Included results (initial): 2
Articles from citation review: 5
Included Results (total): 7

References identified through the search:

- Saverno K, Gothe H, Schuessel K, Biskupiak J, Schulz M, Siebet U, Brixner D (2014). "Consideration of international generic distribution policies on patient outcomes in the United States and Germany." *Pharmazie*, **69**:238-240.
- von der Schulenburg F, Vandoros S, Kanavos P (2011). "The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors." *Health Economics Review*, **1**:18.

References identified through citation review:

- Busse R, Blümel M (2014). "Germany: Health System Review." *Health Systems in Transition*, **16**(2): 1-296.
- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.
- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

Italy

Box E: Italy search results.

Initial search results: 30
Excluded from title/abstract review: 27
Excluded from full article review: 2
Included results (initial): 1
Articles from citation review: 5
Included Results (total): 6

References identified through the search:

- Dylst P, Vulto A, Simoens S (2014). "Analysis of the Italian generic medicines retail market: recommendations to enhance long-term sustainability." *Expert Rev Pharmacoecon Outcomes Res*, **15**(1):33-42.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.
- Ferré F, de Belvis AG, Valerio L, et al (2014). "Italy: Health System Review." *Health Systems in Transition*, **16**(4): 1-168.
- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

The Netherlands

Box F: The Netherlands search results.

Initial search results: 25
Excluded from title/abstract review: 20
Excluded from full article review: 3
Included results (initial): 2
Articles from citation review: 3
Included Results (total): 5

References identified through the search:

- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- von der Schulenburg F, Vandoros S, Kanavos P (2011). "The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors." *Health Economics Review*, **1**:18.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.
- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

Poland

Box G: Poland search results.

Initial search results: 8
Excluded from title/abstract review: 8
Excluded from full article review: 0
Included results (initial): 0
Articles from citation review: 5
Included Results (total): 5

References identified through the search: None.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, 13(1):59-72.
- Sagan A, Panteli D, Borkowski W, et al (2011). "Poland: Health System Review." *Health Systems in Transition*: **13**(8):1-193.

- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

Portugal

Box H: Portugal search results.

Initial search results: 5
Excluded from title/abstract review: 1
Excluded from full article review: 3
Included results (initial): 1
Articles from citation review: 5
Included Results (total): 6

References identified through the search:

- Vončina L, Strizrep T, Godman B, Bennie M, Bishop I, Campbell S, Vlahović-Palčevski V, Gustafsson LL (2011). "Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future." *Expert Rev Pharmacoeconomics Outcomes Res*, **11**(4):469-79.

References identified through citation review:

- Barros P, Machado S, Simões J (2011). "Portugal: Health System Review." *Health Systems in Transition*, **13**(4): 1-156.
- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.
- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.
- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.

- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

Spain

Box I: Spain search results.

Initial search results: 25
Excluded from title/abstract review: 19
Excluded from full article review: 4
Included results (initial): 2
Articles from citation review: 4
Included Results (total): 6

References identified through the search:

- Dylst P, Vulto A, Simoens S (2014). "Analysis of Spanish generic medicines retail market: recommendations to enhance long-term sustainability." *Expert Review of Pharmacoeconomics & Outcomes Research*, **14**(3): 345-53.

- Vončina L, Strizrep T, Godman B, Bennie M, Bishop I, Campbell S, Vlahović-Palčevski V, Gustafsson LL (2011). "Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future." *Expert Rev Pharmacoeconomics Outcomes Res*, **11**(4):469-79.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.

- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.

- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, **13**(1):59-72.

- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, **1**(2):93-100.

Switzerland

Box J: Switzerland search results.

Initial search results: 14
Excluded from title/abstract review: 12
Excluded from full article review: 1
Included results (initial): 1
Articles from citation review: 0
Included Results (total): 1

References identified through the search:

- Decollogny A, Eggli Y, Halfon P, Lufkin TM (2011). "Determinants of generic drug substitution in Switzerland." *BMC Health Services Research*, **11**:17.

References identified through citation review: None.

United Kingdom

Box K: United Kingdom search results.

Initial search results: 75
Excluded from title/abstract review: 61
Excluded from full article review: 7
Included results (initial): 8
Articles from citation review: 3
Included Results (total): 11

References identified through the search:

- Bennie M, Bishop I, Godman B, Barbui C, Raschi E, Campbell S, Miranda J, et al (2013). "Are specific initiatives required to enhance prescribing of general atypical antipsychotics in Scotland?: International implication." *The International Journal of Clinical Practice*, **67**(2):170-180.

- Bennie M, Bishop I, Godman B, Campbell S, Miranda J, Finlayson AE, Gustafsson LL (2013). "Are prescribing initiatives readily transferable across classes: the case of generic losartan in Scotland?" *Quality in Primary Care*, **21**:7-15.

- Dylst P, Vulto A, Simoens S (2012). "How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing?" *Pharmacy Practice*, **10**(1):3-8.

- Godman B, Bishop I, Finlayson AE, Campbell S, Kwon H-Y, Bennie M (2013). "Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries." *Expert Rev Pharmacoecon Outcomes Res*, **13**(4):469-482.

- Hassali MA, Alrasheedy AA, McLachlan A, Nguyen TA, AL-Tamimi SK, Ibrahim MIM, Aljadhey H (2014). "The experiences of implementing generic medicine policy in eight countries: A review and recommendations for successful promotion of generic medicine use." *Saudi Pharmaceutical Journal*, **22**:491-503.

- Mansfield SJ (2014). "Generic drug prices and policy in Australia: room for improvement? A comparative analysis with England." *Australian Health Review*, **38**(1):6-15.

- Vončina L, Strizrep T, Godman B, Bennie M, Bishop I, Campbell S, Vlahović-Palčevski V, Gustafsson LL (2011). "Influence of demand-side measures to enhance renin-angiotensin prescribing efficiency in Europe: implications for the future." *Expert Rev Pharmacoeconomics Outcomes Res*, **11**(4):469-79.

- von der Schulenburg F, Vandoros S, Kanavos P (2011). "The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors." *Health Economics Review*, **1**:18.

References identified through citation review:

- Carone G, Schwierz C, Xavier A (2012). "Cost-containment policies in public pharmaceutical spending in the EU." Economic Papers 461, European Commission. European Union: Brussels. 67 p.

- Dylst P, Vulto A, Simoens S (2013). "Demand-side policies to encourage the use of generic medicines: an overview." *Expert Rev Pharmacoecon Outcomes Res*, 13(1):59-72.

- Vogler S (2012). "The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview." *Generics and Biosimilars Initiative Journal*, 1(2):93-100.

Information from health ministry websites:

I searched the health ministry websites using the respective "search" portals. I only reviewed information published in English or French. I conducted four searches on each website using the terms "generic drug", "generic drugs", "generic medicine", and "generic medicines"; on the French Ministry of Health and Solidarity website, I also used the search term "médicaments génériques". I scanned the descriptions of the search returns for relevant documents or pages.

Belgium: The Federal Public Service for Health, Food Chain Safety and Environment (http://www.health.belgium.be/eportal?fodnlang=en)

No reports or summary pages written in English or French were identified.

France: The Ministry of Health and Solidarity (http://www.sante.gouv.fr/)

- Académie nationale de Pharmacie (2012). "Médicament génériques." Rapport établi à la demande du Ministère en charge de la Santé. 91 p. Available from: http://www.sante.gouv.fr/ [Last accessed: Aug 14, 2015].

- Agence nationale de sécurité du médicament et des produits de santé (2012). "Les médicaments génériques: des médicaments à part entière." Rapport. St Denis, France. 68 p. Available from: http://www.sante.gouv.fr/ [Last accessed: Aug 14, 2015].

- Ministère des affaires sociales, de la santé et des droits des femmes (2015). "Plan national d'action de promotion des médicaments génériques." Rapport. Paris, France. 32 p. Available from: http://www.sante.gouv.fr/ [Last accessed: Aug 14, 2015].

- Autorité de la Concurrence (2013). "Comment dynamiser la concurrence dans le secteur de la distribution du médicament en ville?" Document de la consultation

publique sur le fonctionnement de la concurrence dans le secteur de la distribution du médicament en ville. Décision N°13-SOA-01. Available from : http://www.autoritedelaconcurrence.fr/ [Last accessed: Oct 20, 2015].

- Imbaud D, Morin A, Picard S, Toujas F (2012). "Evaluation de la politique française des médicaments génériques." Inspection générale des affaires sociales, Rapport N°RM2012-115P. Available from: http://www.medicamentsgeneriques.info/ [Last accessed: Oct 19, 2015].

- Sécurité Sociale (2014). "Chapitre IX. La diffusion des médicaments génériques: résultats trop modestes, des coûts élevés." Cour des comptes: Paris. Available from: https://www.ccomptes.fr/ [Last accessed: 20 Oct, 2015].

Note: The last three references were suggested by two of the pharmaceutical policy researchers I contacted.

Germany: The Federal Ministry of Health (www.bmg.bund.de/en.html)

- Federal Republic of Germany (2014). "Medicinal Products Act (The Drug Law) [Arzneimittelgesetz - AMG]." Non-official translation. 237 p. Available from: http://www.bmg.bund.de/ [Last accessed: Aug 14, 2015].

Italy: The Ministry of Health (www.salute.gov.it)

Website is only available in Italian; the English-language version is under construction [Last accessed: November 12, 2015].

One of the pharmaceutical policy researchers I contacted suggested I look at the following report:

- The Medicines Utilisation Monitoring Centre (2013). "National Report on Medicines use in Italy. Year 2013." Available from: http://www.agenziafarmaco.gov.it/ [Last accessed: Oct 19, 2015].

Netherlands: The Ministry of Health, Welfare and Sport (www.government.nl/ministries/vws)

No reports or summary pages written in English or French were identified.

Poland: The Ministry of Health (www.mz.gov.pl/en)

- The Ministry of Health (2015). "Reimbursement." Online Portal. Available from: http://www.mz.gov.pl/ [Last accessed: Aug 14, 2015].

Portugal: The Ministry of Health (http://www.min-saude.pt/portal)

Website is only available in Portuguese [Last accessed: November 12, 2015]

Spain: The Ministry of Health, Social Services and Equality (http://www.msssi.gob.es/en/)

- The Ministry of Health, Social Services and Equality (2006). "Pharmacy." National Health System 2006 Annual Report. Available from: http://www.msssi.gob.es/ [Last accessed: Aug 14, 2015].

Switzerland: The Federal Office of Public Health (http://www.bag.admin.ch/org/?lang=en)

No reports or summary pages written in English or French were identified.

United Kingdom: The Department of Health (https://www.gov.uk/government/organisations/department-of-health)

Through the search portal, I located references to the following legislations for generic medicines.

- National Health Service (2000). "The Health Service Medicines (Control of Prices of Specified Generic Medicines, Regulations 2000)." Available from: http://www.legislation.gov.uk/ [Last accessed: Aug 14, 2015].
- National Health Service (2000). "The Health Service Medicines (Information on the Prices of Specified Generic Medicines, Regulations 2001)." Available from: http://www.legislation.gov.uk/ [Last accessed: Aug 14, 2015].
- Department of Health (2009). "The Pharmaceutical Price Regulation Scheme 2009." Available from: http://www.dh.gov.uk/ [Last accessed: Nov 16, 2015].

Step 2: Internal IMS Health guides

Next, I compared our findings with internal IMS Health guides on the pharmaceutical sectors in the study countries in 2013. These documents outlined the generic drug policies in each country.

Step 3: Input from pharmaceutical policymakers and researchers

Finally, I contacted the following researchers and policymakers to verify the identified generic drug policies in their respective countries. Any errors in the manuscript are my own.

Belgium

- Dr. Francis Arickx (National Institute for Health and Disability Insurance, Brussels, Belgium)
- Ms. Yoeriska Antonissen (National Institute for Health and Disability Insurance, Brussels, Belgium)

France

- Ms. Karen Berg Brigham (URC Eco-Ile-de-France, Paris, France)
- Dr. Guillaume Dedet (WHO Regional Office for Europe, Copenhagen, Denmark)
- Dr. Isabelle Durand-Zaleski (URC Eco-Ile-de-France, Paris, France)

Germany

- Dr. Dimitra Panteli (Technical University of Berlin, Berlin, Germany)

Italy

- Dr. Armando Magrelli (National Centre for Rare Diseases, Rome, Italy)

Netherlands

- Dr. Patrick Jeurissen (Ministry of Health, Welfare and Sport, Amsterdam, Netherlands)

Poland

- Dr. Paweł Kawalec (Jagiellonian University, Krakow, Poland)

Portugal

- Dr. Mónica Oliveira (University of Lisbon, Lisbon, Portugal)
- Dr. Carlos Gouveia Pinto (University of Lisbon, Lisbon, Portugal)
- Dr. Luìs Silva Miguel (University of Lisbon, Lisbon, Portugal)

Spain

- Dr. Jaime Espín (Andalusian School of Public Health, Granada, Spain)

Switzerland

- Dr. Jörg Indermitte (Federal Office of Public Health, Bern, Switzerland)
- Ms. Mareika Studer (Federal Office of Public Health, Bern, Switzerland)

United Kingdom

- Ms. Helena Bowden (Department of Health, London, England)
- Dr. Cathleen Schulte (Department of Health, London, England)

Appendix B: Features of good pharmaceutical procurement

Management Sciences for Health, a nonprofit international health organisation, published its first report on managing access to medicines and health technologies in 1987; subsequent editions were published in 1997 and 2012. The most recent edition offered the following guidance on pharmaceutical procurement.

Box A: Recommendations for good pharmaceutical procurement published by Management Sciences for Health.

Key principles of good pharmaceutical procurement for health systems:

1. Reliable payment and good financial management
2. Procurement by generic name
3. Clear specification of a recognized pharmaceutical quality standard
4. Limitation of procurement to the essential medicines list
5. Increasing procurement volume by aggregating demand
6. Formal supplier qualification and monitoring
7. Competitive procurement
8. Monopsony commitment
9. Order quantities based on reliable estimate of forecasted actual need
10. Transparency and written procedures
11. Separation of key functions
12. Product quality assurance program
13. Annual audit with published results
14. Regular reporting of procurement performance indicators

Source: Reproduced from Management Sciences for Health (2012, p. 322), with permission. [146]

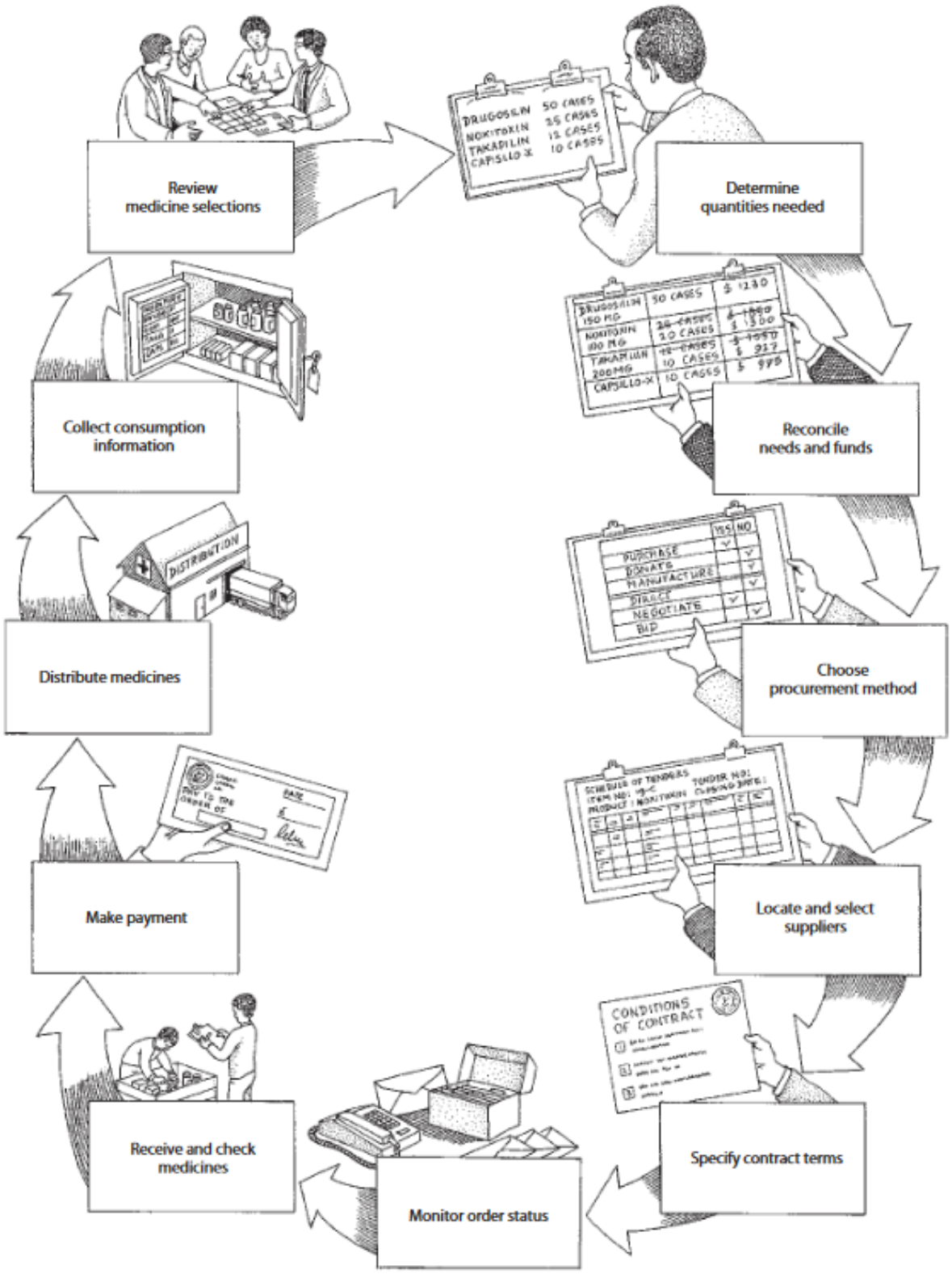


Figure A: Procurement cycle for pharmaceutical products.

Source: Reproduced from Management Sciences for Health (2012, p. 18.4), with permission. [146]

In 1996, the World Health Organization convened an inter-agency pharmaceutical coordination group on Essential Drugs and Medicines Policy, involving advisers from the United Nations Children's Fund (UNICEF), United Nations Population Fund (UNFPA), World Health Organization (WHO), and World Bank. The work of this group built on earlier research by Management Sciences for Health on pharmaceutical procurement.

The group identified four strategic objectives of pharmaceutical procurement and twelve operational principles for good procurement. These principles relate to "efficient and transparent management" (principles 1-3), "drug selection and quantification" (4-6), "financing and competition" (7-10), and "supplier selection and quality assurance" (11-12).

Box B: Recommendations for good pharmaceutical procurement published by the World Health Organization.

Strategic objectives of pharmaceutical procurement:

1. Procure the most cost-effective drugs in the right quantities
2. Select reliable suppliers of high-quality products
3. Ensure timely delivery
4. Achieve the lowest possible total cost

Operational principles for good pharmaceutical procurement:

1. Different procurement functions and responsibilities (selection, quantification, product specification, pre-selection of suppliers and adjudication of tenders) should be divided among different offices, committees and individuals, each with appropriate expertise and resources for the specific function.
2. Procurement procedures should be transparent, following formal written procedures throughout the process and using explicit criteria to award contracts.
3. Procurement should be planned properly and procurement performance should be monitored regularly; monitoring should include an annual external audit.

4. Public sector procurement should be limited to an essential drugs list or national/local formulary list.
5. Procurement and tender documents should list drugs by their international nonproprietary name (INN), or generic name.
6. Order quantities should be based on a reliable estimate of actual need.
7. Mechanisms should be put in place to ensure reliable financing for procurement. Good financial management procedures should be followed to maximize the use of financial resources.
8. Procurement should be effected in the largest possible quantities in order to achieve economies of scale; this applies to both centralized and decentralized systems.
9. Procurement in the public health sector should be based on competitive procurement methods, except for very small or emergency orders.
10. Members of the purchasing groups should purchase all contracted items from the supplier(s) which hold(s) the contract.
11. Prospective suppliers should be pre-qualified, and selected suppliers should be monitored through a process which considers product quality, service reliability, delivery time and financial viability.
12. Procurement procedures/systems should include all assurances that the drugs purchased are of high quality, according to international standards.

Source: Reproduced from World Health Organization (1999, pp. 13-32), with permission. [148]

2

Comparing generic drug markets in Europe and the United States: Prices, volumes, and spending

"I guess the only time most people think about injustice is when it happens to them."
– Charles Bukowski, *Ham on Rye*

Key messages

- This study indicates that there are opportunities for cost savings in generic drug markets in Europe and the United States.
- Regulators should make it easier for generic drugs to reach the market.
- Regulators and payers should apply measures to stimulate price competition among generic drugmakers and to increase generic drug use.
- To meaningfully evaluate policy options, it is important to analyze historical context and understand why similar initiatives failed previously.

Abstract

Context: Rising drug prices are putting pressure on health care budgets. Policymakers are assessing how they can save money through generic drugs.

Methods: We compared generic drug prices and market shares in 13 European countries, using data from 2013, to assess the amount of variation that exists between countries. To place these results in context, we reviewed evidence from recent studies on the prices and use of generics in Europe and the United States. We also surveyed peer-reviewed studies, grey literature, and books published since 2000 to: (i) outline existing generic drug policies in European countries and the United States, (ii) identify ways to increase generic drug use and to promote price competition among generic drug companies, and (iii) explore barriers to implementing reform of generic drug policies, using a historical example from the United States as a case study.

Findings: The prices and market shares of generics vary widely across Europe. For example, prices charged by manufacturers in Switzerland are, on average, more than 2.5 times those in Germany and more than 6 times those in the United Kingdom, based on the results of a commonly used price index. The proportion of prescriptions filled with generics ranges from 17% in Switzerland to 83% in the United Kingdom. By comparison, the United States has historically had low generic drug prices and high rates of generic drug use (84% in 2013), but has in recent years experienced sharp price increases for some off-patent products. There are policy solutions to address issues in Europe and the United States, such as streamlining the generic drug approval process and requiring generic prescribing and substitution where such policies are not yet in place. The history of substitution laws in the United States provides insights into the economic, political, and cultural issues influencing the adoption of generic drug policies.

Conclusions: Governments should apply coherent supply- and demand-side policies in generic drug markets. An immediate priority is to persuade more physicians, pharmacists, and patients that generic drugs are bioequivalent to branded products. Special-interest groups continue to obstruct reform in Europe and the United States.

RISING drug prices are putting pressure on health care budgets. [74,78][1] Drugs account for sizable shares of health care spending in rich countries, with costs of new treatments for diabetes, [189] multiple sclerosis, [190] rheumatoid arthritis, [191] various cancers, [32,58,59,192] and dermatological conditions [193] increasing. There are many reasons, including aggressive pricing strategies by manufacturers [32] and adoption of greater numbers of orphan and personalized drugs with high price tags. [194,195] Governments are responding by looking at ways to negotiate lower prices for patented drugs [196] and to expand the use of health technology assessments to ensure medicines are given to those who will benefit most. [158,197] Policymakers are also assessing how they can save money through generics.

Generic drugs are bioequivalent replicas of brand name drugs, containing the same active ingredients and with identical quality, safety, and efficacy profiles. [64,65,198–200] Any differences are limited to inactive ingredients, like coloring, flavoring, and stabilizing agents. Generics can, in theory, be sold for a fraction of the price of brand name drugs for two reasons. First, it is relatively cheap to bring a bioequivalent product to market. Second, the market for the drug typically already exists, significantly reducing marketing expenses. [201]

The cost-saving potential of greater generic drug use makes it an attractive option for policymakers, especially since many blockbuster drugs went off patent in the last decade, with more soon to follow. Notably, the cholesterol-lowering drug rosuvastatin (Crestor)—one of the best-selling medicines of all time—lost market exclusivity in the United States and many European countries in 2016. [202]

We have four objectives. First, we compare generic drug prices and market shares in 13 European countries, using data from 2013, to assess the amount of variation that exists between countries. To place these findings in context, we review recent studies on prices and use of generic drugs in Europe and the United States. Second, we outline existing generic drug policies in European countries and the United States. Third, given issues identified in the earlier parts, we explore possible measures to increase usage of generics and to stimulate price competition among generic drugmakers. And, fourth, we analyze obstacles to improving generic drug policies, using a historical example from the United States as a case study.

[1] This chapter was published: Wouters OJ, Kanavos PG, McKee M (2017). Comparing generic drug markets in Europe and the United States: Prices, volumes, and spending. *The Milbank Quarterly*, **95**(3): 554-601.

2.1 Methods

2.1.1 Data set

We selected 13 European countries with different generic drug policies: Germany, France, the United Kingdom, Spain, Italy, Poland, Switzerland, the Netherlands, Greece, Portugal, Belgium, Sweden, and Denmark (listed in order of pharmaceutical market size). These countries represent the ten largest generic drug markets in Europe—in terms of spending—as well as three countries (Denmark, Greece, and Sweden) which are often included in European comparative policy analyses.

For each country, we obtained IMS Health data on the 2013 sales of 200 off-patent active ingredients (**Appendix A**), available in 3,156 strength-form combinations. These were the most-prescribed off-patent active ingredients in the European Union (EU) that year, according to IMS Health data. Sales were recorded in terms of volume and monetary value.

Volumes were measured in number of doses, which IMS Health sometimes refers to as "standard units". IMS Health defined the amount in a single dose of each product, which could be 1 tablet, 5 mL of liquid, 1 vial, and so forth. [203] We excluded 129 products (4.1%, 129/3,156) for which there was no information on dosage.

Monetary values were measured in euros, with foreign currencies converted to euros at yearly average exchange rates. [204] These figures were obtained by multiplying the price of a product, excluding value-added taxes, by the number of packs sold over the year. This was done using ex-manufacturer and retail prices separately. Ex-manufacturer prices were those charged by manufacturers to wholesalers, while retail prices were those charged by pharmacists to patients or insurers. **Appendix B** includes further details on the calculations.

The data set lacked certain information. First, it excluded biosimilar products, parallel-traded generic drugs, off-patent brand name drugs, and generics sold in hospital pharmacies. Second, retail data were unavailable for the Netherlands and the United Kingdom. Finally, the sales data did not reflect confidential rebates and discounts.

2.1.2 Price indexes

We calculated Laspeyres indexes to compare drug prices in three steps. [8, 12, 117, 205–208] First, for each active ingredient, we calculated the average price per dose by dividing the total sales across form-strength combinations by the number of doses sold. For instance, omeprazole (Prilosec) was sold in France as 10-mg and 20-mg capsules. The ex-manufacturer sales of these drugs amounted to roughly € 88.5 million and 450 million doses. Accordingly, the average price per dose of omeprazole was €

0.197 (88.5/450). We calculated the ex-manufacturer and retail prices of each active ingredient.

Second, we identified a subset of 80 active ingredients prescribed in all 13 countries. This common sample accounted for between 46% and 72% of total generic drug sales in every country but the United Kingdom (25%). **Table 2.1** shows descriptive statistics on the generic drug markets.

Third, we calculated Laspeyres indexes using weights from a base country, in this case Germany, since it is the largest drug market in Europe by revenue. The rationale behind weighted indexes is that prices of highly consumed active ingredients should be given greater consideration. The indexes are calculated as:

$$I_L = \frac{\sum_{i=1}^{n} p_i^c q_i^c}{\sum_{i=1}^{n} p_i^b q_i^b} \cdot 100$$

where p is the price of an ingredient (i) in a comparator country (c) or the base country (b), and q is the corresponding quantity in doses. The base country is assigned a value of 100.

The Laspeyres results are interpreted as price ratios. For instance, an index value of 140 for *country X* means that prices are, on average, 40% higher there than in the base country (Germany). Conversely, a value of 60 for *country X* indicates that prices are, on average, 40% lower in *country X*. Because we limited our analysis to medicines available in all 13 countries, the indexes show how prices differ between each country. In other words, if values of 140 and 80 are observed for *countries X* and *Y*, respectively, it indicates that prices are, on average, 75% higher in *country X* than in *country Y* (140/80).

2.1.3 Policy analysis

To place the price-index results in context, we first summarized evidence from recent studies on the prices and use of generic drugs in Europe and the United States. We then surveyed peer-reviewed studies, grey literature, and books published since 2000 to: (i) analyse current generic drug policies in Europe and the United States, (ii) identify potential solutions to increase generic drug use and to spur competition among generic manufacturers, and (iii) explore barriers to the introduction of generic drug policies, using the history of substitution laws and bioequivalence regulation in the United States as a case study.

Table 2.1: Descriptive statistics on generic drug markets (2013).

	Population (millions)[a]	Generic spending (billions)[b,c]	Generic spending (per capita)[b,c]	Generic volume (billions of doses)[c]	Generic volume (per capita)[c]	Proportion of generic spend accounted for by the sample[b,c]	Generic market share (volume)[d]	Generic market share (value)[b,d]
Belgium	11.2	€ 0.45	€ 40.60	4.2	251.6	56%	32%	14%
Denmark	5.6	€ 0.17	€ 29.60	2.7	481.6	56%	54%	14%
France	66.0	€ 4.14	€ 62.80	25.6	387.9	52%	30%	16%
Germany	82.1	€ 5.20	€ 63.40	37.6	458.3	51%	80%	37%
Greece	11.0	€ 0.45	€ 41.00	2.3	207.4	67%	20%	15%
Italy	60.2	€ 2.08	€ 34.50	15.3	254.0	47%	19%	11%
Netherlands	16.8	€ 0.50	€ 29.80	7.5	445.7	47%	70%	16%
Poland	38.0	€ 1.55	€ 40.90	16.2	425.5	46%	57%	42%
Portugal	10.5	€ 0.47	€ 45.10	2.8	401.1	49%	39%	23%
Spain	46.6	€ 2.12	€ 45.60	19.4	416.0	54%	47%	21%
Sweden	9.6	€ 0.32	€ 33.80	3.8	399.2	72%	44%	15%
Switzerland	8.1	€ 0.51	€ 63.40	1.8	231.7	71%	17%	16%
United Kingdom	64.1	€ 2.87	€ 44.80	36.3	566.0	25%	83%	33%

[a] Reproduced from the World Bank. [209]

[b] All monetary figures are based on ex-manufacturer prices. The market shares account for reimbursed generics in hospital and retail pharmacies. [210]

[c] Reproduced from IMS Health (2013, Pricing Insights database).

[d] Reproduced from the Organisation for Economic Co-operation and Development, [94] with the exception of the Polish and Swedish figures (IMS Health, 2013).

2.2 Results

2.2.1 Generic drug market shares and prices in Europe and the United States

Table 2.1 shows the proportion of prescriptions filled with generics in 13 European countries. The percentages were low (ie, less than 40%) in Switzerland (17%), Italy (19%), Greece (20%), France (30%), Belgium (32%), and Portugal (39%). They were moderate (ie, 40% to 60%) in Sweden (44%), Spain (47%), Denmark (54%), and Poland (57%); and high (ie, greater than 60%) in the Netherlands (70%), Germany (80%), and the United Kingdom (83%).

2.2.1.1 Price indexes

Figure 2.1 compares ex-manufacturer prices in each country. The figure shows wide variation in prices. For example, Swiss ex-manufacturer prices were, on average, more than 2.5 times German ones and more than 6 times British ones.

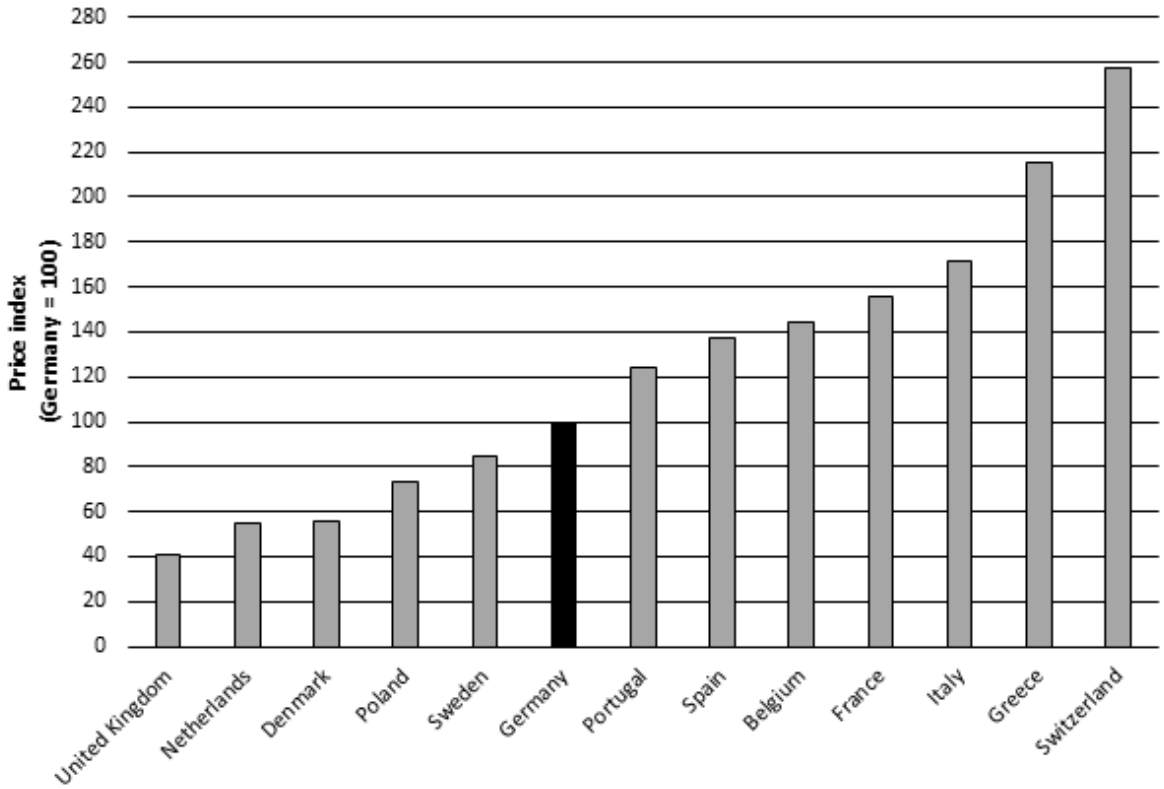


Figure 2.1: Ex-manufacturer prices of generics (2013).

Source: Derived from authors' analysis of data from the Pricing Insights database (IMS Health, 2013).

Figure 2.2 compares retail prices in 11 European countries. The spread between the Swiss and German retail prices was smaller than the difference between the ex-manufacturer prices. Retail prices in Portugal, Spain, and Belgium were lower than in Germany, whereas the opposite was true at the ex-manufacturer level. Retail prices include distribution costs (ie, transport, processing, and storage) and markups charged by wholesalers and pharmacies.

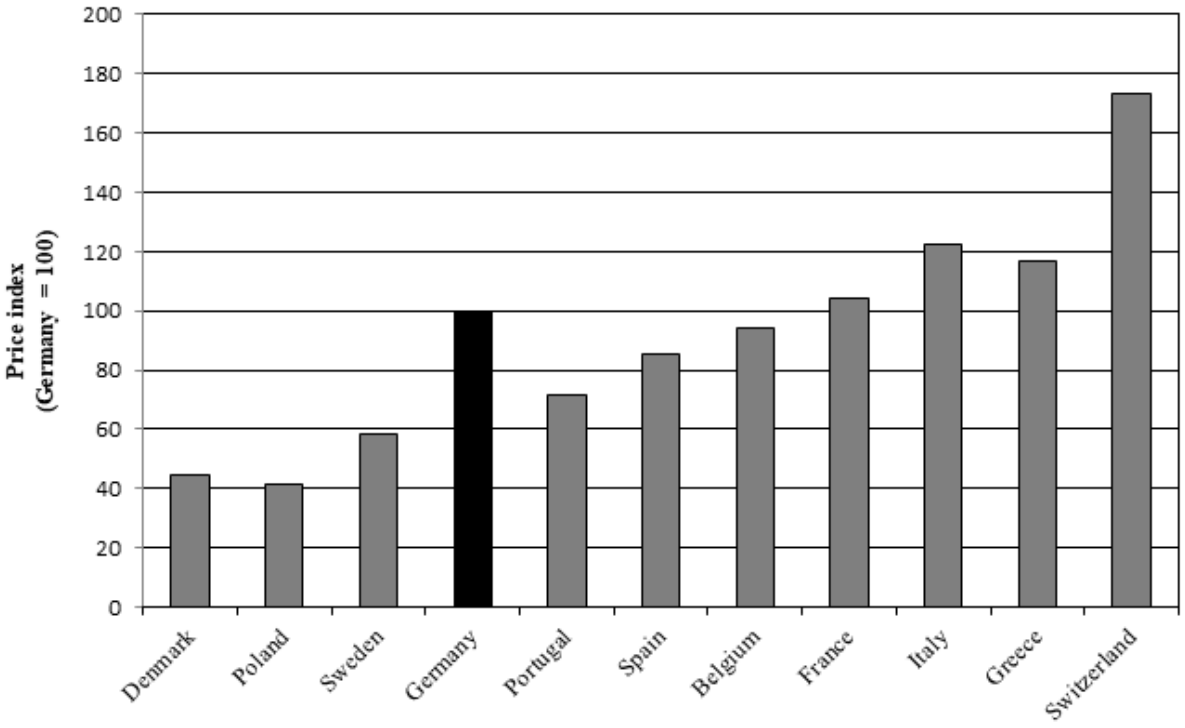


Figure 2.2: Retail prices of generics (2013).

Note: Retail prices were unavailable for the Netherlands and the United Kingdom.

Source: Derived from authors' analysis of data from the Pricing Insights database (IMS Health, 2013).

Table 2.2 shows the ex-manufacturer prices of seven of the most consumed products in the sample. Atorvastatin (Lipitor) and simvastatin (Zocor) are cholesterol-reducing drugs; amlodipine (Norvasc) is a calcium channel blocker used to treat high blood pressure and coronary heart disease; metformin (Glucophage) is a type 2 diabetes medication; and esomeprazole (Nexium), omeprazole (Prilosec), and pantoprazole (Protonix) are proton-pump inhibitors used to treat heartburn and related conditions. Prices of all seven products differ among countries. For instance, the price per dose of omeprazole was 30 times greater in Switzerland than in the United Kingdom (€ 0.811 vs € 0.027). Even after excluding Greece and Switzerland, the two countries that generally had the highest prices, there were large price discrepancies.

Table 2.2: Ex-manufacturer prices (€ per dose) of seven top-selling active ingredients (2013).

	Amlodipine	Atorvastatin	Esomeprazole	Metformin	Omeprazole	Pantoprazole	Simvastatin
Belgium	€ 0.11	€ 0.20	€ 0.19	€ 0.03	€ 0.24	€ 0.20	€ 0.12
Denmark	€ 0.01	€ 0.12	€ 0.27	€ 0.01	€ 0.04	€ 0.03	€ 0.02
France	€ 0.14	€ 0.27	€ 0.19	€ 0.06	€ 0.20	€ 0.19	€ 0.19
Germany	€ 0.01	€ 0.07	€ 0.16	€ 0.02	€ 0.12	€ 0.17	€ 0.08
Greece	€ 0.17	€ 0.52	€ 0.27	€ 0.04	€ 0.45	€ 0.40	€ 0.40
Italy	€ 0.09	€ 0.13	€ 0.26	€ 0.03	€ 0.21	€ 0.22	€ 0.11
Netherlands	€ 0.02	€ 0.09	€ 0.11	€ 0.02	€ 0.03	€ 0.04	€ 0.02
Poland	€ 0.06	€ 0.12	€ 0.15	€ 0.04	€ 0.17	€ 0.09	€ 0.10
Portugal	€ 0.07	€ 0.12	€ 0.17	€ 0.04	€ 0.09	€ 0.09	€ 0.08
Spain	€ 0.04	€ 0.29	€ 0.43	€ 0.02	€ 0.06	€ 0.32	€ 0.04
Sweden	€ 0.02	€ 0.10	€ 0.18	€ 0.03	€ 0.11	€ 0.15	€ 0.05
Switzerland	€ 0.32	€ 0.40	€ 0.47	€ 0.05	€ 0.81	€ 0.30	€ 0.48
United Kingdom	€ 0.01	€ 0.03	€ 0.14	€ 0.02	€ 0.03	€ 0.03	€ 0.02
% difference (highest/lowest)	2,723%	1,990%	450%	469%	3,027%	1,492%	2,382%

Source: Derived from authors' analysis of data from the Pricing Insights database (IMS Health, 2013).

Small price differences can have a large budget impact for high-volume drugs. For example, roughly 294 million doses of simvastatin were consumed in France in 2013. For simvastatin alone, if France had paid the UK price per dose (€ 0.020 instead of € 0.192), spending would have been more than € 50 million less. There are caveats: volumes might not remain constant if prices change, and there might be differences in production and supply-chain costs that prevent price equalization across countries.

2.2.1.2 Recent evidence

Recent studies indicate there are opportunities for cost savings in off-patent drug markets in Europe and the United States.

A high-profile inquiry by the European Commission into generic competition found that patients in EU countries have to wait an average of about 7 months for generics to become available, starting from when brand name drugs lost market exclusivity. [10] The inquiry report, published in 2009, estimated that these delays cost payers in EU countries € 3 billion (US$ 3.4 billion) per year, based on retail prices. [10] Those findings were echoed by a 2014 study, which found significant delays in the availability of generics in many European countries. [9]

The European Commission's report showed that generics are slow to penetrate markets: after 2 years on the market, generics account for less than half of sales in EU member states. [10] The report also found that prices are slow to drop in many countries. Variation in prices and market shares between European countries has been attributed to differences in pricing and reimbursement regulations, prescribing policies, and generic substitution laws, among other factors. [8, 10, 11]

By comparison, the United States has historically had high rates of generic drug use—84% of prescriptions were filled with generics in 2013 [94]—and low prices. [74] In recent years, however, it has seen a decrease in competition in the generics sector. Between 2012 and 2013, the total cost of 280 widely used generic medicines only fell by 4% in the United States, a slower rate of decline than in the previous 7 years. [211] This trend was due to a combination of issues, including supply-chain disruptions, loopholes in regulations by the US Food and Drug Administration (FDA), tough market conditions driving firms out of business, a flurry of mergers and acquisitions, and backlogs in the processing of generic drug applications by the FDA. [35, 212–214]

In extreme cases, reduced competition has enabled individual companies to drastically raise the prices of generic drugs. [68, 215] For example, the price of pyrimethamine (Daraprim), an off-patent anti-infective medication, went up by about 5,500% overnight in 2015. [216, 217] Such price hikes have affected numerous generic drugs, including the widely used antibiotic doxycycline (Doryx) and the cholesterol-lowering drug pravastatin (Pravachol). The cost of 500 doxycycline capsules rose from US$ 20 in October 2013

to US$ 1,928 in April 2014, while the cost of a 1-year supply of pravastatin rose from US$ 27 to US$ 196 during the same period, according to an analysis by the senior citizen group AARP. [218] The US Government Accountability Office reported that between 2010 and 2015 there were "extraordinary price increases" of 100% or more for 315 out of the 1,441 generics they studied. [219] Many of the affected medicines have been around for decades at low cost. [74, 214, 219] (There have also been documented cases of large price hikes for generic drugs in some European countries, like the U.K. [220])

Moreover, recent studies show that many American and European physicians, pharmacists, and patients do not perceive brand name and generic drugs to be bioequivalent. [51, 95–104] A 2016 study found that 30% of surveyed physicians in the United States preferred prescribing brand name drugs over their generic counterparts, while 27% believed generics cause more adverse effects than brand name drugs. [99] A 2013 US study reported that 2 in 5 physicians "sometimes" or "often" prescribe brand name drugs instead of equivalent generics when patients request the former. [221]

In summary, there are shortcomings in generic drug markets in Europe and the United States, notably delays in the availability of generics, high prices, and low utilization rates. These issues affect countries to varying degrees. In the next section, we outline contemporary generic drug policies in Europe and the United States to identify lessons that might be drawn from different approaches.

2.2.2 Generic drug policies in Europe and the United States

There are vast differences between countries in terms of regulatory structures, lobbying powers of special-interest groups, patent-litigation systems, political economies of health care systems, and perceptions of generics among patients and health care professionals. [222] Such differences influence the adoption and effectiveness of policies.

Figure 2.3 shows the patchwork of policies in place in Europe. Generic drug substitution is mandatory in 13 countries, voluntary in 14, and forbidden in five. The situation with respect to generic prescribing is similarly diverse. Internal reference pricing, which limits how much insurers will reimburse for generics, is used in most countries. [13, 123, 124] In several countries, health insurers buy generic drugs in bulk from the manufacturers that offer the best prices, a policy referred to as tendering. [140, 223] For example, a health insurer might put out a tender for 1 million packs of 20-mg simvastatin and ask generic manufacturers to submit confidential bids. The winning manufacturer is asked to supply the entire market for the duration of the contract, which typically ranges from 1 to 2 years. [140]

Figure 2.3: Internal reference pricing (A), generic prescribing (B), generic substitution (C), and tendering (D) in EU and EFTA countries (2016).

EFTA, European Free Trade Association; EU, European Union; IRP, internal reference pricing.

Note: These maps show the policies used by the 28 EU member states and the four EFTA signatories (Iceland, Lichtenstein, Norway, and Switzerland) for non-hospital pharmacies. We populated the maps based on a 2016 report published by the World Health Organization. [224] If information was missing, we used older sources dating as far back as 2009. The policies in some countries may have changed since then. In Spain, only the autonomous community of Andalusia issues tenders. Generic prescribing refers to the prescribing of drugs by their international nonproprietary names. The Danish and Swedish tendering systems operate differently to the others. In each country, the relevant national government agency asks generic manufacturers to offer their best prices. Usually, the least expensive generics become the only ones that pharmacists can dispense; if a patient wants a brand name drug, they are required to pay the difference out-of-pocket. The bidding process is repeated every 2 weeks in Denmark, and every 4 weeks in Sweden. There are safeguards to reduce the risk of supply disruptions.

Source: Derived from authors' analysis of the data [118, 121, 140, 151, 152, 223, 224]; the map toolkit is licensed under the Creative Commons Attribution-NoDerivs 3.0 Unported License.

Figure 2.3 gives a broad overview of policies, but the way these policies are implemented varies considerably. Other supportive measures are often used to influence generic drug usage, such as charging higher co-payments on branded drugs that have generic equivalents to encourage patients to choose the latter.

National governments in all but three EU member states (Denmark, Germany, and the United Kingdom) impose price controls on generics (ie, maximum allowable prices). [118] Often these controls are linked to the prices of brand name drugs. In Spain, for instance, the first company to sell a generic version of a drug must price its product at least 40% below the price of the brand name drug at the time of loss of market exclusivity; subsequent generic entrants must be priced at or below this level. Many EU governments also retain the right to block large price increases for prescription drugs, including generics, if necessary to protect public health or reduce pressure on the public purse. [224] As nearly all EU countries have universal health care systems, funded either through government tax revenues or taxes on employers and employees, a population-based focus has strong political support from consumers and non-industry stakeholders in these nations. [225]

In the United States, by comparison, generic prescribing is voluntary in all 50 states. Neither internal reference pricing nor tendering is used for generic drugs sold in non-hospital pharmacies. There are no government price controls on generics, and substitution laws differ from state to state, as shown in **Figure 2.4**. [56]

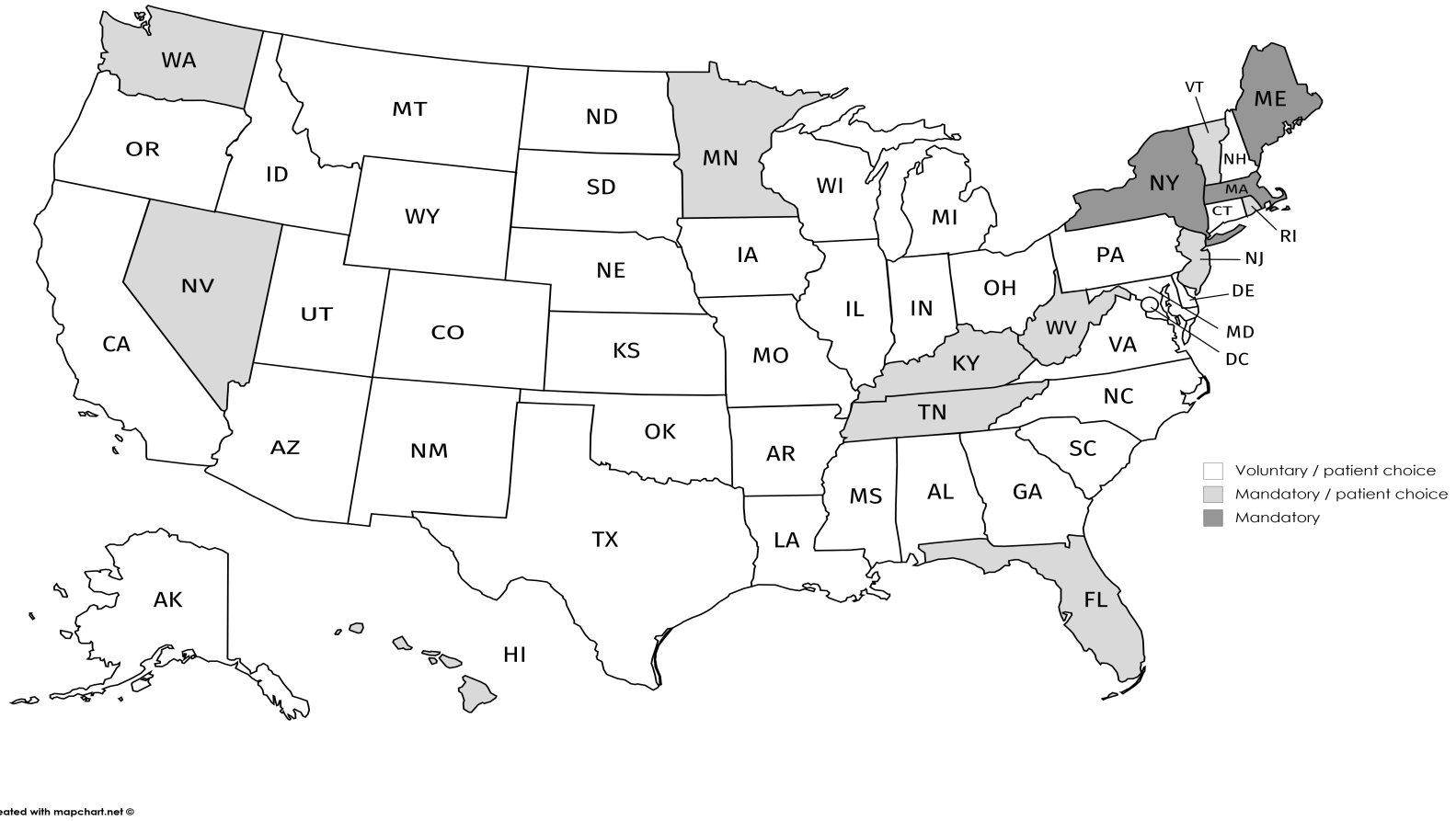


Figure 2.4: Generic drug substitution laws in the United States (2010).

Note: States with "patient choice" grant patients the right to refuse generic drug substitution, usually at a higher cost.

Source: Derived from authors' analysis of data [56]; the map toolkit is licensed under the Creative Commons Attribution-ShareAlike 3.0 Unported License.

Pricing, prescribing, and substitution policies can affect the prices and usage of generics. [10] To illustrate this, **Figure 2.5** shows how ex-manufacturer prices and market shares of ramipril (Altace), a drug widely used to treat high blood pressure, evolved between 1998 and 2010 in 4 countries. Ramipril lost patent protection in each country in either November 2002 or March 2003, as indicated by the vertical lines.[2]

The figure shows that it took over a year for the first generic version of ramipril to come on the market in the United Kingdom and Spain, compared to 2 years in Sweden and 3 years in France. The trends in prices and market shares in each country varied considerably. In the United Kingdom, the generic price fell to about a fifth of the branded price within 3 months of the first generic being launched. During this time, the price of the branded version remained unchanged and generic ramipril captured over 90% of the British market. In Spain, on the other hand, the generic competitor was introduced at about 60% of the branded price and only slowly gained market share, reaching around 10% after 1 year of being on the market and only 25% after 3 years. The branded price then fell to match the generic, which showed no sign of responding to competition. In Sweden, at launch, the generic price was only 10% of the branded price, which rapidly fell to a similar level. The generic market share continued to rise steeply, to almost 100%. In France, although the prices moved in step, the price of the generic drug remained about two-thirds that of the branded. Again, the generic gained a high market share within a few years of entering the market. By the end of 2009, generic ramipril cost 7 times more in France (€ 0.236 per dose) than in Sweden (€ 0.033).

[2]The vertical lines show the date of patent expiry (November 2002 in France, Sweden, and the United Kingdom; March 2003 in Spain). The Swedish and British prices were converted to € using official exchange rates. The data correspond to sales in non-hospital pharmacies (except for Sweden, where the data include sales in hospital and non-hospital pharmacies). Data on sales of branded ramipril in France between January 1998 and December 1999 were unavailable. Prices and market shares were measured on a quarterly basis.

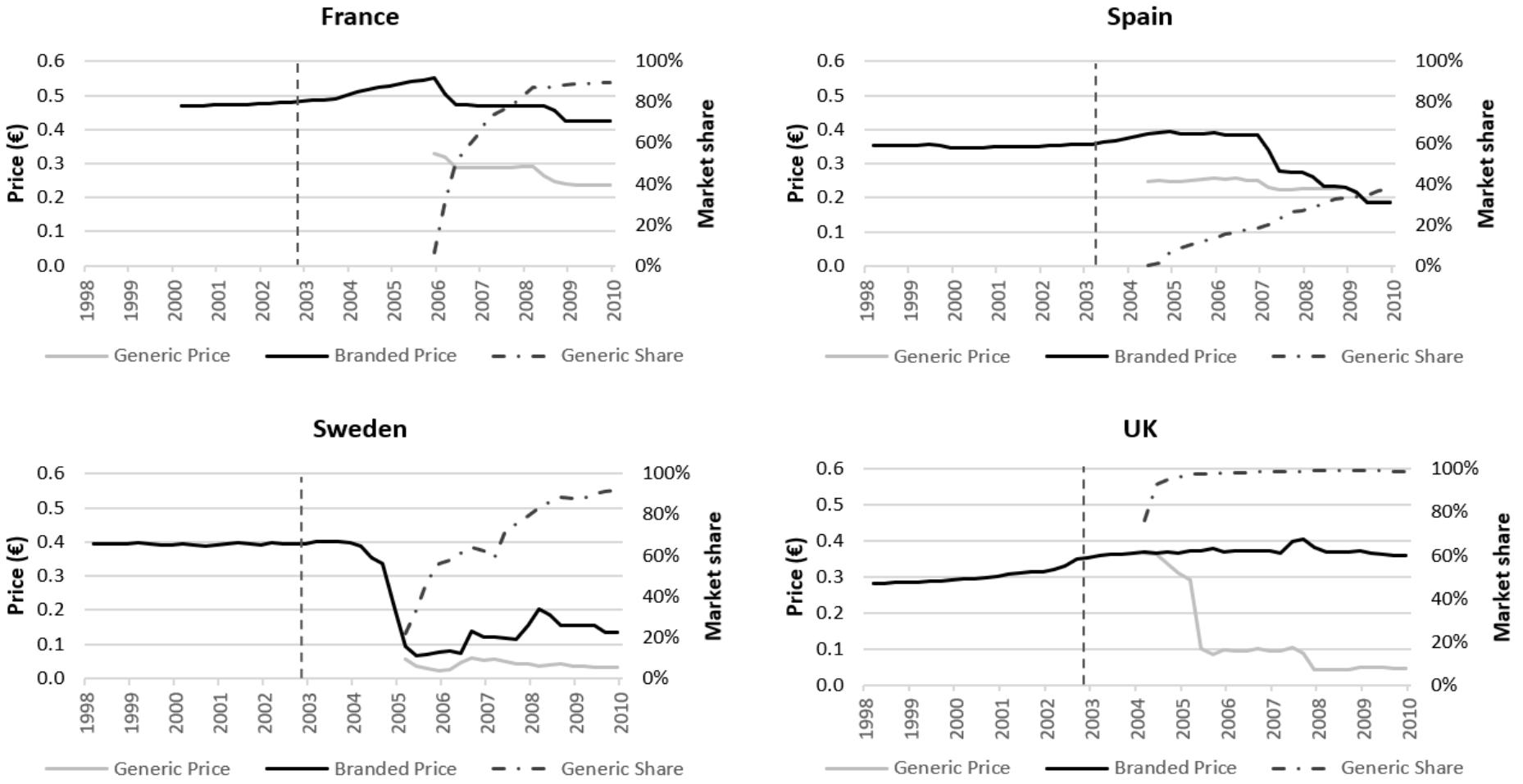


Figure 2.5: Ex-manufacturer prices (€ per dose) and market shares (%) of brand name and generic ramipril in four countries (1998-2010).

Source: Derived from authors' analysis of data from the Midas database (IMS Health, 2010).

2.2.3 Possible policy solutions

2.2.3.1 Facilitate generic market entry

First, national regulators should streamline the generic drug approval process. [93,226] In response to recent price hikes in the United States, Kesselheim et al called for regulators to prioritize applications from manufacturers trying to bring to market a generic medicine sold by three or fewer firms. [74,212,227] This would put downward pressure on prices and make it harder for individual companies to have much influence over prices. For off-patent drugs facing limited or no competition, Kesselheim et al further recommended that the FDA temporarily import generics from countries with equally high regulatory standards, like Canada and EU member states, to avoid paying high premiums. [74,228]

Second, in countries with backlogs of applications for generic drug approval, governments could allocate more resources to national regulators to speed up the review process [74] or could charge generic firms fees to increase resources available for the drug approval process, as is done by the FDA. [229] In the European Union, levels of backlogs vary greatly between national regulatory agencies, despite efforts to harmonize such processes across the union. [10] In the United States, it currently takes about 15 months, on average, for generic drugmakers to receive an initial response from the FDA. [230] Over 4,000 generic drugs were awaiting approval from the FDA as of mid-2016. [231]

Third, regulators should address the anticompetitive tactics used by brand name firms to delay generic drug launches. Brand name manufacturers frequently file patent infringement lawsuits against generic drugmakers for launching their drugs too early, preventing the marketing of generic products while the companies are tied up in court. [10] Some such lawsuits might reflect calculations by brand name firms that the extra revenue obtained after patent expiry is likely to exceed the legal fees incurred. [232] Brand name firms have employed other strategies to hinder market entry for generic drugs, like filing patent clusters (ie, complex webs of primary and secondary patents on pharmaceutical products and manufacturing processes that serve to extend periods of market exclusivity). [10,233,234] Some medicines are protected by as many as 1,300 patents, [10] making it difficult for generic drugmakers to determine when they can legally enter the market. The US Congress proposed new legislation in 2015 that could make it easier for generic drug companies to challenge patents without the need for lengthy and costly litigation. [235] The bill is still under consideration. The European Commission has called for similar measures. [10]

Fourth, regulators should block pay-for-delay deals, where brand name drugmakers offer generic manufacturers cash, or something else of value, to delay the introduction of generic drugs onto the market. [10] Brand name drugmakers continue to enjoy

monopolies, meaning consumers pay higher prices for longer. These deals happen in both Europe and the United States. In 2009, the US Federal Trade Commission (FTC) estimated that eliminating pay-for-delay deals would save consumers and the federal government over US$ 3.5 billion a year. [236] A 2013 Supreme Court ruling gave the FTC the authority to block such deals, which it has begun to do. Yet there continue to be legal disputes over what constitutes a pay-for-delay deal, which hamper the FTC's efforts.

Finally, regulators should facilitate access to samples of brand name products for generic drugmakers. Since 2007, some brand name manufacturers have taken advantage of a legal loophole in the United States to block access to samples, citing restrictions imposed by the FDA through risk evaluation and mitigation strategies. [237, 238] This prevents generic drug companies from conducting bioequivalence tests prior to patent expiry. These test results are needed for companies to receive marketing authorization at the time of patent expiry. Several countermeasures have been proposed by Congress and the FDA, but none have been implemented to date. [238]

2.2.3.2 Encourage price competition

Studies on pricing policies indicate that allowing generic drug companies to set their own prices, while giving physicians and pharmacists incentives to prescribe and dispense the least expensive generics, is more effective at driving down prices over time than government-mandated price controls. [10, 46, 108, 116, 117, 239] This is the approach adopted by policymakers in Denmark, Sweden, the United Kingdom, and the United States, [11] although the Swedish authorities reserve the right to block large price increases for generics. An analysis of IMS Health data conducted by the FDA found that drug prices in the United States drop, on average, by around 50% with two generic competitors on the market, around 70% with five on the market, and around 90% with 15 or more on the market. [188] However, safeguards are needed to prevent large, unjustified price hikes for drugs available in generic versions. For example, increases exceeding a percentage threshold could be blocked by national authorities on economic or public health grounds, with exceptions for causes outside the control of manufacturers which are verifiable (eg, changes in the prices of ingredients).

Tendering is another way to encourage price competition, especially if market competition fails to achieve large price reductions for generic medicines. As mentioned earlier, tendering refers to the purchase of generics in bulk, usually from the suppliers offering the lowest prices. It has been shown to lower administrative costs, drive down the prices of generics, and improve price transparency. [129, 140, 141, 223] In the Netherlands, for example, the introduction of tendering resulted in the retail prices of some generics—including amlodipine, omeprazole, and simvastatin (**Table 2.2**)—

dropping by 80% to 90% overnight in non-hospital pharmacies. [129] The color, shape, and size of a pill might change after a tender if a new manufacturer is asked to supply the market, so physicians and pharmacists need to communicate such changes to patients to promote treatment adherence. [240–242] Also, European payers in charge of tendering sometimes split contracts between two or more manufacturers, as long as the bids are close to each other, to minimize the risk of supply disruptions and to maintain competition. [140] There is no conclusive evidence, though, that disruptions occur more often in countries that rely on tendering than in others.

2.2.3.3 Promote generic dispensing and prescribing

Countries should require pharmacists to substitute generic drugs for brand name medicines. The Swedish national government, for example, introduced mandatory generic substitution in 2002, which led to a spike in generic drug use. [155] The European Commission found that generic drugs enter the market sooner, on average, in EU member states with mandatory substitution. [10] Currently, generic substitution is mandatory in only 11 EU countries and 14 US states. [56, 224]

Governments should encourage or require physicians to prescribe drugs by their generic names. [11, 150] A recent study estimated that physicians blocking generic drug substitution costs the United States over US$ 7.5 billion per year, including US$ 1.2 billion in out-of-pocket fees for patients. [243] This practice is also costly in European countries, including France [244] and Switzerland. [245] There may be legitimate reasons for prescribing brand name drugs instead of generic ones—for example, a patient might be allergic to an inactive ingredient in a generic medicine. [240] However, in many cases, those decisions are likely due to habit or misconceptions about generic medicines among physicians. [56] Academic detailing (ie, having trained experts with no conflicts of interest provide unbiased information to clinicians about the effectiveness, safety, and costs of drugs) could help correct suboptimal prescribing. [246] A meta-analysis conducted for Cochrane found, based on data from 25 randomized controlled trials, that academic detailing improves compliance with desired prescribing practices. [246] Financial incentives aimed at improving rates of generic prescribing were also shown to be effective, although the evidence base is limited. [247, 248]

Moreover, regulators in some countries allow pharmacists to substitute a generic for a brand name drug with a different active ingredient, as long as both drugs belong to the same therapeutic class and have the same indication. For example, if a doctor prescribes a patient rosuvastatin, a cholesterol-lowering drug not yet available in generic form in some countries, a pharmacist could give the patient generic simvastatin instead. [249] A recent study estimated that the United States spends an extra US$ 73.0 billion per year—about 10% of total drug spending—on brand name drugs with

available therapeutic substitutes. [250] This estimate included US$ 24.6 billion in out-of-pocket expenses. [250] Most of the estimated excess spending was on brand name drugs in five classes: statins, a class of cholesterol-reducing drugs (US$ 10.9 billion); atypical antipsychotics, a class of drugs used to treat psychiatric conditions (US$ 9.99 billion); proton pump inhibitors, a class of drugs used to treat heartburn and related conditions (US$ 6.12 billion); selective serotonin reuptake inhibitors, a class of drugs used to treat depression (US$ 6.08 billion); and angiotensin receptor blockers, a class of drugs used to lower blood pressure (US$ 5.53 billion). [250]

Therapeutic substitutes can vary in terms of side effects and other properties, so this form of substitution is less straightforward to implement than substitution of bioequivalent products. For therapeutic substitution to be more widely practiced, the relevant authorities and clinical organizations should develop appropriate protocols and strengthen coordination between physicians, pharmacists, and insurers. [55,250,251] A challenge is to get buy-in from trade groups for physicians, many of which have, in the past, opposed such restrictions on prescribing and have raised concerns about the potential adverse health consequences for patients. [250,252] In the United States, some patient organizations have also been skeptical of therapeutic substitution, worried that legislators are too focused on cutting costs at the expense of quality of care. [55]

2.2.4 Barriers to reforming generic drug policies: A case study from the United States

Having reviewed a range of policy options, we now draw on the experience of one country, the United States, to explore barriers to reform and offer thoughts on how they might be overcome. While we focus on the history of substitution and bioequivalence policies in the United States as a case study, similar analyses could be done for any country.

The history of generic drug substitution in the United States (**Box 2.1**) shows how trade groups for brand name drugmakers and clinicians have consistently banded together to resist generic drug policy reform in the United States. [50,253,254] It is a history marked by political conflicts, vested economic interests, and intense lobbying by stakeholders. [55] **Figure 2.6** highlights key events and milestones.

Regulation of bioequivalence has played a key role in the evolution of substitution policies in the United States. [55,201,255] In the 1950s and '60s, when US lawmakers started calling for generic prescribing and substitution, there was little clarity about how to verify that generic drugs would produce the same therapeutic effects as their brand name counterparts. A scandal erupted in 1967 when it was found that some patients who consumed generic versions of chloramphenicol (Chloromycetin), a widely used antibiotic, had no traces of the active ingredient in their bloodstreams. It was later

shown that the coating used by some generic manufacturers prevented the drug from dissolving in the gastrointestinal tract. [255]

In response, between 1967 and 1975, the US FDA commissioned five separate external committees to provide input on how to assess the therapeutic equivalence of generic and brand name drugs. [55] The proliferation of committees and recommendations slowed down the market entry of generic drugs, hurt the public perception of generics, hampered the campaign to roll back anti-substitution laws, and delayed other changes to generic drug policies during this period. [50, 55, 256] The scientific and regulatory uncertainty around bioequivalence created space for brand name manufacturers and their trade groups to nurture brand loyalty and to claim, often without evidence, that there were meaningful differences between branded and generic medicines. [55, 256] Not until 1984 did the FDA settle on a coherent and widely accepted set of bioequivalence standards—based on the rate and extent of absorption of the active ingredient into the bloodstream [199]—as part of the Drug Price Competition and Patent Term Restoration Act, more commonly known as the Hatch-Waxman Act. [255]

The issues raised by the proponents and critics of generic drug policy reform have remained similar over the last 50 years in the United States. [50, 257] The evolution of substitution and bioequivalence regulation provides insights into the economic, political, cultural, and scientific issues influencing policy changes. Such insights can help policymakers avoid past pitfalls.

Box 2.1: History of drug substitution in the United States.

Generic drug substitution

The first instances of generic drug substitution were reported in the late 1940s. In response, the National Pharmaceutical Council (NPC), a trade organization for the brand name drug industry, began aggressively lobbying against substitution, saying it would stifle innovation. The group further claimed that substitution would reduce quality of care, citing the scientific uncertainty that existed at the time over whether generic drugs were as effective as brand name drugs. [255]

The NPC forged an alliance with the American Medical Association (AMA) and the American Pharmacists Association (APhA), two major trade groups for clinicians and pharmacists. The AMA argued that substitution diminished the role of physicians, while the APhA said it was a violation of the ethical and professional standards of the trade. (In an apparent *quid pro quo*, the NPC helped pharmacists lobby against supermarkets, which were beginning to sell prescription and over-the-counter drugs.) The AMA was further concerned that government intervention on dispensing was a step toward socialized medicine, which they opposed.

The anti-substitution campaign was largely successful: by 1959, 44 states had enacted laws blocking generic drug substitution.

During the 1960s and '70s, when state health care budgets were ballooning, state and municipal governments started looking at ways to cut health care spending. Meanwhile, there was growing support for substitution among pharmacists, who sought a more active role in the care of patients. In 1972, Kentucky became the first state to abolish its anti-substitution law. By 1984, all 50 states had legalized generic drug substitution.

However, state policies differed in three ways. First, generic substitution was compulsory in some states and voluntary in others. Second, patients in many states could refuse substitution. Finally, some states restricted which drugs pharmacists could substitute.

The rollback of anti-substitution laws on a state level resulted in a patchwork of policies, most of which remain in place today. Physicians in all states can block substitution, usually by ticking a box on the prescription pad which reads "dispense as written". [56] The poorer states have some of the weakest substitution laws in the country, leading one commentator to recently note that "the cost savings of generic substitution [in the United States] now appear to benefit populations in inverse proportion to economic need". [55]

To date, all attempts by federal legislators to enforce a minimum standard of substitution have been voted down, and the politics and economics of substitution have continued to play out at the state level. [258] Still, substitution laws have helped dramatically increase the rate of generic drug use in the United States: around 10% of prescriptions were filled generically in 1958, compared to 88% in 2015.

Therapeutic drug substitution

In the 1980s, state lawmakers and hospital administrators turned their attention to therapeutic substitution. Proponents argued that many new drugs offered little or no additional therapeutic benefit over existing ones and that they should be substituted for older, cheaper medicines—preferably generics. This would generate savings and incentivize drug companies to develop innovative products. Trade groups for brand name drugmakers and clinicians opposed therapeutic substitution, claiming it would harm patients.

Oregon passed the first therapeutic substitution law in 1981, and hospitals around the country began implementing a two-tiered approach: automatic therapeutic substitution in clear-cut cases (eg, cephalosporins, anti-allergy drugs, and heartburn treatments) and prior authorization in less straightforward cases (eg, beta blockers and anti-cancer drugs). Between 1987 and 1993, the proportion of health maintenance organizations that allowed therapeutic substitution in non-hospital pharmacies doubled to 70%.

Private and public insurers increasingly turned to pharmacy benefit managers (PBMs), who serve as intermediaries between drug companies and payers, to help coordinate therapeutic substitution. PBMs negotiate lower drug prices and rebates on behalf of large patient populations. Most

PBMs operate formularies specifying the preferred products for different therapeutic indications. These organizations help dictate the nature and extent of generic and therapeutic substitution. They often rely on tiered co-payment systems, whereby patients are required to pay more for brand name drugs.

The lack of transparency with PBMs, however, meant that insurers were unsure about how much of the negotiated discounts was passed on to them, and how much was kept by PBMs. Some PBMs were bought by pharmaceutical companies, introducing further conflicts of interest.

In 2000, partly in response to the rapid growth and opaqueness of PBMs, the Oregon state legislature implemented guidelines on which medicines should be prescribed to Medicaid patients for specific conditions, known as a preferred drug list. [259, 260] The preferred drug list was the "public, transparent, evidence-based analogue of the private formulary-shaping activities of the PBMs". [55] Idaho and Washington quickly followed suit and developed their own lists.

These three states joined forces with the Pacific Northwest Evidence-based Practice Center in 2003 to form the Drug Effectiveness Review Project (DERP), a collaboration between Medicaid and public pharmacy programs in member states to promote evidence-based prescribing. By 2008, the DERP consortium comprised 15 states and two nonprofit organizations, and 33 states operated preferred drug lists, most of which promoted therapeutic substitution wherever possible.

The recent economic downturn put the project under financial strain. In 2014, there were only nine paying members in the consortium. Still, DERP paved the way for future research into comparative effectiveness, a field fraught with ethical, political, methodological, organizational, and procedural issues.

Source: Derived from authors' analysis of data [50, 55, 261]; other references are shown in the text.

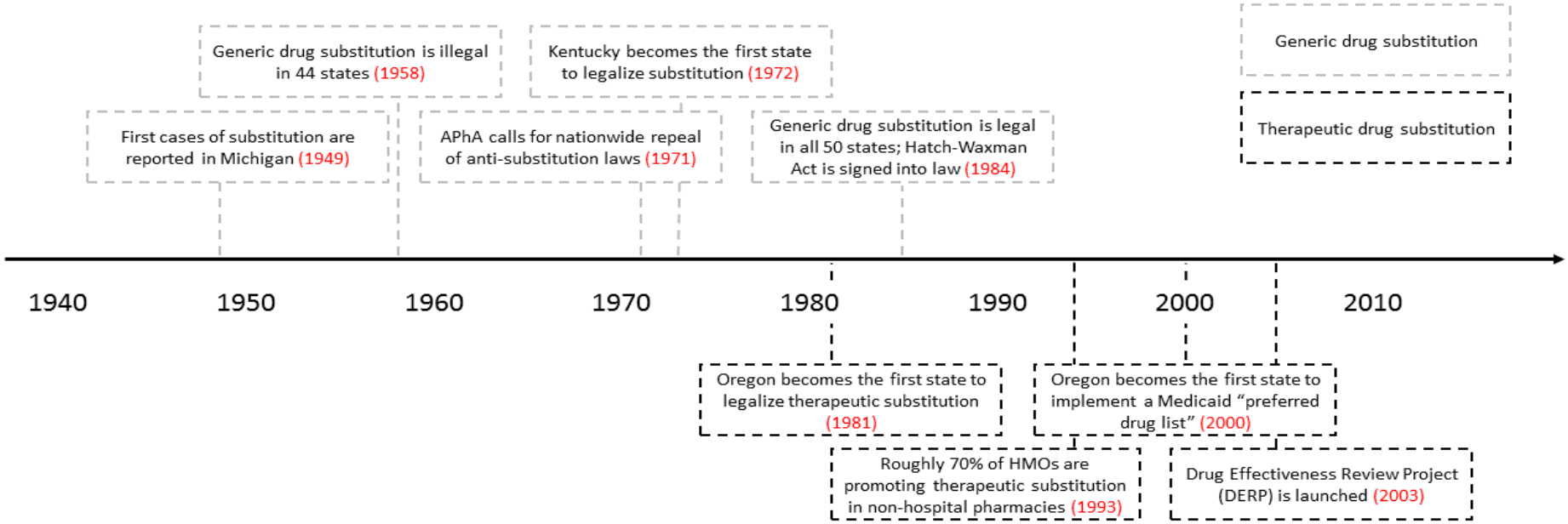


Figure 2.6: Key events and milestones for US drug substitution.

APhA, American Pharmacists Association; HMO, health maintenance organization.

Source: Derived from authors' analysis of the data. [55, 261]

2.2.4.1 Current opportunities for reform

Recent developments point to an opportunity for reform of generic drug policies in the United States.

In the past few years, a series of price scandals shifted public attention from the high prices of new medicines to the rising costs of generics, raising pressure on companies and policymakers to contain costs. [262] A 2015 national survey by the Kaiser Family Foundation found that roughly 3 in 4 Americans believe prescription drug prices are unreasonably high, and, of those, 76% say pharmaceutical companies are mostly to blame. [263] These findings may partly reflect the reputational damage to generic drugmakers caused by recent scandals, as well as the increase in the number of patients facing higher deductibles for medicines. [264]

A subsequent Kaiser poll, in 2016, found that the vast majority of Americans are in favor of government action to curb prescription drug prices. [265] According to the results, more than 8 in 10 Americans (82%) favor allowing Medicare to negotiate prices with companies, while 66% support the creation of an independent group to oversee the pricing of prescription drugs and 71% believe patients should be allowed to buy medicines imported from Canada. [265]

The increasing roles of federal and state governments in health care has further renewed attention on cost containment. [55, 261, 266] A growing number of government officials, including Senators Bernie Sanders (D-VT), Susan Collins (R-ME), Elijah Cummings (D-MD), and Claire McCaskill (D-MO) are looking at ways to improve competition in the off-patent drug market to reduce spending, with some arguing that state and federal governments should be allowed to block unjustified price increases on generics. [267, 268] Competition authorities are also investigating potential price collusion between generic companies. [220, 269] Private health insurers, which have a strong interest in keeping generic prices low, have joined the debate, arguing on the side of lawmakers on this issue. They were largely absent from discussions in the 1970s, '80s, and '90s when the prices of drugs were rising more slowly than those of other health care goods and services. [55]

The outcome of the 2016 presidential election could provide further momentum for improving generic drug policies. During the campaign, now-President Donald Trump supported giving Medicare greater power to negotiate drug prices and allowing states to import less expensive drugs from Canada and elsewhere. He launched an attack on the pharmaceutical industry at a press conference a few days prior to his inauguration. "Pharma has a lot of lobbies, a lot of lobbyists, and a lot of power", Trump said at the press conference. "And there's very little bidding on drugs. We're the largest buyer of drugs in the world, and yet we don't bid properly. And we're going to start bidding and we're going to save billions of dollars". Since taking office, Trump

has reiterated his support for Medicare drug price negotiations. He has also stated his desire to streamline the FDA drug approval process, but without offering specifics on how he would like to see the process for generic drugs changed.

Scott Gottlieb, Trump's new FDA commissioner who has close links to the pharmaceutical industry and a conservative think tank, also criticized the costs and delays of generic drug approvals. In his first remarks to FDA staff, Gottlieb urged the agency to take "meaningful steps to get more low cost alternatives to the market, to increase competition, and to give consumers more options". He went on to say that the FDA should "make sure the generic drug process isn't being inappropriately gamed to delay competition and disadvantage consumers". [270] There are concerns, however, that changes to FDA procedures may harm the organization's ability to guarantee the efficacy, quality, and safety of approved drugs, including generics. [271] While it remains to be seen how these developments play out in practice, the available evidence suggests a willingness by the Trump administration to address price hikes and to ensure the availability of low-cost generics. It is critical, though, that any changes to FDA procedures do not undermine the agency's ability to ensure that approved generics, and new medicines, meet adequate regulatory standards.

Yet, at this writing, American health policy is extremely uncertain, [272–276] and there are reasons why changes to generic drug policies may prove elusive.

In January 2017, the Republican-controlled Congress approved a budget resolution that sets the stage for a major overhaul of the health care system, an action supported by Trump's health secretary. [274] In May, Republican lawmakers in the House of Representatives passed a bill to repeal and replace the Affordable Care Act. Among other things, the bill would eliminate tax penalties for Americans who do not have health insurance, remove a mandate for larger companies to offer affordable insurance to employees, increase annual limits on how much individuals and families can contribute to health savings accounts, cut taxes on high-income individuals and other groups imposed by the Affordable Care Act, repeal income-based tax credits and subsidies for out-pocket costs, remove caps on how much health insurers can charge older customers in monthly premiums, and cut federal funding for Medicaid, a publicly funded insurance program for low-income individuals and families. [277]

An analysis conducted by the non-partisan US Congressional Budget Office (CBO) estimated that the House bill would save the federal government over US$ 100 billion in a decade, but would also drastically increase the number of uninsured over the next 10 years and lead to hikes in health care premiums in the coming 3 years. [278] In many states, health care premiums and out-of-pocket costs would soar for chronically ill patients, and decline for young and healthy individuals. It is unclear what impact such changes would have on the generic drug market, with the CBO report silent on this issue.

The bill moved to the Senate for a debate and vote, where Republican lawmakers proposed an amended version of the legislation, which included only modest changes. However, the Senate bill was defeated in July 2017 following opposition from lawmakers on both sides of the aisle and key stakeholders, including the American Hospital Association and AARP. At the time of writing, Senate Republicans have indicated that they will postpone efforts to repeal and replace the Affordable Care Act, although Republican lawmakers can table new health care legislation at any point.

Moreover, the American Medical Association and the Pharmaceutical Research and Manufacturers of America, two of the largest and most influential lobbying organizations in the United States, continue to oppose government intervention in the generic drug market (**Box 2.1**), such as stronger substitution laws and measures to block large price increases. [50] Although both groups supported the Affordable Care Act, they did so only after having received assurances that there would be no price controls on medicines and no importation of cheaper medicines from other countries, among other conditions. [50]

2.3 Discussion

Addressing issues in the generic drug sector can enhance equitable access to medicines in countries where patients face high out-of-pocket drug costs, like Cyprus, [279] Greece, [280] and the United States. [281–283] Several studies indicate that patients who use generic medicines instead of brand name ones are more likely to adhere to treatment, [284,285] probably because of greater affordability, which can improve health outcomes. [284]

Yet, as our results show, there remain large differences in the usage and prices of generics in Europe and the United States. The barriers to market entry for generic companies vary between countries, as do pricing and reimbursement policies. Beyond such features of the market, there are differences in whether, and to what extent, patients and health care professionals perceive generic and branded medicines to be bioequivalent. [97, 98, 102] In some countries, negative perceptions of generics may have contributed to slower uptake of stronger prescribing and substitution measures.

Governments should apply coherent supply- and demand-side policies in generic drug markets. [2] There are interesting examples from smaller European countries, like Denmark, [286] Norway, [287] and Sweden, [286] which have achieved low generic drug prices. There is no one-size-fits-all solution, though, and there are different ways of achieving similar results. For instance, the United Kingdom is one of the few EU countries to forbid generic substitution. The electronic prescribing system in the United Kingdom, however, automatically prompts physicians to prescribe generic drugs when available. The country has one of the highest rates of generic drug use in the world, [288] although some analysts argue that substitution should still be made mandatory in the United Kingdom since physicians can be influenced by the marketing of drug companies. [289]

The appropriate steps to reduce generic drug prices and to boost demand for such medicines will vary between countries. For example, in nations with historically high rates of generic drug use and low generic drug prices, but which are experiencing generic drug shortages, like the United States, the emphasis should be on facilitating market entry for generic drug companies. In countries with low rates of generic drug use, like Greece and Italy, more should be done to improve the perceptions of generics among physicians, pharmacists, and patients.

Finally, it is important to trace the cultural, political, regulatory, and scientific issues influencing the adoption of generic drug policies. Historical analyses can help policy-makers avoid past stumbling blocks when trying to enact reform. [290] For example, in a comparative study of drug regulation in the United States and Germany, Arthur A. Daemmrich analyzed the evolution of the medical and political settings of each country during the 20th century, highlighting points of convergence and divergence. [222]

Daemmrich noted that legislative changes to prescription-drug laws in the United States often occur in response to public scandals. In Germany, by contrast, changes tend to follow protracted negotiations between lawmakers and stakeholders. [222] Drug regulation is highly politicized and adversarial in the United States, but much less so in Germany, where health care is widely seen as a right. [222] Such political and cultural factors help to explain differences in generic drug policies between countries. Moreover, pharmaceutical policies involve balancing the interests of the health care system with those of the pharmaceutical industry, with this balance varying between countries. [291]

2.3.1 Limitations

The price comparisons in this study have limitations. First, an assumption behind the Laspeyres index is that demand for prescription generic drugs is price inelastic (ie, change in the price of a generic does not affect demand). Although empirical data suggest that this is unlikely to be true, [41,292] other types of weighted indexes make assumptions that might be less likely to hold. [12,117,206] Laspeyres indexes are therefore commonly used to compare drug prices. [12,205,206,286,293]

Second, the IMS Health data do not reflect confidential rebates and discounts. The list prices (ie, official prices before discounts) may overestimate the actual prices paid for some products. [294] Even so, list prices are meaningful to payers since they are the starting point for discount negotiations. It is important to strengthen price transparency in generic drug markets, since opaque pricing makes it easier for drugmakers to charge the highest prices markets will bear.

Third, to aggregate price data across drug forms and strengths, it is necessary to use a common unit of volume. As Danzon and Kim explained, "the ideal unit would be a quality-constant ... course of therapy for a given drug, which should be applicable to all [forms] and strengths. Such ideal units are not observable". [206] In calculating prices per dose, we implicitly assume that a single dose of a drug, in any form or strength, is of equal therapeutic value to all patients. Some studies have instead calculated prices per gram of active ingredient, but this measure suffers from other limitations. [206]

Finally, we had to exclude 4.1% of the drugs in our sample due to missing information on dosage. These were mostly aerosol, cream, gel, injectable, and powder products. This might have influenced our findings if there were systematic differences across countries in the prices of those types of products. Still, the common sample accounted for a large share of total generic sales in every country but the United Kingdom (25%). The UK results should be interpreted with caution.

2.4 Conclusions

Greater use of generic medicines is one way to constrain growth in health care spending at a time when this is a political imperative everywhere. Yet across high-income countries, generic prices and market shares vary widely. This is despite the existence of effective policies to reduce delays in generic availability, stimulate price competition, and increase generic drug use. There are, however, signs of change. European payers and policymakers are showing growing interest in tendering to lower prices, something that seems to be effective.

Given the mixed progress so far, it is critical to understand why previous initiatives failed. Much can be learned from policy analyses, such as the one in this paper. These typically highlight the role played by special-interest groups in obstructing reform.

Finally, it is important to be realistic about what can be achieved. Despite some widely publicized examples of profiteering, discussed earlier, most of the growth in drug spending will continue to be driven by new medicines. For some treatments, like certain cancer immunotherapies, the complex manufacturing process means that the scope for off-patent products is still limited. Yet there are opportunities for significant cost savings from generics in many countries and, even where there are historically strong generic markets, like the United States, regulators, policymakers, and payers can do more to ensure timely generic drug availability.

Appendix A: Sample of Medicines

Table A. List of the 200 most-prescribed off-patent active ingredients in the European Union in 2013 (anatomical main group in parentheses).

Acetylcysteine (R/S/V)	Acetylsalicylic acid (A/B/N)
Aciclovir (D/J/S)	**Alendronic acid (M)**
Alfuzosin (G)	**Allopurinol (M)**
Alprazolam (N)	Alprostadil (C/G)
Amiodarone (C)	Amisulpride (N)
Amitriptyline (N)	**Amlodipine (C)**
Amlodipine / perindopril (C)	Amoxicillin (J)
Amoxicillin / clavulanic acid (J)	**Anastrozole (L)**
Apomorphine (G/N)	**Atenolol (C)**
Atorvastatin (C)	Azathioprine (L)
Azithromycin (J/S)	Beclometasone (A/D/R)
Betahistine (N)	Betamethasone (A/C/D/H/R/S)
Bicalutamide (L)	**Bisoprolol (C)**
Bisoprolol / hydrochlorothiazide (C)	Bromazepam (N)
Budesonide (A/D/R)	Buprenorphine (N)
Candesartan cilexetil (C)	Candesartan cilexetil / hydrochlorothiazide (C)
Carbamazepine (N)	Carbidopa / levodopa (N)
Carvedilol (C)	Cefpodoxime proxetil (J)
Ceftriaxone (J)	Cefuroxime axetil (J/S)
Cetirizine (R)	Ciclosporin (L/S)
Ciprofloxacin (J/S)	**Citalopram (N)**
Clarithromycin (J)	**Clindamycin (D/G/J)**
Clopidogrel (B)	Clozapine (N)
Codeine (N/R)	Codeine / paracetamol (N)
Cyproterone ethinylestradiol (G)	Desloratadine (R)
Desmopressin (H)	Desogestrel / ethinylestradiol (G)
Dexamethasone (A/C/D/H/R/S)	Diazepam (N)

Diclofenac (D/M/S)
Diltiazem (C)
Domperidone (A)
Doxazosin (C)
Drospirenone / ethinylestradiol (G)
Enalapril (C)
Erythromycin (D/J/S)
Esomeprazole (A)
Estradiol / norethisterone (G)
Ethinylestradiol / levonorgestrel (G)
Fenofibrate (C)
Finasteride (D/G)
Fluconazole (D/J)
Fluticasone / salmeterol (R)
Formoterol (R)
Gabapentin (N)
Gliclazide (A)
Hyaluronic acid (D/M/R/S)
Hydrochlorothiazide / lisinopril (C)
Hydrochlorothiazide / ramipril (C)
Hydrocortisone (A/C/D/H/S)
Ibandronic acid (M)
Indapamide (C)
Iodine / levothyroxine sodium (H)
Irbesartan (C)
Isosorbide mononitrate (C)
Ketoprofen (M)
Lansoprazole (A)
Leflunomide (L)
Letrozole (L)
Levetiracetam (N)
Levofloxacin (J/S)
Dienogest / ethinylestradiol (G)
Docetaxel (L)
Donepezil (N)
Doxycycline (A/J)
Ebastine (R)
Enalapril / hydrochlorothiazide (C)
Escitalopram (N)
Estradiol (G)
Ethinylestradiol / gestodene (G)
Felodipine (C)
Fentanyl (N)
Flucloxacillin (J)
Fluoxetine (N)
Fluvastatin (C)
Furosemide (C)
Galantamine (N)
Glimepiride (A)
Hydrochlorothiazide (C)
Hydrochlorothiazide / losartan (C)
Hydrochlorothiazide / valsartan (C)
Hydromorphone (N)
Ibuprofen (C/G/M)
Indapamide / perindopril (C)
Ipratropium bromide (R)
Irinotecan (L)
Isotretinoin (D)
Lamotrigine (N)
Latanoprost (S)
Lercanidipine (C)
Leuprorelin (L)
Levocetirizine (R)
Levothyroxine sodium (H)

Lidocaine (C/D/N/R/S)
Lorazepam (N)
Losartan (C)
Mesalazine (A)
Metformin (A)
Methotrexate (L)
Metoprolol (C)
Mirtazapine (N)
Montelukast (R)
Moxonidine (C)
Naproxen (G/M)
Nifedipine (C)
Ofloxacin (J/S)
Omeprazole (A)
Oxaliplatin (L)
Paclitaxel (L)
Paracetamol (N)
Paroxetine (N)
Perindopril (C)
Piracetam (N)
Pravastatin (C)
Prednisone (A/H)
Propranolol (C)
Rabeprazole (A)
Ranitidine (A)
Rilmenidine (C)
Risperidone (N)
Rosuvastatin (C)
Sertraline (N)
Simvastatin (C)
Lisinopril (C)
Lormetazepam (N)
Memantine (N)
Metamizole sodium (N)
Methadone (N)
Methylphenidate (N)
Metronidazole (A/D/G/J/P)
Molsidomine (C)
Morphine (N)
Naloxone / tilidine (N/V)
Nebivolol (C)
Nitroglycerin (C)
Olanzapine (N)
Ondansetron (A)
Oxycodone (N)
Pantoprazole (A)
Paracetamol / tramadol (N)
Penicillin (J/S)
Phenytoin (N)
Pramipexole (N)
Prednisolone (A/C/D/H/R/S)
Progesterone (G)
Quetiapine (N)
Ramipril (C)
Repaglinide (A)
Risedronic acid (M)
Ropinirole (N)
Salbutamol (R)
Sildenafil (G)
Spironolactone (C)

Sumatriptan (N)	Tamsulosin (G)
Temazepam (N)	Temozolomide (L)
Terbinafine (D)	**Testosterone (G)**
Timolol (C/S)	Tolterodine (G)
Topiramate (N)	Torasemide (C)
Tramadol (N)	Trazodone (N)
Trimebutine (A)	Trimetazidine (C)
Valaciclovir (J)	Valproic acid (N)
Valsartan (C)	**Venlafaxine (N)**
Verapamil (C)	Warfarin (B)
Zolpidem (N)	Zopiclone (N)

Note: The data included over-the-counter products, such as ibuprofen and paracetamol, if these were prescribed by a licensed health care practitioner. The active ingredients listed in bold were available in at least one form-strength combination in each country. These 80 ingredients comprised the common sample analyzed in this paper.

Source: Reproduced from IMS Health 2013 (Pricing Insights database); anatomical main groups from the WHOCC ATC/DDD Index (2015).

Appendix B: Description of IMS Health Data

Prices

IMS Health collects data on pack prices of medicines in European countries from government price lists, wholesaler invoices, and other validated sources. The company collects data at different levels of the distribution chain, based on data availability. IMS Health regularly—usually quarterly—audits price levels to obtain up-to-date price and volume data for each country. The company has internal quality assurance procedures.

When data are unavailable at a level of the distribution chain, IMS Health adopts the same approach taken by national health ministries, or the relevant authorities, to calculate ex-manufacturer and/or retail prices. In Spain, for example, IMS Health only collects data on retail prices, exclusive of value-added taxes, and then calculates ex-manufacturer prices based on official mark-ups regulated by the government (**Table A**).

Table A. Price build-up of medicines in Spain (2013).

Ex-manufacturer price (per pack)	Corresponding wholesale mark-up
€ 0.00 - € 91.63	7.6% of the wholesale price
€ 91.64 +	€ 7.54 (flat fee)

Ex-manufacturer price (per pack)	Corresponding retail mark-up
€ 0.00 - € 91.63	27.9% of the retail price (excl. VAT)
€ 91.64 - € 200.00	€ 38.37 (flat fee)
€ 200.01 - € 500.00	€ 43.37 (flat fee)
€ 500.01 +	€ 48.37 (flat fee)

VAT, value-added tax.

Source: Reproduced from IMS Health (2013).

In some countries, IMS Health collects data on wholesale prices (ie, prices charged by wholesalers to pharmacies), which they use to calculate ex-manufacturer and retail prices. For countries where distribution margins are unregulated, IMS Health estimates average margins, which can vary by product group.

Refer to IMS Health documentation for more information about data sources in each country.

Sales

IMS Health uses price and volume data to report aggregate sales, since a common denominator (eg, doses) is needed to compare prices across drug forms and strengths.

IMS Health calculates total sales of a product by multiplying the pack price by the number of packs sold (**Table B**). IMS Health relies on the latest price in a quarter. The company excludes value-added taxes to ensure comparability across countries. The sales figures do not reflect discounts, rebates, clawbacks, and other forms of confidential price reductions.

Table B. Example calculations for one quarter.

Product	Country	Retail price per pack	# of packs sold	Sales calculation	Total retail sales
A	Italy	€ 12.67	12,750	12,750 * € 12.67	€ 161,542.50
B	Sweden	15.50 kr	5,000	5,000 * 15.50 kr	77,500.00 kr
C	United Kingdom	£8.23	7,934	7,934 * £8.23	£65,296.82

Source: Reproduced from IMS Health 2013 (Pricing Insights database).

3

A comparison of generic drug prices in seven European countries: A methodological analysis

"When faced with a difficult question, we often answer an easier one instead, usually without noticing the substitution."

– Daniel Kahneman, *Thinking, Fast and Slow*

Key messages

- There are methodological challenges to comparing generic drug prices internationally.
- Estimates can vary widely depending on the methods used to calculate price indexes.
- Results can also differ depending on whether one looks at the prices charged by manufacturers or those charged by pharmacists.
- Health care stakeholders should be aware of the limitations of drug price comparisons.

Abstract

Context: Policymakers and researchers frequently compare the prices of medicines between countries. Such comparisons often serve as barometers of how pricing and reimbursement policies are performing. The aim of this study was to examine methodological challenges to comparing generic drug prices.

Methods: We calculated all commonly used price indexes based on 2013 IMS Health data on sales of 3,156 generic drugs in seven European countries.

Findings: There were large differences in generic drug prices between countries. However, the results varied depending on the choice of index, base country, unit of volume, method of currency conversion, and therapeutic category. The results also differed depending on whether one looked at the prices charged by manufacturers or those charged by pharmacists.

Conclusions: Price indexes are a useful statistical approach for comparing drug prices across countries, but researchers and policymakers should interpret price indexes with caution given their limitations. More research is needed to determine the drivers of price differences between countries. The data suggest that some governments should aim to reduce distribution costs for generic drugs.

MANY European countries are facing severe cost pressures on health care budgets, in part due to rising drug spending.[1] In this context, the savings from greater use of less expensive generic drugs can help pay for other health care services. Yet recent European Commission reports point to market failures for generic drugs. [10,295] It is therefore important to regularly compare generic drug prices in countries with similar income levels in order to give public payers a sense of whether they are over-paying for generic drugs or not. Such comparisons can serve as barometers of how pricing and reimbursement policies are performing. [4,117,207,293,296–305]

Previous comparisons of generic drug prices have found that prices varied markedly across European and North American countries. [8,12,142,205,286,287,306–309] The studies often relied on different methods and samples, however, making it difficult to compare findings. In addition, most analyses have had small sample sizes, which may have biased the results. Moreover, some earlier findings are likely out of date given how often pricing and reimbursement regulations are changed.

As important, the impact of distribution margins and taxes on generic drug prices has been underexplored, even though studies indicate that those costs can account for more than 90% of the retail price of a generic drug, ie, the price charged by pharmacists to patients or third-party payers. [295] Nearly all studies have looked at ex-manufacturer prices, ie, those charged by manufacturers to wholesalers, which do not account for distribution costs.

In this study, we compared the ex-manufacturer and retail prices of a large sample of generic drugs in seven European countries in 2013. We calculated all commonly used price indexes to outline the methodological challenges to comparing generic drug prices. It is critical that policymakers are aware of the advantages and limitations of these types of analyses, given that the results of price comparisons might be used to justify changes to pharmaceutical policies.

[1]This chapter was published: Wouters OJ, Kanavos PG (2017). A comparison of generic drug prices in seven European countries: A methodological analysis. *BMC Health Services Research*, **17**(242): 1-7.

3.1 Methods

We acquired 2013 data from IMS Health on volumes and sales of 200 off-patent ingredients in seven country with similar income levels: Belgium, Denmark, France, Germany, Italy, Spain, and Sweden. These ingredients were available in 3,156 strength-form combinations.[2] Volumes were recorded in doses and grams of active ingredient.[3] Sales were recorded in euros based on average exchange rates for the year.[4] We excluded 213 products (6.7%, 213/3156) with missing volume data.

We restricted our analysis to the 110 active ingredients sold in all seven countries, which accounted for 54 (Italy) to 87% (Sweden) of total spend on generics in each country. For each ingredient, we calculated the average price per dose and the average price per gram, both at the ex-manufacturer and retail levels. To do this, we divided total sales in euros across form-strength combinations by number of doses or grams sold.[5]

We then calculated four indexes—unweighted, Paasche, Laspeyres, and Fisher—using prices per gram and prices per dose. [206] Unweighted indexes (I_U) were calculated as

$$I_U = \frac{\sum_{i=1}^{n} p_i^c}{\sum_{i=1}^{n} p_i^b}$$

where p was the price of active ingredient i in the comparator country or the base country. We selected Germany as the base country, which takes a value of 100 in all indexes.

The other indexes were weighted to account for consumption patterns. Paasche (I_P) and Laspeyres indexes (I_L) were computed as

$$I_P = \frac{\sum_{i=1}^{n} p_i^c q_i^c}{\sum_{i=1}^{n} p_i^b q_i^c}$$

and

$$I_L = \frac{\sum_{i=1}^{n} p_i^c q_i^b}{\sum_{i=1}^{n} p_i^b q_i^b}$$

where q was the quantity in the comparator or base country (ie, doses or grams). Finally,

[2]The dataset excluded generic drugs sold in hospital pharmacies, off-patent originator drugs, parallel-traded products, and off-patent biological drugs.

[3]IMS Health refers to doses as "standard units".

[4]These values were calculated by multiplying the number of packs sold of each product by the corresponding prices on a quarterly basis. For these calculations, IMS Health relied on the latest prices in each quarter from validated sources, such as government price lists and wholesaler invoices, excluding value-added taxes.

[5]If sales of either <1,000 doses or <€ 1,000 were recorded in a country for a drug, we decided *a priori* to exclude the sales figures for that country, as was done in previous studies. [12, 117, 206] Those values may reflect data-entry errors or inconsistencies in reporting across countries.

Fisher indexes (I_F) were calculated as

$$I_F = \sqrt{I_P \cdot I_L}$$

3.1.1 Sensitivity and subgroup analyses

The results of Laspeyres indexes can vary depending on which country is selected as the base, since this determines which quantity weights are used. For instance, atorvastatin, a cholesterol-reducing drug, was only the 40^{th} most prescribed generic drug in Germany, in terms of number of doses sold, whereas it was one of the ten most prescribed generic drugs in three of the other countries. As a sensitivity analysis, we re-calculated all the price indexes with France as the base country.

Because medicines are traded goods, [310] we used exchange rate adjustments in the baseline analyses. However, the results of price indexes can differ depending on whether exchange rates or purchasing power parities (PPPs) are used to convert monetary values to a common currency. Since exchange rates are sensitive to currency fluctuations, we re-calculated all of the indexes based on PPP conversion factors. PPPs, which are measured in national currency units per US dollar, account for cross-country differences in the prices of goods and services. In this way, they equalize the purchasing power of different currencies.

Finally, we compared the prices of generic drugs in different therapeutic subgroups. To do this, we categorized the 110 active ingredients by anatomical main groups using the ATC/DDD system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology. **Table 3.1** shows the breakdown of active ingredients by group. We excluded ingredients that belonged to more than one group. For example, timolol is a beta blocker used to treat both high blood pressure (ATC group C) and glaucoma (ATC group S). We then compared the prices of the active ingredients belonging to the two largest groups in our sample: cardiovascular system drugs (n = 25) and nervous system drugs (n = 29). The subgroup analysis used exchange-rate conversions and Germany as the base country.

The full results of the sensitivity and subgroup analyses can be found in **Appendix A**.

Table 3.1: The breakdown of active ingredients in the common sample (n = 110) by anatomical main group.

Code	Anatomical main group	Count
A	Alimentary tract and metabolism	8
B	Blood and blood-forming organs	1
C	Cardiovascular system	25
D	Dermatologicals	0[a]
G	Genito-urinary system and sex hormones	7
H	Systemic hormonal preparations (excl. sex hormones and insulins)	1
J	Anti-infectives for systemic use	3
L	Antineoplastic and immunomodulating agents	4
M	Musculo-skeletal system	4
N	Nervous system	29
P	Antiparasitic products, insecticides and repellants	0[a]
R	Respiratory system	5
S	Sensory organs	1
V	Various	0
-	Belong to multiple anatomical main groups	22

[a] All D and P medicines belonged to multiple groups

Source: World Health Organization Collaborating Centre ATC/DDD index (2015).

3.2 Results

3.2.1 Ex-manufacturer vs. retail prices

Table 3.2 summarises the main results with Germany as the base country. Prices varied markedly across countries. Denmark and Sweden consistently had the lowest ex-manufacturer and retail prices among the seven countries, while Italy had the highest in most weighted indexes. In the Laspeyres (dose) index, for example, the Italian ex-manufacturer prices were, on average, 1.6 times the German ones and 2.6 times the Danish ones. **Figure** 3.1 (panel a) shows that Belgium, France, and Spain had higher ex-manufacturer prices than Germany, but the opposite was true at the retail level.

3.2.2 Unit of volume (doses vs. grams of active ingredient)

The results of the unweighted indexes fluctuated widely depending on which unit of volume was used (**Table** 3.2). By contrast, most of the weighted results remained similar across the two units of volume.[6] There were some exceptions: in the Laspeyres indexes, for example, the French ex-manufacturer prices were lower than those in Italy when doses were used, whereas they were higher when grams of active ingredients were used (**Table** 3.2).

3.2.3 Weighting (Laspeyres vs. Paasche vs. Fisher)

The Paasche indexes were always lower than the Laspeyres indexes at both the ex-manufacturer and retail levels (**Table** 3.2 and **Figure** 3.1 [panel b]). The Fisher results—which are the geometric means of the Laspeyres and Paasche indexes—fell between the latter two.

3.2.4 Base country

Figure 3.1 (panel c) shows that the Laspeyres values dropped in all countries, except Denmark, when the French weights were used.[7] This indicates that those drugs which were more highly consumed in France than in Germany were also cheaper in most of the other countries.

[6] For the common sample of 110 active ingredients, the average number of grams of active ingredient per dose ranged from 0.09 grams in Sweden to 0.19 grams in Spain.

[7] For ease of comparison to the other results, all prices are expressed in relation to those in Germany (index value = 100).

3.2.5 Currency conversion (exchange rates vs. purchasing power parities)

The results were largely unchanged when PPPs—rather than exchange rates—were used to convert sales in local currencies to a common unit. This suggests that variation in drug prices between these seven countries were, for the most part, not due to differences in the costs of goods and services.

3.2.6 Subgroup analyses

Figure 3.1 (panel d) shows the ex-manufacturer prices of cardiovascular system drugs and nervous system drugs. The amount of price variation differed across therapeutic groups. In the full sample, there was a 2.5-fold difference in prices between the countries with the highest and lowest prices. By comparison, there were 3.1 and 3.5-fold differences in the prices of nervous system and cardiovascular drugs, respectively. Germany had the second highest prices for nervous system drugs, whereas it had among the lowest prices for cardiovascular system drugs.

Table 3.2: Ex-manufacturer and retail prices with Germany as the base (2013).

	Belgium	Denmark	France	Germany	Italy	Spain	Sweden
Ex-manufacturer							
Unweighted-D	78.05	48.02	99.31	100	109.84	136.86	65.36
Unweighted-G	115.45	55.07	63.62	100	50.57	63.09	57.28
Laspeyres-D	136.67	61.11	144.46	100	156.66	134.47	85.7
Laspeyres-G	126.9	68.63	164.92	100	154.2	124.26	101.59
Paasche-D	108.75	34.38	87.07	100	105.59	78.32	56.5
Paasche-G	97.19	39.96	87.55	100	63.88	65.26	67.43
Fisher-D	121.92	45.84	112.15	100	128.62	102.62	69.58
Fisher-G	111.06	52.37	120.16	100	99.24	90.05	82.76
Retail							
Unweighted-D	70.97	48.96	98.38	100	117.57	129.61	52.91
Unweighted-G	104.09	58.36	57.03	100	56.97	62.75	47.49
Laspeyres-D	92.23	48.29	97.06	100	114.67	86.01	59.12
Laspeyres-G	87.29	54.93	114.85	100	112.28	79.22	69.87
Paasche-D	70.46	32.5	62.17	100	76.27	46.43	44.01
Paasche-G	63.99	37.28	62.92	100	47.73	40.55	52.69
Fisher-D	80.61	39.61	77.68	100	93.52	63.19	51.01
Fisher-G	74.73	45.25	85.01	100	73.2	56.68	60.68

D, doses; G, grams of active ingredient

Source: IMS Health 2013 (Pricing Insights database).

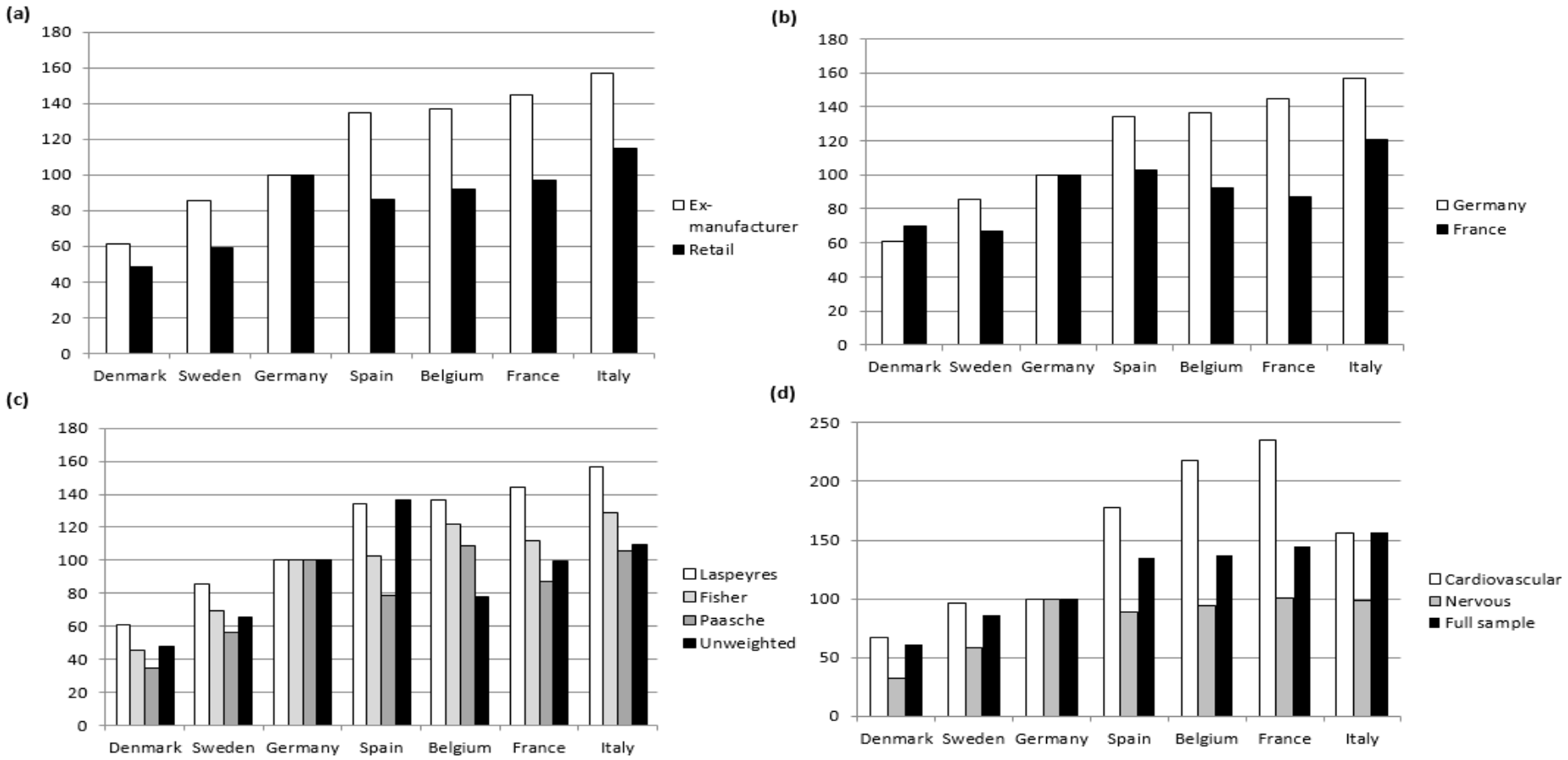


Figure 3.1: Results for different types of price indexes in 2013 with Germany as the base country.

Note: For ease of interpretation, the unit of volume is the number of doses in all the price indexes. **(a)** Comparison of retail and ex-manufacturer prices (n = 110) in a Laspeyres index. **(b)** Contrast of ex-manufacturer prices (n = 110) in a Laspeyres index with German versus French weights. **(c)** Ex-manufacturer prices (n = 110) in weighted and unweighted indexes. **(d)** Comparison of ex-manufacturer prices of cardiovascular system drugs (n = 25), nervous system drugs (n = 29), and all drugs (n = 110) in a Laspeyres index. (**Source**: IMS Health 2013, Pricing Insights database.)

3.3 Discussion

In this analysis, we explored differences in the ex-manufacturer and retail prices of generic drugs across seven countries in 2013 using various price indexes.

The ex-manufacturer and retail prices varied widely across countries. This is consistent with earlier studies comparing the prices of patented drugs at both levels. [295,303,304] More research is needed to disentangle the impact of supply- and demand-side policies, such as pricing, reimbursement, prescribing, and substitution rules, on the ex-manufacturer and retail prices of generics. [224] Prices variation is also likely due, in part, to differences in the regulation of wholesaler and pharmacy margins. [295,311]

There are various methods for comparing drug prices across settings, [206,312] and they often produce remarkably different results. For example, the ex-manufacturer Laspeyres index (dose) in **Table 3.2** suggests that the sample of generic drugs was about 60% more expensive in Italy than in Germany. On the other hand, the ex-manufacturer Paasche index (grams of active ingredient) indicates that the sample was about 35% cheaper in Italy than in Germany.

There were even larger differences between some of the weighted and unweighted indexes. It might be especially important to use weighted indexes when comparing generic drug prices, since studies suggest that these prices are closely linked to volume. [21,185] Earlier studies have shown that the results of unweighted and weighted indexes can differ sharply, [117,206] which is consistent with our findings. Extreme prices can skew the results of unweighted indexes, so these indexes are generally considered less reliable than weighted ones for comparing drug prices. [206]

There is no consensus on which weighting method is most appropriate for comparing drug prices, as each has advantages and disadvantages (**Box 3.1**). [206,302] Academic and government studies have variously calculated unweighted, [299,300] Fisher, [301] Paasche, [117,206] and Laspeyres indexes, [12,117,206,313] often using different units of volume and/or base countries. The likely reason why Paasche results are usually lower than Laspeyres results, a finding which has been reported in previous drug price indexes, [117,206] is that patients tend to consume more of the drugs that are cheaper in their countries. Therefore, when prices are weighted by local consumption, the indexes show lower average prices—relative to the base country—than when prices are weighted by consumption in the base country.

The unit of volume can influence the results if there are large, systematic differences between countries in the average strength per dose. [206] For example, previous studies have found that price index results for Japan vary significantly depending on whether number of doses or grams of active ingredient serve as the unit of volume. [12,117,205,206,296] The authors of those studies attributed this finding to the tendency of Japanese clinicians to prescribe higher quantities of lower-strength products.

Box 3.1: Key advantages and disadvantages of each type of price index for pharmaceutical products.

Unweighted index

1. *Pros*: It requires no volume data and is simple to calculate.
2. *Cons*: Unweighted indexes do not reflect consumption patterns. The results can be skewed by price outliers.

Laspeyres index

1. *Pros*: It assumes that the consumption pattern in the base country would remain the same even if it paid the prices observed in the comparator country, which, depending on the country, might be accurate. It only requires volume data for a single country.
2. *Cons*: The assumption above might not hold true. The results depend on the choice of base country.

Paasche index

1. *Pros*: It assumes that the consumption pattern in the base country would look exactly like that of a comparator country if both had the same prices, which, depending on the country, might be accurate.
2. *Cons*: The assumption above might not hold true. Also, a Paasche index requires volume data for all study countries.

Fisher index

1. *Pros*: Because it uses an average of the quantities in the base country and the comparator, the prices lie between those in Paasche and Laspeyres indices. This might be a good approach if one is unsure about the true price elasticity. The index also has certain theoretical advantages over the others. [206]
2. *Cons*: Conversely, depending on the true price elasticity, the results might be less accurate than those of a Paasche or Laspeyres index. A Fisher index also requires volume data for all study countries.

Despite such methodological challenges, it is still possible to glean useful information from price indexes. In particular, it is important to look for consistency across indexes. As an example, our results indicate that Denmark and Sweden had the lowest ex-manufacturer prices in nearly all weighted indexes, regardless of whether Germany or France served as the base country. This strongly suggests that generic drugs were cheaper in Denmark and Sweden in 2013 than in the other five countries. By contrast, the Italian ex-manufacturer and retail prices were among the highest in all weighted indexes. Ideally, the results of price indexes should be interpreted alongside other quantitative and qualitative data about the impact of individual policies on drug prices. On their own, price indexes do not provide causal evidence on the effects of pricing and reimbursement rules, generic substitution laws, and other factors on the prices of generic drugs.

The findings in this study raise questions which merit further research. Both Sweden and Denmark operate tender-like systems for generic drugs,[8] which may account for the low prices observed in each country. [314,315] Tendering refers to the bulk purchase of generic drugs from the manufacturers that offer the lowest prices. [140] More work is needed to understand the impact of tendering on drug prices, and whether any observed price reductions can be sustained over time. There is concern that relying only on tendering could create product shortages, drive generic drug firms out of business, and lead to higher generic drug prices over time. [140] There is little evidence, however, on the long-term effects of tendering.

It is also important to examine why there are large differences in the prices of drugs in various therapeutic areas, both within and between countries. Such variation may, in part, reflect market factors. For example, the marketing exclusivity for a drug can expire at different times across high-income countries depending on when the drug was approved in each jurisdiction. Also, some studies have observed an inverse relationship between the number of competitors in the market and generic drug prices. [45,187] The speed of generic entry, in turn, has been found to be correlated with how much brand-name firms record in revenue in the years leading up to patent expiry. [9,167] In other words, generic firms tend to prioritize more lucrative drug markets.

3.3.1 Limitations

This study has limitations, most of which are inherent to drug price indexes.

[8]National government authorities in Denmark and Sweden operate tender-like systems: the relevant authority in each country asks drug makers to offer their best prices, and, in most cases, the cheapest products are the only ones which public payers will reimburse. This bidding process is repeated every two and four weeks in Denmark and Sweden, respectively. Payers in Germany and Spain also tender for generic drugs, but the tender results were kept confidential in 2013. The data, therefore, did not reflect tendering outcomes in either country.

First, the data did not account for confidential discounts, which can be as high as 50% for some generic drugs in certain countries. All list prices may, therefore, not have corresponded to the actual prices paid. [294] However, if profits from discounts accrue to wholesalers or pharmacists, then list prices are more important to payers.

Second, Paasche and Laspeyres indexes are underpinned by assumptions about the relationship between generic drug prices and usage which may not always hold. Specifically, the results of Laspeyres indexes are valid if demand for prescription medicines is price inelastic. While empirical findings contradict this assumption, [41, 292] the Paasche index instead assumes that the consumption pattern in the base country would look exactly like that of the comparator country if both had the same prices. The latter assumption might be less likely to hold true, since there are differences between countries in standards of care, disease prevalence rates, prescription drug coverage, and patient preferences—all of which can affect demand. [206]

Third, by restricting the analysis to a common sample of drugs, we reduced the sample size. In some previous price indexes for patented drugs, researchers instead conducted a series of comparisons between the base country and one other country at a time, looking at the drugs available in both countries. Such comparisons, which are called bilateral analyses, maximize the sample size for each country pair. We chose to instead calculate what are known as multilateral indexes, which compare the prices of a sample of drugs available in all study countries. Multilateral indexes provide information on how prices compare across all the countries rather than just between each pair. While a common sample might over-represent older, internationally available products, [206] this is less of a concern when comparing generic drug prices. However, it is important to note that two countries with identical prices could show up as having differing price levels in a Paasche index if consumption patterns differ. Thus, multilateral price comparisons using Paasche indexes should be interpreted with caution.

Fourth, we used common units of volume to aggregate data across formulations of active ingredients. [206] In using prices per dose, however, we assumed that a dose of a drug provides the same therapeutic benefit to any patients, regardless of strength-form combination. By contrast, prices per gram of active ingredient are sensitive to the selection of drugs, given that drug strengths often vary considerably between drugs. [301] The price per defined daily dose is an alternative metric. A defined daily dose is the "assumed average maintenance dose per day for a drug used for its main indication in adults". [316] We could not identify this dose for each drug in our dataset, as we did not have information about drug indications. However, defined daily doses are not always of equal therapeutic value to all patients, and they may not accurately reflect consumption patterns. [206] For example, a defined daily dose is not adjusted for differences in the duration of treatment. They are, therefore, not necessarily a better

unit of comparison than doses or grams of active ingredient. [206, 316] Also, because defined daily doses are specified in terms of grams of active ingredient per day, indexes based on defined daily doses and indexes based on grams should generate similar findings if the average number of treatment days are fairly consistent across countries for most drugs. [117]

Fifth, the drugs were listed by active ingredient, and no information was available on the indications for which the drugs were prescribed. However, a prior study found that the results of price indexes were "virtually unchanged" when products were defined by active ingredient instead of active ingredient plus indication. [206]

Lastly, we had to exclude 6.7% of drugs (213/3,156) due to missing volume data.

3.4 Conclusions

Generic drug policy is an important topic given rising drug expenditures and concerns about the financial sustainability of many health care systems. More research is needed to better understand the causes of variation in the prices of generic drugs across countries. This will help to identify which measures are most effective at reducing prices. Our findings suggest that some countries should focus on containing the distribution costs for generic drugs.

There are a number of methodological issues that can arise when trying to compare drug prices internationally. Drugs often differ across countries in terms of names, pack sizes, formulations, strengths, and manufacturers. They can also vary in terms of whether they are sold over-the-counter or through prescriptions, and whether they are sold in hospital or retail pharmacies. There is a trade-off between matching all of these factors—which produces more accurate price comparisons of individual products—and the sample size.

Once a sample of drugs has been chosen, there are various ways of calculating price indexes to aggregate the data, each with its own advantages and disadvantages, as discussed in this paper. There is no gold standard for comparing drug prices. Our results showed that such comparisons are highly sensitive to the choice of method—for example, Laspeyres versus Paasche indexes—which is consistent with the findings of earlier studies of patented drugs.

Overall, price indexes are a useful statistical approach for comparing drug prices across countries, but policymakers and researchers should interpret price indexes with caution given their limitations.

Appendix A: Sensitivity and subgroup analyses

Table A. Ex-manufacturer and retail prices with France as the base country (2013).

	Belgium	Denmark	France	Germany	Italy	Spain	Sweden
Ex-manufacturer prices							
Unweighted-D	78.59	48.36	100	100.69	110.61	137.81	65.81
Unweighted-G	181.48	86.56	100	157.19	79.49	99.17	90.04
Laspeyres-D	106.44	80.64	100	114.84	138.8	117.96	77.23
Laspeyres-G	99.42	77.05	100	114.22	127.4	94.44	85.43
Paasche-D	98.02	29	100	69.22	91.58	68.71	51.07
Paasche-G	79.74	28.07	100	60.64	79.08	62.68	50.09
Fisher-D	102.14	48.36	100	89.16	112.74	90.03	62.8
Fisher-G	89.04	46.5	100	83.22	100.37	76.94	65.41
Retail prices							
Unweighted-D	72.14	49.77	100	101.65	119.51	131.74	53.78
Unweighted-G	182.51	102.33	100	175.35	99.89	110.03	83.27
Laspeyres-D	108.28	87.73	100	160.86	147.25	111.29	78.87
Laspeyres-G	101.04	84.89	100	158.94	134.96	89.03	86.43
Paasche-D	98.3	36.75	100	103.03	99.04	63.62	54.21
Paasche-G	79.61	35.29	100	87.07	85.97	57.72	52.45
Fisher-D	103.17	56.78	100	128.74	120.76	84.15	65.39
Fisher-G	89.69	54.73	100	117.64	107.71	71.69	67.33

D, doses; G, grams of active ingredient

Source: IMS Health 2013 (Pricing Insights database).

Table B. Ex-manufacturer and retail prices based on PPP adjustments with Germany as the base country (2013).

	Belgium	Denmark	France	Germany	Italy	Spain	Sweden
Ex-manufacturer							
Unweighted-D	74.39	37.15	94.28	100	114.45	157.94	51.18
Unweighted-G	110.04	42.6	60.39	100	52.69	72.81	44.86
Laspeyres-D	130.26	47.27	137.13	100	163.24	155.18	67.11
Laspeyres-G	120.95	53.09	156.56	100	160.67	143.4	79.55
Paasche-D	103.66	26.6	82.66	100	110.02	90.38	44.24
Paasche-G	92.63	30.91	83.11	100	66.56	75.32	52.8
Fisher-D	116.2	35.46	106.47	100	134.01	118.43	54.49
Fisher-G	105.85	40.51	114.07	100	103.41	103.92	64.81
Retail							
Unweighted-D	67.65	37.87	93.39	100	122.5	149.57	41.43
Unweighted-G	99.21	45.15	54.14	100	59.36	72.41	37.19
Laspeyres-D	87.91	37.35	92.14	100	119.48	99.26	46.29
Laspeyres-G	83.19	42.49	109.03	100	116.99	91.42	54.71
Paasche-D	67.15	25.14	59.01	100	79.48	53.58	34.46
Paasche-G	60.99	28.84	59.73	100	49.73	46.79	41.26
Fisher-D	76.83	30.64	73.74	100	97.45	72.93	39.94
Fisher-G	71.23	35.01	80.7	100	76.28	65.41	47.51

D, doses; G, grams of active ingredient; PPP, purchasing power parity

Source: IMS Health 2013 (Pricing Insights database).

Table C. Ex-manufacturer and retail prices of cardiovascular system medicines (n = 25) with Germany as the base country (2013).

	Belgium	Denmark	France	Germany	Italy	Spain	Sweden
Ex-manufacturer							
Unweighted-D	132.27	93.24	138.78	100	108.37	131.4	61.37
Unweighted-G	36.83	69.01	45.56	100	31.82	36.26	33.94
Laspeyres-D	218.08	67.45	235.22	100	155.92	178.09	96.41
Laspeyres-G	193.33	64.03	262.42	100	169.33	176.21	107.84
Paasche-D	186.92	48.96	161.27	100	128.38	130.94	64.06
Paasche-G	106.46	46.44	117.94	100	33.18	58.58	72.16
Fisher-D	201.9	57.47	194.77	100	141.48	152.7	78.59
Fisher-G	143.46	54.53	175.93	100	74.95	101.59	88.21
Retail							
Unweighted-D	90.57	69.55	99.8	100	86.25	88.17	48.71
Unweighted-G	24.12	44.57	30.43	100	23.9	23	25.4
Laspeyres-D	113.15	46.28	128.59	100	91.25	86.76	61.19
Laspeyres-G	99.94	44.82	143.99	100	99.15	85.93	68.32
Paasche-D	101.7	37.28	104.37	100	82.95	74.95	47.63
Paasche-G	63.24	36.23	77.73	100	24.45	36.06	53.52
Fisher-D	107.27	41.53	115.85	100	87	80.64	53.99
Fisher-G	79.5	40.3	105.79	100	49.23	55.67	60.47

D, doses; G, grams of active ingredient

Source: IMS Health 2013 (Pricing Insights database).

Table D. Ex-manufacturer and retail prices of nervous system medicines (n = 29) with Germany as the base country (2013).

	Belgium	Denmark	France	Germany	Italy	Spain	Sweden
Ex-manufacturer							
Unweighted-D	74.2	28.15	87.51	100	84.09	91.41	47.57
Unweighted-G	137.93	45.23	56.84	100	43.7	55.74	20.52
Laspeyres-D	94.62	32.29	100.38	100	98.14	89.11	58.15
Laspeyres-G	103.92	36.06	97.08	100	80.77	82.69	64.8
Paasche-D	102.02	27.7	93.4	100	118.6	87.31	51.84
Paasche-G	113.27	32.57	96.33	100	111.16	75.89	55.55
Fisher-D	98.25	29.91	96.83	100	107.89	88.21	54.9
Fisher-G	108.49	34.27	96.7	100	94.75	79.21	60
Retail							
Unweighted-D	65.19	31.71	77.06	100	91.51	85.08	40.67
Unweighted-G	124.59	50.17	50.38	100	50.17	55.89	18.27
Laspeyres-D	78.43	34.25	84.33	100	99.31	77.62	47.36
Laspeyres-G	86.15	37.94	83.98	100	82.6	72.55	53.61
Paasche-D	65.12	29.9	60.59	100	90.42	58.44	41.42
Paasche-G	64.49	33.97	66.05	100	82.54	53.66	45.16
Fisher-D	71.47	32	71.48	100	94.76	67.35	44.29
Fisher-G	74.53	35.9	74.48	100	82.57	62.39	49.2

D, doses; G, grams of active ingredient

Source: IMS Health 2013 (Pricing Insights database).

4

The impact of pharmaceutical tendering on prices and market concentration in South Africa over a 14-year period

"There are more profits in pharmaceuticals than in oil. My message to [drug companies] is that they are in a sector that is very sensitive. They mustn't fish from our troubled waters."

– Dr. Aaron Motsoaledi, *Minister of Health of South Africa (Dec. 2010)*

Key messages

- Tendering was linked to large price cuts for many medicines in South Africa.
- It did not appear to have an adverse effect on market concentration.
- Yet there has been a drop in the number of firms winning contracts over time.
- The South African government should improve its forecasts of drug demand.

Abstract

Context: The procurement of medicines through government tenders is increasingly common, yet little has been written about the impact of tenders on prices, competition, and supply security in the pharmaceutical sector. In this study, we investigated the South African tendering system for medicines, which has been in operation since 1982. The objective of this paper was to (i) outline a conceptual framework for analyzing the system and (ii) present evidence on its impact on prices and competition over the past 15 years.

Methods: We calculated Herfindahl-Hirschman indexes to measure market concentration in tenders issued between 2003 and 2016. We estimated price indexes to track how medicine prices evolved over this period.

Findings: Since 2003, there have been large price decreases for medicines in most therapeutic categories. For instance, the average prices of antiretroviral therapies, anti-infective medicines, small-volume parenterals, drops and inhalers, solid-dose medicines, and family-planning agents dropped by roughly 40% or more over this period. Many tender contracts in South Africa remained competitive over time, based on the Herfindahl-Hirschman results, with some notable exceptions. However, the number of different firms winning contracts decreased over time in most tender categories. Also, there were large discrepancies between the drug quantities the health ministry estimated it would need to meet patient demand and the quantities the ministry went on to procure during tender periods.

Conclusions: Tendering may be an effective policy to lower drug costs. South African government officials should monitor the availability and prices of medicines to ensure continued access to affordable medicines for patients, as it may be undermined by the decreasing number of firms winning contracts over time. Given the large discrepancy between forecasts and procurements, the government would benefit from improving the accuracy of its demand forecasts.

PHARMACEUTICAL tendering refers to the bulk purchase of medicines from suppliers at agreed-upon prices over contracted periods.[1] The procurement of medicines through government tenders is increasingly common in the face of budgetary pressures. [2,111,140,142,143,224,279,317–319] Tendering is a form of strategic purchasing of health care inputs, which the World Health Organization (WHO) defines as "active, evidence-based engagement in defining the service-mix and volume, and selecting the provider-mix in order to maximize societal objectives." [320] Put differently, strategic purchasing is "the on-going search for the best means to optimize health systems performance by deciding which interventions should be purchased, how they should be purchased and from what providers". [321] The strategic purchasing of medicines from pharmaceutical firms is vital for improving health system performance (ie, improve quality, efficiency, equity, and responsiveness of health care service provision [321]), promoting universal health coverage, and ensuring timely access to affordable medicines for patients. [322] **Figure 4.1** shows the relationships between purchasers, providers (eg, drug suppliers), government agencies, and patients during strategic purchasing.

Studies have looked at the impact of tendering on the prices of and spending on medicines sold in hospital pharmacies, [136–138,323,324] off-patent biologicals (ie, biosimilars), [135] vaccines, [139] and medicines sold in retail pharmacies. [62,129,141,144,325,326] The latter set of studies have generally found that the introduction of tenders was associated with large price decreases for generic medicines. In the Netherlands, for example, the prices of some generic drugs dropped by as much as 90% overnight in retail pharmacies when insurers first started issuing tenders, suggesting that tenders can scoop significant one-off savings from price competition. [129] Danzon and colleagues found, based on regression analysis of data from 37 low- and middle-income countries, that originator and generic drugs procured for international non-governmental organisations (NGOs) through tenders were priced, on average, 42% and 34% lower than the same products sold in retail pharmacies in these countries. [62] In China, where tendering at provincial level was introduced by 2010 in all regions through government-led bidding platforms, the national government reported that prices of essential medicines dropped by 17%, on average, between 2009 and 2011. [130]

However, such results cannot necessarily be generalized across therapeutic groups or medicine forms (tablets versus creams, for instance), and it is not clear whether subsequent tenders would sustain such low prices—or if prices would instead creep back up as manufacturers drop out of the market. The study periods of existing analyses have been short: all studies have examined six years of data or fewer, with the exception

[1]This chapter was published: Wouters OJ, Sandberg DM, Pillay A, Kanavos PG (2019). The impact of pharmaceutical tendering on prices and market concentration in South Africa over a 14-year period. *Social Science & Medicine*, **220**: 362-370. This chapter presents the submitted version of the paper. Some of the results and text were updated or re-analysed during the peer review process.

of one study which looked at data on medicines sold in hospital pharmacies over an eight-year period. [323] The majority of studies have examined at most four consecutive years of data, [62, 136, 138, 139, 144, 324, 327–332] with several of these studies looking at drugs sold in hospital pharmacies, biosimilars, or vaccines. Moreover, data from more countries, especially developing ones, are needed to determine which features of tendering systems are associated with lower prices.

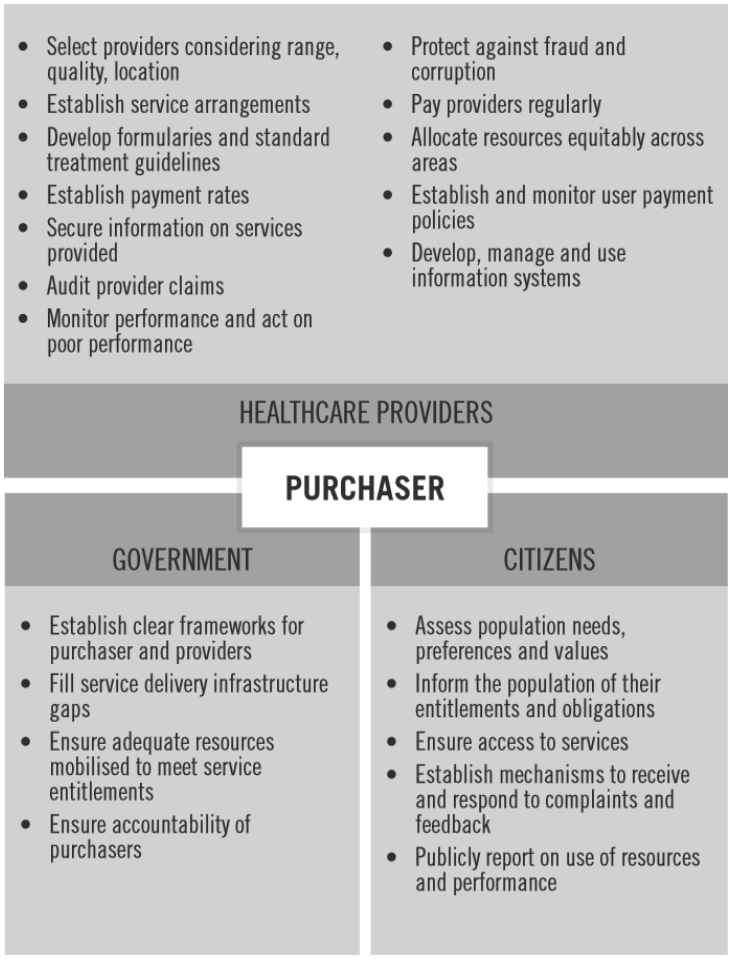


Figure 4.1: Key strategic purchasing actions in relation to purchaser, providers, government, and citizens.

Source: Reproduced from WHO (2016, p. 5), with permission. [321]

The short-term cost savings from tendering must be weighed against the potential adverse long-term effects on competition. Proponents of tendering claim it will result in prices which more accurately reflect costs of production. [129, 141] Critics claims tendering will drive losing firms out of business and lead to higher prices over time, as manufacturers exit the market. [70, 129, 140, 333] Yet there is little empirical evidence on the effects of tendering on the prices, competition, and supply security in the pharmaceutical sector over a period of six years or longer.

In this study, we investigated the South African tendering system for medicines, which has been in operation since 1982 in the public health care system. South Africa is categorized by the World Bank as an upper-middle-income country, ranked 32nd in the world in terms of gross domestic product (GDP). Its population of around 55 million faces one of the worst Gini coefficients globally at 0.634.

Total health expenditure is about 8.8% of GDP, according to recent government figures. About 48% and 52% of health spending is publicly and privately funded, respectively. By contrast, the average total health expenditure among member states of the Organization for Economic Co-operation and Development (OECD) is 12.4% and the average among low- and middle-income countries is 5.8%. Out-of-pocket health spending has steadily decreased over the past two decades in South Africa—from 29.9% of private expenditure in 1995 to 12.5% in 2014. [344] In 2015, pharmaceutical spending was estimated at 35.6 billion rand (US$ 2.6 billion), or US$ 47.3 per capita, with over 80% of this amount spent in the private sector. [345] Roughly two-thirds (63%) of prescriptions are filled generically in South Africa—about the same amount as in Denmark [94]—with generics accounting for 36% of total drug spending. [346]

South Africa is home to the largest number of people living with human immunodeficiency virus (HIV) in the world. The challenges for both health and economic development are vast. [347–351] It is against this backdrop that the health ministry is compelled to leverage procurement to maximize health outcomes within budgetary constraints.

The aims of this study were to: (i) outline a conceptual framework for analyzing the South African tendering system for medicines and (ii) present evidence on its impact on prices and competition in the country's pharmaceutical sector over the past 15 years. This is one of very few studies to present evidence on the effects of tendering over a period of six years or longer.

4.1 Methods

4.1.1 Documentary analysis

To outline a conceptual framework for medicine tenders in South Africa, we reviewed all tender contracts awarded by the national government between 2003 and 2016, as well as relevant legislation. We accessed all contracts via the National Treasury and National Department of Health (NDoH) websites, as well as in person from NDoH archives (Pretoria, South Africa). These contracts outline the conditions of award with which manufacturers must comply.

The conceptual framework was developed through internal discussions between the authors and senior officials from the NDoH. The framework outlines the key variables the NDoH considers when awarding tenders: price, equity, local economic growth, and supply security.

4.1.2 Quantitative data analysis

Tender contracts contain information on medicine prices, quantities, manufacturers, and lead times.[2] We calculated Herfindahl-Hirschman indexes (HHIs) to measure the degree of market concentration in each medicine tender issued by the government since 2003. A HHI is calculated by summing the squared market shares of every manufacturer

$$HHI = \sum_{i=1}^{N} s_i^2$$

HHIs are measured on a scale of 0 to 10,000, with a score of close to 0 indicating perfect competition, and a score of 10,000 indicating a monopoly. We adopted the US Department of Justice definition of market concentration: an HHI of 1,499 or lower indicates a competitive market, an HHI of 1,500 to 2,499 indicates a moderately concentrated market, and an HHI of 2,500 or higher indicates a highly concentrated market.

To track how the prices of medicines in each tender category evolved between 2003 and 2016, we calculated Laspeyres, Paasche, and Fisher indexes. [206, 208] Laspeyres indexes (P_L) are estimated as

$$P_L = \frac{\sum_j^n p_j^t q_j^0}{\sum_j^n p_j^0 q_j^0}$$

where p_{jt} is the price of product j at time t, and q_{j0} is the quantity of product j in the first period (measured in number of packs), and p_{j0} is the price of product j in the first

[2] A lead time is defined by the health ministry as "the [maximum permissible] time from submission of order to supplier to time of receipt by the department as confirmed by the Proof of Delivery document". [352]

period. Paasche indexes (P_S) are calculated as

$$P_S = \frac{\sum_j^n p_j^t q_j^t}{\sum_j^n p_j^0 q_j^t}$$

and Fisher indexes are quantified as

$$P_F = \sqrt{P_L \cdot P_S}$$

We restricted the price-index analysis to medicines included in every tender since 2003, which resulted in a sample of 7 anti-tuberculosis medicines, 39 anti-infective medicines, 5 family-planning agents, 32 oncological products, 117 small-volume parenterals, 32 drops and inhalers, 34 semi-solid medicines, 116 solid-dose medicines, 11 biological products, 12 large-volume parenterals, 20 liquids and spirits, and 8 antiretroviral therapies. We excluded data on diagnostic agents (ie, category 5 in **Box 4.1**) and packaging materials (ie, category 14), since these categories do not include medicinal products. As a sensitivity analysis, we dropped the first two tender contracts in each category to increase the sample size; these results are presented in **Appendix A**.[3]

We then examined prices changes for medicines in six therapeutic classes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, atypical antipsychotics, calcium channel blockers, proton-pump inhibitors, selective serotonin reuptake inhibitors, and statins. These medicines have been selected as "tracer" drugs in other studies of the impact of tendering on drug prices. [129, 141] We also analyzed price changes for oncology products which were priced at ZAR 300 or more per pack in 2003 and which have been included in every tender since then, as well as price changes for first- and second-line therapies for HIV and tuberculosis (TB).

For each of these medicines, we compared the estimated quantities in the respective tender contracts issued between 2012 and 2014 to the quantities the government went on to procure in each tender period.[4] Data on procured quantities were obtained from the "Republic of South Africa Pharmaceutical Database" (Jan. 2011 - Apr. 2017). This database is generated from a web-based reporting platform through which contracted suppliers provide information on all transactions (ie, orders received and delivered) to allow the government to monitor stock levels.

Finally, we compared the prices of these medicines to those in the private sector, which were obtained from the "Private-Sector Database of Medicine Prices" (Jan. 2009 -

[3]We excluded biological products, large-volume parenterals, liquids and spirits, and small-volume parenterals from the sensitivity analysis, as there have been four or fewer tenders issued since 2003 for these categories. Dropping the first two tenders would have resulted in short time series.

[4]We looked at the 2012 and 2014 tenders given the availability of complete data for each period. We excluded oncology products due to lack of data.

Apr. 2017).[5] If a product was sold by multiple manufacturers in the private sector then the lowest price was used for the comparison.

All data were analyzed in Stata 14 (StataCorp), with prices adjusted for inflation based on consumer price indexes. [353] We calculated weighted prices for split awards.[6]

[5]We did not examine the private-sector prices of medicines for HIV, acquired immune deficiency syndrome (AIDS), and TB, since these products are primarily sold in public facilities.

[6]For instance, if one firm was asked to supply 60% of the contracted volume at a price of 5 ZAR per pack, and another was asked to supply 40% of the volume at a price of 10 ZAR per pack, the weighted price was 7 ZAR (5*0.6 + 10*0.4).The method applied by the NDoH to split awards is outlined in the conceptual framework.

4.2 Results

4.2.1 Conceptual framework

In the South African public sector, the NDoH issues tenders to set the prices of essential medicines.[7] The NDoH divides medicines into fourteen categories (**Box 4.1**). The health ministry puts out a tender for all medicines in each category every two-to-three years. Tenders outline the quantity of each product that is needed, as well as other relevant information like lead times. The NDoH accepts bids from national and international manufacturers with the right to sell a product in South Africa.

Although tendering happens at national level, procurement is done independently by the nine provincial authorities. The estimation and quantification of volumes also starts at provincial level, with the NDoH playing an oversight role.

Demand is estimated based on usage in previous years and epidemiological forecasts.[8] The national and provincial health departments consider other relevant information, such as forthcoming changes to clinical guidelines which are expected to increase or decrease demand for products. The quantities are not binding: the NDoH can procure smaller or larger amounts of drugs than those specified on the tender contracts. However, provincial health departments must confirm that they have adequate funds to pay for the estimated quantities, in accordance with the Preferential Procurement Policy Framework Act of 2000. **Figure 4.2** illustrates the tendering process.

4.2.1.1 Price

Whilst an auction is designed to sell something so as to maximize profit for the auctioneer, tenders aim to encourage price competition for a specific item. The purchaser determines the rules of bidding and attempts to gain the greatest value for the lowest price, minimizing the cost faced by reducing the profit margins for the bidders. [354] Tenders are expected to reduce the prices of products being procured through economies of scale and scope through centralized procurement, as well as reduce administrative inefficiencies from fragmented distribution systems. These theoretical advantages require the buyer to exercise its monopsony power to purchase medicines on behalf of a large population. [130, 325]

[7] Medicines which have not yet been reviewed for inclusion on the essential medicines list are sometimes tendered for, as are certain high-volume products which have been excluded from the list for historical reasons.

[8] The forecasting procedures have changed over time; more simplistic methods were used in the past due to lack of data and resources.

Box 4.1: List of medicine tender categories in South Africa (2017).

1. Anti-tuberculosis medicines
2. Anti-infective medicines (ie, antibiotic, anti-fungal, antiprotozoal, and anti-viral agents)
3. Family planning agents
4. Oncology and immunological agents
5. Diagnostic agents and contrast media
6. Small-volume parenterals and insulin devices
7. Drops, aerosols, inhalers, and inhalants
8. Semi-solid-dose medicines (incl. powders)
9. Solid-dose medicines and transdermal patches
10. Biological preparations
11. Large-volume parenterals
12. Pharmaceutical liquids, alcohols, ethers, glycerin, and methylated spirits
13. Antiretroviral medicines
14. Pharmaceutical packaging materials

Note: The groupings have changed since 2003. For instance, between 2003 and 2008, the second group only included antibiotics. In 2009, the group was expanded to include other types of anti-infective medicines.

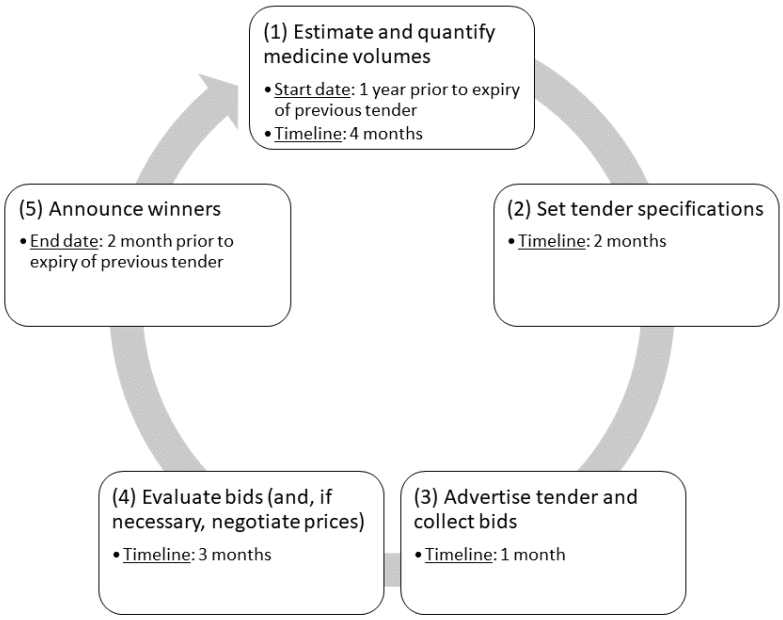


Figure 4.2: Overview of tendering steps and duration.

Note: The timeline is indicative, and durations may vary. In the past, administrative inefficiencies on the part of the National Department of Health have occasionally resulted in delays in the transition between tender contracts. In such cases, outgoing firms have been asked by the health ministry to supply medicines beyond their contracted periods, which increases the risk of supply disruptions.

In a basic tender model, the buyer awards each contract to the supplier offering the lowest price. Bids in public tenders are usually sealed, meaning bidders do not know the prices offered by competitors, unless there is collusion. [137] If the award is based solely on price, and if there are enough competitors, each supplier is incentivized to bid the lowest price at which it still makes a profit. This would make the supplier indifferent as to whether the tender is won or not.[9]

The NDoH, however, also considers other variables than price when awarding tender contracts, as outlined in the conditions of award. The winning bid will be the one that maximizes the utility of the NDoH, defined as

$$U = P + V$$

[9]For patent-protected products sold by a single manufacturer, the tendering process is effectively a negotiation: if the health ministry concludes that a bid is unreasonably high, it will ask for a price reduction. This ad hoc assessment is largely based on the prices of products in the same therapeutic class and the estimated budget impact. The NDoH uses the lowest price in the private sector as an upper limit. In 2010, the government started comparing the prices of single-source products with those in other countries to ensure that it does not overpay for these products. For HIV drugs, for instance, the health ministry looks at countries with comparable demand, whereas for oncology products it looks at countries with low prices from the same suppliers.

where P refers to price and V refers to a value function. Emphasis on V often means the purchaser pays a premium P.

In the following sub-sections, we examine the parameters of the value function, V, for the South African government when it procures medicines.[10,11]

4.2.1.2 Equity

In South Africa, the Preferential Procurement Policy Framework Act of 2000 requires the government to use tenders to redistribute wealth and opportunities to certain groups to redress past inequalities. This is given legal and binding expression for all tender contracts worth more than ZAR 1 million in the country. For these tenders, a 90/10 points system determines the winner.

First, the firm offering the lowest price automatically receives 90 points. Points for other firms are allocated based on the formula

$$P_s = 90\ (1 - \frac{B_t - B_{min}}{B_{min}})$$

where P_s is the points scored, B_t is the bid by supplier t, and B_{min} is the lowest bid. In this way, each firm receives a deduction which is proportional to their distance from the lowest bid.

Second, the remaining 10 points are allocated based on "preference scores", as per the rules set out in the Broad-Based Black Economic Empowerment Act of 2003. In brief, each company is rated on a 10-point scale based on criteria, such as the proportion of equity owners that belong to previously disadvantaged racial groups under Apartheid and the proportion of the management team that belong to these groups.[12] This information is provided by individual companies with supporting documentation. The scores may be audited by accredited verification agencies. This system is meant to provide a transparent and predictable way to facilitate structural economic change.[13]

[10]The Medicines and Related Substances Control Act 101 of 1965, the Public Finance Management Act No. 1 of 1999, the Preferential Procurement Policy Framework Act of 2000, the South African National Drug Policy of 1996, the Pharmacy Act 53 of 1974, and the Health Act 63 of 1977 outline the terms and conditions for the registration, manufacturing, distribution, and consumption of medicines in the country. Tendering procedures must adhere to these laws and their subsequent amendments.

[11]Ordinarily, when goods are required by multiple South African government departments, tenders are administered by the National Treasury. Until 2011 this was the case with pharmaceuticals and medical devices, which were required by the NDoH, Department of Correctional Services, and the South African Military Health Service. In 2011, however, the NDoH gained control of the tender process for all medicines used in the public sector.

[12]Between 1994 and 2000, factors like previous disadvantage were evaluated and included to varying degrees in all centralized tenders, including those for pharmaceuticals, on an ad hoc basis. With the introduction of the Preferential Procurement Policy Framework Act of 2000, the applicable formulas became applied more transparently and systematically to all government procurement.

[13]It is outside the scope of this paper to discuss the merits and demerits of this employment equity scheme. Bolton [355] analyzed the legal aspects of procurement in South Africa, including the complexity of

As such, the utility function is

$$U = 0.9P + 0.1B$$

where B is the empowerment score.

4.2.1.3 Local economic growth

Since 2011, pharmaceutical tenders in South Africa include a "local designation" criterion for selected products: the health ministry is willing to pay a premium corresponding to up to 10 points to local drug makers for these items.[14] This is part of a broader move, under the National Development Plan 2030, to promote local economic growth, industry diversification, job creation, inequality reduction, and a positive trade balance. [364] The most recent Industrial Policy Action Plan (2017/18-2019/20) named the pharmaceutical sector as an area of local strategic importance for state investment.

Local designation is also meant to strengthen medium to long-term supply security, as the Department of Trade and Industry (DTI) is concerned about the fragility of global politics and economics and the risk of supplies being terminated. [365] Currently, South Africa imports about 95% of active pharmaceutical ingredients sold in the country, including all ingredients for antiretroviral and tuberculosis medicines. [337]

Local designation alters the weights in the value function for designated products

$$U = 0.8P + 0.1B + 0.1I$$

where I is local industry status. Thus, the NDoH is willing to pay a premium of up to 20 points for designated medicines supplied by local companies with high empowerment scores.

4.2.1.4 Supply security

In a winner-takes-all tender, where a single company is asked to supply a medicine for the duration of the contract, the risk of supply disruptions, intuitively, increases. [134] In the case of a supply disruption, the government can buy off-contract from another supplier, but this comes with additional financial and transactional costs. Theoretical studies indicate that the splitting of awards can be economically advantageous for buyers when considering a whole portfolio of products being procured if it reduces the occurrence of supply disruptions and the associated costs. [366–369]

balancing cost-effectiveness and equity goals. Much has been written internationally about the role of state procurement as a tool to achieve policy objectives. [356–363]

[14] A product cannot receive a local designation if the health ministry deems there is a potential risk to supply security. The national health ministry sometimes allows local manufacturers to match the lowest price for designated products.

To reduce the risk of supply disruptions, the health ministry sometimes splits contracts between multiple manufacturers. Splits are based on overall points scored. If two manufacturers score equal points, the award is split evenly (50-50). If the difference in points is between 0.1 and 5, the award is split 60-40, with the higher-scoring firm asked to supply the larger quantity. If the difference is 5.1 to 10 points, the split is 70-30. And if the difference is 10.1 to 20 points, the split is 80-20. This means that the health ministry is willing to pay an additional premium of up to 20 points to secure multiple sources of some medicines.[15]

The health ministry adheres to the formula for splitting awards, unless a manufacturer reports capacity constraints.[16] In such cases, the ministry may deviate from this algorithm at its discretion. The NDoH generally also splits awards, regardless of point differentials, in three other situations: (i) the required volume is high, meaning there is a heightened risk of supply disruptions, (ii) the product is of strategic importance for the country (eg, first-line antiretroviral drugs used to treat HIV and AIDS), or (iii) the highest scoring bidder had poor performance history in the previous tender.

4.2.1.5 Summary

Continuing with the simple formulaic representation of interests, a full utility function from a health system and industrial perspective can be written as

$$U = P + V(B, I, S)$$

That is, the best tender outcome would be one that achieves the lowest possible price, considering broad-based black economic empowerment (B), preference for local industry (I), and supply security (S).[17]

Once a tender has been awarded, the winning bidder enters into a contract with the NDoH based on the conditions specified in the tender advertisement. The NDoH manages the relationship, ensuring the supplier complies with these conditions. In this way, public service tenders differ markedly from commercial auctions: rather than a one-off economic transaction, service provision requires the purchaser to continually navigate issues with high political and economic stakes.

In any contractual relationship, it is important to allow for risk sharing to deal with exogenous shocks that affect production costs and demand. In South Africa, tender

[15] If the difference in points exceeds 20, the health ministry will occasionally still split the award 90/10.

[16] The health ministry sometimes splits contracts between three or more firms, at its discretion, while taking into consideration the price and logistical implications of such splits.

[17] Product quality and due diligences are pre-selection criteria which are not considered in the bid evaluations. It is worth noting, though, that the Global Fund does not consider the South African Medicines Control Council to be a "stringent regulatory authority", as per the fund's Quality Assurance Policy for Pharmaceutical Products from July 1, 2009.

prices are eligible for adjustments every six months for exchange-rate fluctuations.[18] The health ministry strives to be responsive to changes in exchange rates, while minimising the administrative burden from frequent price updates. Previously, manufacturers could also claim adjustments for increases to production costs, such as changes to the prices of active ingredients sourced abroad, with adequate documentation.[19] The health ministry eliminated price adjustments for changes to cost structures in 2013 to reduce gaming among drug manufacturers.

Figure 4.3 shows a timeline of important events and milestones affecting the tendering system since the fall of Apartheid in 1994.

[18] Due to extreme exchange-rate fluctuations in the South African rand in recent years, an optional 3-monthly adjustment was implemented in February 2016 if variance to the base rate exceeded 10%.

[19] Each bidder must provide a breakdown of costs: raw materials, active pharmaceutical ingredients, inactive ingredients, formulation and packaging, logistics, and gross profit margin. Bidders must also disclose the sources of active ingredients so that the health ministry can evaluate the risk of supply disruptions.

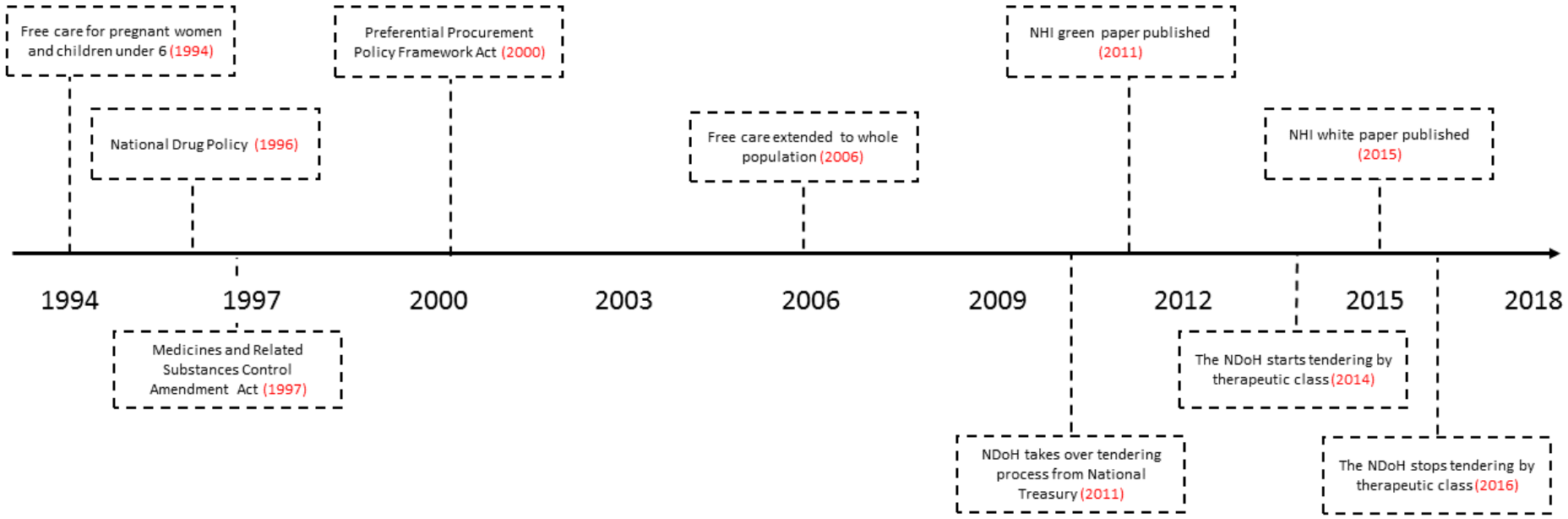


Figure 4.3: Key events in the South African health care system (1994 - present).
Source: Authors based on [335, 347, 370]

4.2.2 Tender outcomes

4.2.2.1 Overview

Between 2003 and 2016, the South African government tendered for 7,645 products (2,198 unique products), ranging from 63 biological products to 3,004 solid-dose medicines. The two largest categories, solid-dose and anti-infective medicines, accounted for more than half the products (50.2%, 4,345/8,655). The average price per pack during this period was ZAR 283.24, and the median price was ZAR 46.09.[20] The cheapest product was a lubricating jelly (2.5 g sachets) priced at ZAR 0.36 per pack in 2003. The most expensive product was a human coagulation factor VIIa concentrate (5 mg injection) priced at ZAR 63,925.21 per pack in 2016.[21]

Table 4.1 shows the projected budget impact of tenders issued between 2003 and 2016, based on the prices and estimated quantities listed in contracts. The value of tenders in the public sector roughly doubled between 2004-2005 and 2014-2015, reaching ZAR 27.3 billion. Most of this increase was driven by spending on medicines in three categories: solid-dose, antiretroviral, and tuberculosis therapies. Estimated spending on solid-dose drugs rose by 65% (4.73/2.87 billion) in real terms between the first and most recent tenders, while it increased by 124% (14.19/6.33) for antiretroviral medicines. Spending on tuberculosis medicines went up by roughly 49% (0.94/0.63) over this period. In most other categories, expenditures remained similar over time or, in a few cases, decreased slightly.

Volumes have increased over time in all contracts (authors' calculations). For solid-dose tenders, for instance, an estimated 1.1 billion kg of active ingredients (3.1 billion defined daily doses) were procured in 2003, compared to 2.7 billion kg in 2016 (9.4 billion defined daily doses).[22]

There has been an increase in the number of split contracts. From 2003 to 2010, the NDoH issued 195 split contracts between as many as seven firms. Since 2010, it has awarded 218 split contracts between as many as six firms. Between 2003 and 2016, most split contracts were awarded in one of six categories: anti-infective (94 split contracts), family-planning (21), oncological (25), small-volume-parenteral (29), solid-dose (185), and antiretroviral medicines (21).

[20] All currencies are reported in 2017 rand.

[21] By comparison, 7,546 unique products were sold in the private sector between 2009 and 2016 at an average price of ZAR 1,120.35 per pack, and a median price of ZAR 170.26. The most expensive product was ipilimumab (5 mg/ml intravenous therapy), priced at ZAR 243,448.67 per pack in 2015.

[22] Excluding combination products with multiple active ingredients, as well as minerals, proteases, saccharins, and vitamins.

Table 4.1: Estimated budget impact of each tender in billions of ZAR (2003-2016).

	2003/04	2005/06	2007/08	2009/10	2011/12	2013/14	2015/16
Anti-tuberculosis medicines	-	-	0.63	0.17	0.60	1.05	0.98
Anti-infective medicines	2.08	2.45	1.16	2.53	1.23	1.64	2.07
Family planning agents	0.87	0.56	0.45	0.31	0.38	0.27	0.32
Oncological products	0.42	0.76	0.46	0.50	0.57	0.38	0.42
Small-volume parenterals	-	-	2.16	1.72	1.45	1.91	-
Drops and inhalers	-	0.66	0.68	0.86	0.70	0.79	-
Semi-solid medicines	0.48	0.59	0.69	0.71	0.53	0.58	-
Solid-dose medicines	2.87	2.85	4.06	3.32	3.14	2.95	4.73
Biological products	-	-	-	-	0.69	0.93	0.84
Large-volume parenterals	-	-	0.92	-	0.56	0.96	-
Liquids and spirits	-	-	0.59	0.20	1.10	0.68	-
Antiretroviral therapies	6.33	-	6.41	5.29	-	6.66	14.84

4.2.2.2 Herfindahl-Hirschman indexes

Between 2003 and 2016, 183 different companies were awarded at least one tender contract. More than half the contracts (50.6%, 4402/8701) were awarded to 13 companies: Aspen Pharmacare (1,021 contracts), Adcock Ingraham (759), Fresenius (366), Pfizer (325), Sanofi-Aventis (277), Sandoz (264), GlaxoSmithKline (243), Be-Tabs Pharmaceuticals (233), Novartis (227), Biotech Laboratories (192), Roche (187), Barrs Pharmaceutical Industries (158), and Janssen (150). Five of these firms (Aspen, Adcock Ingraham, Be-Tabs Pharmaceuticals, Biotech Laboratories, and Barrs Pharmaceutical Industries) are South African drug manufacturers which mostly produce generic products.[23]

Table 4.2 shows the HHIs for each tender since 2003. The results indicate that many markets have stayed competitive over time, including those for solid-dose, semi-solid, oncological, and anti-infective medicines. For instance, the solid-dose tender had an HHI of 836 in 2003, compared to 1,174 in 2016. The market for antiretroviral therapies grew increasingly competitive over time.

The markets for biologicals, drops and inhalers, large-volume parenterals, anti-TB medicines, and family-planning agents were highly concentrated in most years. The largest percentage increases between the earliest and latest tenders occurred in the markets for semi-solid medicines (778 to 1,848 between 2003 and 2014) and family-planning agents (1,439 to 2,666 between 2003 and 2015). The market for family-planning agents was the only one to go from highly competitive to highly concentrated at any point over the past 15 years.

The number of manufacturers winning at least one contract has decreased over time in most categories. For example, the number of winners in the solid-dose tender dropped from 51 to 35 between 2003 and 2016, while the number of winners in the oncological tender fell from 25 to 13 during this time (**Table** 4.2).

[23] Be-Tabs Pharmaceuticals was acquired by the Indian drug firm Ranbaxy Laboratories in 2006.

Table 4.2: Herfindahl-Hirschman indexes for each tender (2003-2016) with number of different winning firms in parentheses.

	2003/04	2005/06	2007/08	2009/10	2011/12	2013/14	2015/16
Anti-tuberculosis medicines	-	-	4173 (6)	3513 (4)	3828 (6)	5508 (10)	5233 (9)
Anti-infective medicines	1467 (25)	1376 (28)	1735 (27)	1513 (24)	1340 (22)	959 (28)	783 (24)
Family planning agents	1439 (16)	2616 (9)	2544 (9)	2847 (9)	3395 (7)	2387 (6)	2666 (7)
Oncological products	939 (25)	772 (28)	855 (28)	865 (25)	1093 (20)	1308 (14)	1211 (13)
Small-volume parenterals	-	-	1840 (39)	1020 (30)	1062 (25)	936 (28)	-
Drops and inhalers	-	2623 (19)	4905 (17)	3176 (14)	3119 (16)	3136 (11)	-
Semi-solid medicines	778 (38)	1433 (33)	938 (36)	1018 (36)	1381 (30)	1848 (22)	-
Solid-dose medicines	836 (51)	742 (51)	687 (49)	1017 (54)	961 (47)	1099 (38)	1174 (35)
Biological products	-	-	-	-	3684 (7)	2982 (6)	2725 (6)
Large-volume parenterals	-	-	4801 (15)	-	5517 (8)	5969 (4)	-
Liquids and spirits	-	-	882 (25)	2021 (15)	1949 (32)	1307 (18)	-
Antiretroviral therapies	2701 (7)	-	2758 (9)	2431 (9)	-	1440 (14)	2054 (8)

Note: A Herfindahl-Hirschman index of 1,499 or lower indicates a highly competitive market, a score of 1,500 to 2,499 indicates a moderately concentrated market, and a score of 2,500 or higher indicates a highly concentrated market.

4.2.2.3 Price indexes

Figure 4.4 shows price trends by tender category. The results were largely consistent across the three types of price indexes.

Trends varied between categories. The prices of antiretroviral therapies, oncological products, small-volume parenterals, and solid-dose medicines fell consistently over time. For example, the Laspeyres results indicate that the prices of medicines in the oncological tenders dropped by an average of 61% between 2003 and 2016, while the prices of antiretroviral therapies decreased by an average of 78% between 2004 and 2015.

The prices of anti-infective medicines, drops and inhalers, and family-planning agents decreased by roughly 50% between the first and last tenders, but with price increases in some of the intervening years. The prices of anti-TB and semi-solid medicines only dropped by around 15% over this period, whereas the prices of biological products, semi-solid medicines, and liquids and spirits remained stable.

The figure shows spikes in the prices of anti-infective and solid-dose products in the most recent tenders. The NDoH stopped tendering by therapeutic group in the 2016 solid-dose tender, which may account for part of this increase. There have also been global shortages of benzathine penicillin, which may explain the price increases for anti-infective medicines in the 2013 and 2015 tenders.

The results of the sensitivity analysis (**Appendix A**) are similar to those shown in **Figure** 4.4.

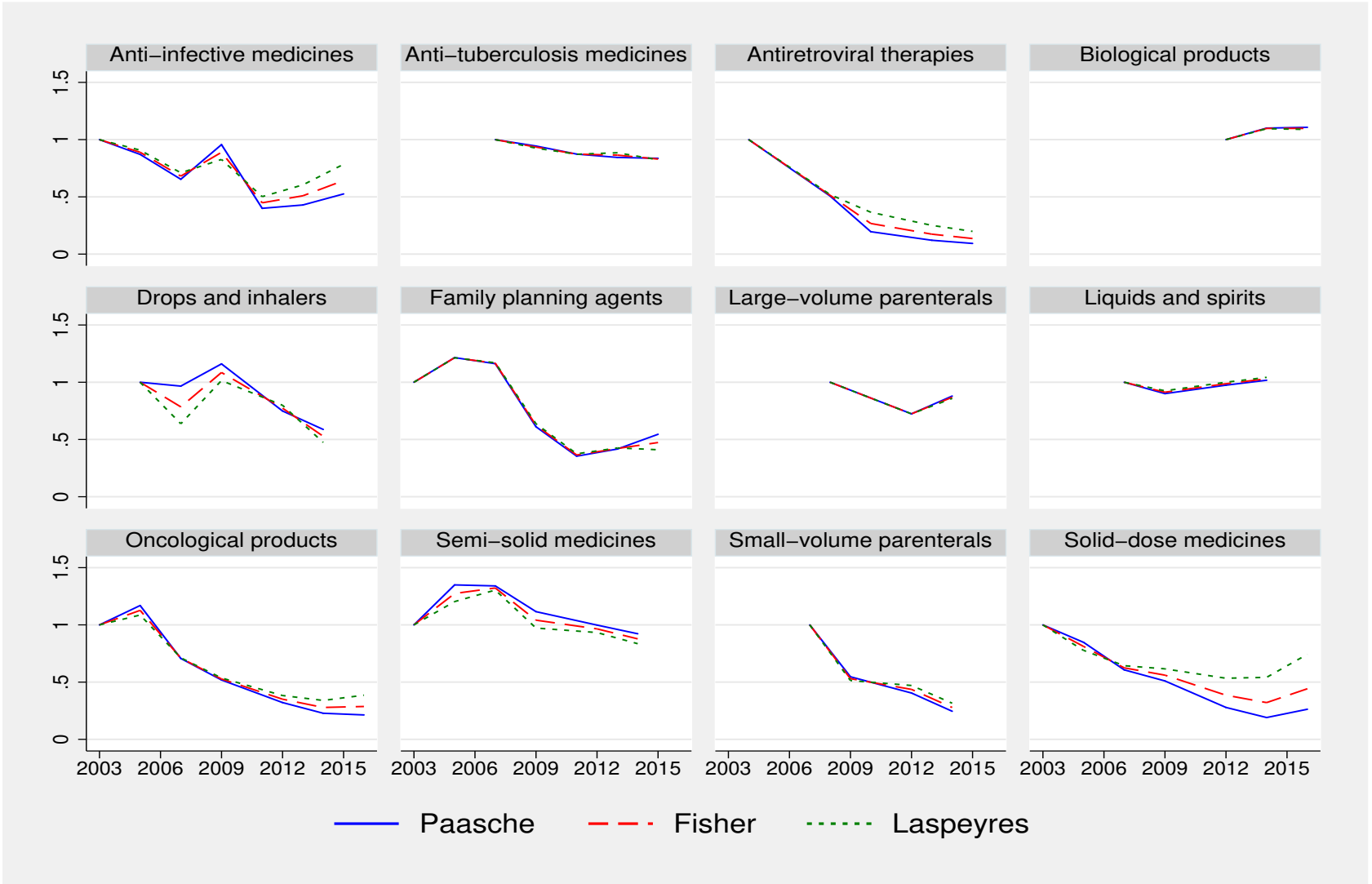


Figure 4.4: Price trends by medicine category (2003-2016).

4.2.2.4 Sub-group analyses

Table 4.3 presents the prices of solid-dose products in seven therapeutic classes: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, atypical antipsychotics, calcium channel blockers, proton-pump inhibitors, selective serotonin reuptake inhibitors, and statins. The prices of all products in these classes (2003-2016) can be found in **Appendix B**.

The prices of nine products fell by more than half upon generic entry: amlodipine 5 mg (80% drop in price), amlodipine 10 mg (71%), atorvastatin 10 mg (74%), atorvastatin 20 mg (82%), pravastatin 20 mg (57%), risperidone 2 mg (95%), risperidone 3 mg (96%), simvastatin 10 mg (76%), and simvastatin 20 mg (65%). The prices of citalopram 20 mg, clozapine 25 mg, and clozapine 100 mg fell by 40%, 45%, and 35% respectively. These decreases were sustained over time.

All strength-pack-size combinations of enalapril and fluoxetine were already available in generic versions in 2003. The prices of both ingredients remained low over the 15-year period, with the exception of an increase in the prices of both fluoxetine products in 2016.

Table 4.4 shows the prices of all first and second-line therapies used to treat TB. The prices of ethambutol (400 mg, 60 tablets) and rifampicin (150 mg) increased between 2007 and 2015, while the price of most strength-form combinations of isoniazid and pyrazinamide remained stable. The prices of ethionamide went down over this period.

Table 4.5 displays the prices of 20 oncology products with a high budget impact. Nine of the products became available in generic versions between 2003 and 2016.[24] The prices of four products (docetaxel 20 mg, docetaxel 80 mg, gemcitabine 200 mg, and gemcitabine 1g) decreased by more than 40% when the first generic hit the market. Prices of the other five products fell by between 15% and 35%, with the exception of mercaptopurine 50 mg which increased in price by 2% the year a generic entered the market.

Table 4.6 lists the prices of all first and second-line therapies for HIV and AIDS. The prices of most of these products dropped considerably between 2004 and 2015. Between 2004 and 2010, efavirenz was the antiretroviral therapy with the largest budget impact. Efavirenz tablets of various strengths accounted for 29% of the total value of the antiretroviral tender in 2004, 35% in 2008, and 25% in 2010. However, the percentage dropped to 11% in 2013 and 3% in 2015, when the combination therapy efavirenz/emtricitabine/tenofovir became available and captured 72% and 46% of the market, respectively.

[24] Six products were already available as generics in 2003.

Table 4.3: Changes in prices (ZAR per pack) of selected solid-dose medicines (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Amlodipine	5	30	109.96	34.63	6.78	4.13	2.93	2.41	3.19
Amlodipine	10	30	252.15	92.65	26.67	6.77	3.88	3.44	4.23
Atorvastatin	10	30	210.44	55.23	49.25	36.32	16.30	12.39	11.10
Atorvastatin	20	30	381.07	67.97	60.61	44.82	22.73	22.93	17.66
Citalopram	20	30	72.04	43.31	16.92	9.76	9.36	7.08	8.00
Clozapine	25	100	183.77	103.12	84.57	46.15	39.92	34.29	36.10
Clozapine	100	100	463.26	268.12	219.88	143.12	123.81	110.38	115.60
Enalapril	5	30	5.40	3.98	3.21	3.36	2.99	2.94	3.13
Enalapril	10	30	6.66	4.41	3.60	3.68	3.18	3.74	4.57
Enalapril	20	30	10.50	7.01	6.16	4.64	4.24	4.92	7.08
Fluoxetine	20	100	30.84	18.56	16.12	15.45	15.14	11.13	21.63
Fluoxetine	20	30	18.67	7.59	9.55	9.21	8.97	3.61	6.00
Pravastatin	20	30	377.69	360.93	156.32	30.57	20.38	16.99	19.95
Risperidone	2	30	394.59	402.90	377.22	17.00	10.76	5.01	5.59
Risperidone	3	30	591.85	604.31	565.80	20.09	12.35	8.15	7.70
Simvastatin	10	30	50.92	12.41	7.74	5.44	4.16	4.46	6.00
Simvastatin	20	30	56.59	19.79	11.47	8.32	6.36	6.37	7.70

Note: The gray cells indicate the year in which the first generic became available.

Table 4.4: Changes in prices (ZAR per pack) of first- and second-line anti-TB medicines (2007-2015).

	Strength (mg)	Pack size (tablets)	2007	2009	2011	2013	2015
Ethambutol	400	100	57.75	53.45	46.46	51.20	45.17
Ethambutol	400	60	22.54	33.26	33.34	34.72	32.76
Ethionamide	250	100	270.96	-	151.23	145.28	96.55
Ethionamide	250	250	628.48	581.01	451.19	433.41	283.69
Ethionamide	250	30	70.38	-	50.52	48.53	35.26
Ethionamide	250	60	180.63	-	100.83	96.85	67.35
Isoniazid	100	100	-	-	19.77	18.74	18.76
Isoniazid	100	1000	-	-	100.91	94.90	-
Isoniazid	100	30	-	-	9.88	9.31	9.27
Isoniazid	300	30	-	-	16.94	15.25	15.40
Pyrazinamide	500	100	39.54	-	38.83	33.40	40.11
Pyrazinamide	500	1000	428.25	-	355.84	-	-
Pyrazinamide	500	30	16.65	-	-	14.57	17.62
Pyrazinamide	500	60	28.60	-	31.07	26.64	30.33
Rifampicin	150	100	75.68	67.30	72.26	96.50	95.78
Rifampicin	450	100	153.90	144.64	129.81	-	-
Rifampicin	600	100	193.57	187.72	105.05	139.28	-
Terizidone	250	100	1035.40	-	795.00	793.67	789.95

Table 4.5: Changes in prices (ZAR per pack) of selected oncology medicines (2003-2016).

	Strength (mg)	Pack size (injection)*	2003	2005	2007	2009	2012	2014	2016
Bleomycin	15	1	445.53	340.30	318.16	321.92	258.13	230.13	296.40
Carboplatin	450	1	599.89	574.97	487.35	366.31	282.01	414.84	353.40
Ciclosporin	100	1	2,804.48	2,062.43	1,471.26	1,298.31	1,148.06	1,074.70	901.62
Cisplatin	50	1	380.97	192.12	156.45	118.05	73.41	61.74	70.68
Docetaxel	20	1	2,139.68	2,143.90	1,249.79	1,050.36	363.57	273.17	225.00
Docetaxel	80	1	7,564.51	7,579.43	4,279.17	3,596.32	1,456.62	863.42	650.00
Epirubicin	50	1	656.12	338.78	270.71	193.39	184.01	139.44	245.10
Gemcitabine	200	1	432.26	412.49	172.82	165.58	93.82	70.09	51.30
Gemcitabine	1	1	2,053.23	1,959.31	864.14	827.91	448.62	282.01	176.70
Goserelin	3.6	1	1,469.68	1,340.58	1,195.40	1,004.64	465.88	435.73	478.80
Idarubicin	10	1	1,068.42	1,167.17	1,124.03	1,039.13	898.88	921.58	998.81
Interferon alfa-2a	3	1	360.20	294.75	262.83	186.41	161.26	127.95	232.13
Interferon alfa-2a	4.5	1	430.80	408.67	309.74	258.45	223.57	191.93	246.98
Mercaptopurine	50	25	679.29	778.98	736.29	711.61	723.48	834.62	991.62
Methotrexate	100	1	3,153.21	2,846.79	2,583.90	2,747.05	879.60	784.29	869.83
Paclitaxel	30	1	1,177.90	758.94	605.05	440.48	121.64	89.63	99.42
Paclitaxel	100	1	3,533.71	2,418.99	2,188.50	1,468.30	203.11	149.65	140.35
Tacrolimus	5	50	10,260.99	9,368.11	8,154.43	6,526.85	5,645.93	4,530.13	4,075.50
Vinorelbine	10	1	410.65	48.47	475.40	225.66	113.64	85.13	79.94
Vinorelbine	50	1	2,053.23	2,423.35	2,377.00	1,128.29	568.22	423.12	380.00

* Except mercaptopurine and tacrolimus, which are taken as tablets. **Note:** The gray cells indicate the year in which the first generic became available.

Table 4.6: Changes in prices (ZAR per pack) of first- and second-line antiretroviral drugs (2004-2015).

	Strength (mg)	Pack size (tablets)	2004	2008	2010	2013	2015
Abacavir	300	60		463.04	166.64	118.16	124.78
Didanosine	100	60	134.97	98.11	87.46	73.67	-
Didanosine	250	30	-	269.22	94.87	72.35	-
Didanosine	400	30	-	347.43	140.83	116.34	-
Efavirenz	600	30	400.35	159.70	51.35	34.93	31.18
Efavirenz, Emtricitabine, and Tenofovir	300	30	-	-	-	103.42	109.02
Lamivudine	150	60	66.27	43.23	25.52	17.77	-
Lamivudine	300	30	-	61.47	28.93	19.23	16.84
Lamivudine and Zidovudine	150	6	-	82.45	-	-	-
Lamivudine and Zidovudine	150	60	-	132.77	95.22	-	-
Lamivudine and Zidovudine	300	60	-	-	-	76.96	86.09
Lopinavir and Ritonavir	80	1	584.62	461.50	400.89	246.15	-
Lopinavir and Ritonavir	80	120	-	-	-	-	155.32
Nevirapine	200	60	77.73	46.45	30.12	21.40	28.79
Stavudine	20	60	36.63	24.52	17.68	15.91	16.47
Stavudine	30	60	38.10	24.72	17.42	14.42	-
Tenofovir	300	30	-	230.68	72.97	34.56	31.77
Zidovudine	100	100	211.49	102.45	58.91	42.94	58.85
Zidovudine	300	60	144.81	102.83	81.17	51.37	68.84

4.2.2.5 Procurement figures

Table 4.7 shows the estimated and procured quantities for selected medicines. **Appendix C** gives the full results for every medicine in the sub-group analysis for which data were available (2011-2016).

The table shows large discrepancies between the two quantities for many products. For example, the NDoH estimated that it would require 279,500 packs of risperidone 1 mg (30 tablets) in the 2012 tender (August 1, 2012 - July 31, 2014), whereas it actually procured 155,719 packs (44% less). Over the same period, the department forecasted that it would need 1,262,900 packs of enalapril 5 mg (28 tablets), but went on to procure over 2 million packs (62% more).

In total, the NDoH estimated that it would require 34,594,171 packs of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, atypical antipsychotics, calcium channel blockers, proton-pump inhibitors, selective serotonin reuptake inhibitors, and statins in the 2012 tender, and 121,566,800 packs in the 2014 tender. In the end, the department procured 16,640,339 packs (52% less) in the 2012 tender, and 83,593,114 packs (31% less) in the 2014 tender, suggesting that the forecasts for these products became more accurate over time (**Appendix C**).

In the 2013 tender for antiretroviral drugs, the estimated quantities of all products totaled 16,821,770 packs, whereas only 7,295,537 packs were procured, or 57% less than predicted. In the 2013 anti-tuberculosis tender, the estimated quantities of all products totaled 130,871,700 packs, whereas only 101,796,577 packs were procured, or 22% less than predicted.

4.2.2.6 Public vs. private-sector prices

Table 4.8 shows the retail prices of statins in the private and public sectors in 2009, 2012, 2014, and 2016—the years in which the four most recent solid-dose tenders were issued. The private-sector prices were always higher than the tender prices. For example, the price of a 30-tablet pack of atorvastatin 20 mg cost 511% more in the private sector in 2009, and 178% more in 2016. Price differences for other products ranged from 127% (atorvastatin 40 mg in 2014) to 996% (pravastatin 20 mg in 2014).

Appendix D presents the private and public-sector prices of all medicines included in the sub-group analyses above.

Table 4.7: Estimated versus actual procurement figures for selected solid-dose medicines in the 2012 and 2014 tenders.

			2012 Tender			2014 Tender		
	Strength (mg)	Pack size (tablets)	Estimated volume	Actual volume	% diff.	Estimated volume	Actual volume	% diff.
Amisulpride	50	30	5,700	5,279	-7.39%	18,700	31,283	67.29%
Amisulpride	200	30	43,200	29,115	-32.60%	105,200	134,839	28.17%
Amlodipine	5	30	10,119,872	784,200	-92.25%	27,923,400	19,526,680	-30.07%
Amlodipine	10	30	2,032,900	367,424	-81.93%	3,228,100	7,117,977	120.50%
Atorvastatin	20	30	393,900	10,976	-97.21%	382,000	224,738	-41.17%
Citalopram	20	30	713,900	121,006	-83.05%	800,500	939,472	17.36%
Enalapril	5	28	1,262,900	2,043,530	61.81%	261,100	7,627,046	2821.12%
Fluoxetine	20	100	190,800	215,995	13.20%	126,000	247,710	96.60%
Losartan	50	30	172,100	41,136	-76.10%	320,100	371,039	15.91%
Risperidone	0.5	30	15,000	10,125	-32.50%	69,200	135,018	95.11%
Risperidone	1	30	279,500	155,719	-44.29%	574,500	547,342	-4.73%
Risperidone	2	30	733,400	83,417	-88.63%	908,300	728,915	-19.75%
Risperidone	3	30	243,100	46,047	-81.06%	349,700	295,323	-15.55%
Simvastatin	10	28	3,244,900	637,187	-80.36%	26,347,200	8,088,499	-69.30%
Simvastatin	20	28	2,914,100	210,600	-92.77%	5,852,800	4,118,794	-29.63%

Table 4.8: Public vs private-sector prices for statins (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Atorvastatin	10	30	36.32	172.42	475%	16.30	73.66	452%	12.39	33.56	271%	11.10	29.94	270%
Atorvastatin	20	30	44.82	229.25	511%	22.73	89.60	394%	22.93	35.65	155%	17.66	31.49	178%
Atorvastatin	40	30	57.19	229.25	401%	33.84	94.86	280%	43.35	54.86	127%	29.29	51.55	176%
Atorvastatin	80	30	77.28	382.17	495%	62.71	129.01	206%	-	-	-	-	-	-
Fluvastatin	20	30	90.00	179.07	199%	79.52	158.22	199%	-	-	-	-	-	-
Pravastatin	10	30	27.92	108.18	388%	18.75	142.37	759%	14.90	134.32	901%	-	-	-
Pravastatin	20	30	30.57	139.09	455%	20.38	181.79	892%	16.99	169.26	996%	19.95	161.88	811%
Simvastatin	10	30	5.44	40.65	748%	4.16	29.95	720%	4.46	22.70	510%	6.00	23.50	392%
Simvastatin	20	30	8.32	54.10	650%	6.36	29.95	471%	6.37	23.55	370%	7.70	26.11	339%
Total			377.86	1534.17	406%	264.75	929.42	351%	121.38	473.91	390%	91.69	324.47	354%

4.3 Discussion

The results indicate that tendering can achieve large price decreases for medicines, and that such decreases can be sustained over time. The public-sector prices of medicines in South Africa are considerably lower than those in the private sector. Moreover, the HHI findings suggests that many tender contracts remained competitive between 2003 and 2016. However, there were notable exceptions: the prices of some products increased over this period, and certain tender contracts grew increasingly uncompetitive. Also, the number of different firms winning tender contracts decreased over time in most tender categories.

These findings highlight the need for health ministry officials and other stakeholders to closely monitor the impact of tendering on medicine prices and availability to mitigate issues. The NDoH and its provincial counterparts should also work to improve the accuracy of forecasting methods. In past tenders, there were large discrepancies between the estimated and procured quantities for many products. This can make it difficult for pharmaceutical firms to plan production and delivery schedules, and likely increases the risk of stock-outs. The results of this study are worrisome since forecasting estimates should be easier for the selected products than for infectious disease products, given the epidemiologic profile of the country and the high budget impact of these items.

It is possible to glean policy lessons from the South African experience with tendering. Policymakers in countries looking to tender for essential medicines should consider (i) weighting of value parameters, (ii) issues which may arise during the management of tender contracts, and (iii) barriers to generic competition. All three affect prices and supply security.

4.3.1 Weighting

Although the 90/10 points system provides a framework for awarding tender contracts in South Africa, it is important to remember that factors other than price influence the award of tender contracts. As outlined by Gray and Smit, [371] improving access to medicines in South Africa is often a case of "colliding interests", with tensions between promoting health and local industrial objectives.

The utility function framework adopted in this analysis is useful insofar as it assists in adopting a more structured approach to understanding the factors driving tender processes. In reality, though, the utility functions of stakeholders are not linear, with ad hoc decisions common. It is important to promote a transparent and explicit tender procedure, and to foster dialog between policymakers, industry representatives, and the public about the trade-offs inherent in the tendering process.

Perceptions about how various factors should be weighted differ between government stakeholders, with the health ministry generally placing more emphasis on price and DTI focusing on economic and industrial development. The interest in price for the NDoH is motivated by a desire to increase both cost savings and access, particularly for antiretroviral therapies. DTI favors an increase in the number of local industry designations to promote economic growth, citing several studies in support of local designation of the pharmaceutical industry. [372–380]

It is important to consider the potential health-related costs of increased medicines prices. Findings in other sectors suggest that subsidizing inefficient bidders can have adverse long-term effects on prices and spending. [381] Also, some local producers keep their manufacturing facilities abroad, so the value added to the domestic economy may be limited. There needs to be clarity around the verifiable benefits of designating the pharmaceutical sector as one of high importance to the local economy, as such a move may have adverse effects on competition and medicine prices.

The South African government also attaches considerable weight to broad-based black economic empowerment scores for historical reasons. Unequivocally, addressing past injustices and promoting equitable development lie at the heart of industrial objectives in the country. The combination of enormously unequal income distribution, [382] low education levels, [383] and lack of access to essential health care services [384] results in a vicious cycle of poverty and social exclusion for many, tracing back to the structural inequalities inherited from the racially divided Apartheid state.

Overall, there is a trade-off between obtaining the lowest possible prices and achieving other policy objectives. Policymakers in countries considering the use of tenders should apply clear and transparent criteria for the award of tenders, with input from relevant stakeholders.

4.3.2 Contract management

Risk management of awarded contracts is essential to prevent shortages. [385–389]

The federalist-fiscal arrangement in South Africa means that although tendering is conducted centrally by the NDoH, the procurement of, and payment for, medicines is done by provinces, with provincially held budgets. Representatives from each provincial health department are involved throughout the tender process, as are stakeholders from policy and finance units in the national government. The uncertainty around estimated and actual demand is a potential cause of supply disruptions in South Africa. As shown in this paper, the estimated quantities sometimes far exceed, or fall well short of, the amounts needed. This makes it difficult for suppliers to determine the capacity at which to operate to meet orders within lead times. It may be important to start a dialogue with suppliers to understand the challenges they are facing, with an aim to

introduce corrective measures prior to issues arising.

Challenges also exist in coordinating information sharing between the NDoH, provincial health departments, and suppliers to ensure adequate stock levels and to manage the supply chain. Information systems are not standardized across provinces, resulting in usage and demand data which are poor and patchy. Maladministration and miscommunication on the part of provinces causes poor order and payment coordination, with late payments common. This puts suppliers under undue financial pressure, which might influence their willingness to reserve extra capacity. The failure of some suppliers to meet contractual agreements has also previously caused shortages, [389] as have budget deficits and government corruption. [386] In past tenders, delays in the award of pharmaceutical tenders by the NDoH have also precipitated supply disruptions. [389] In short, it is critical to manage relationships between provincial purchasers and suppliers in order to ensure accountability for stock-outs and to minimize demand and supply-side issues. [390]

In 2015, the health ministry launched an early warning system to identify products at risk of shortages in South Africa. Previously, stock-outs were often only identified once facilities alerted the NDoH about shortages. For instance, in 2012, country-wide stock-outs of tenofovir, a widely used antiretroviral therapy, caused public outrage and concern. In the same year, there were shortages of aspirin, the anti-TB medicine isoniazid, and the antibiotic cotrimoxazole, as well as various pediatric medications, vaccines, and vitamins.[25] In recent years, South Africa has experienced shortages of other essential medicines, like the HIV drug lopinavir/ritonavir.

The effects of stock-outs are significant. Apart from the cost implications for the government of buying off-contract—often at a substantial premium—and the patient-borne costs of having to return to clinics to pick up medicines, treatment compliance is paramount in managing infection rates in a country with a high infectious disease burden, like South Africa. [392, 393] Stock-outs can also harm patient motivation and trust in the health care system. [394]

Finally, purchasers need market knowledge about cost functions to spot gaming and to negotiate prices effectively, especially for fragile tender markets. For example, firms producing tuberculosis and family-planning agents are unable to manufacture other products at the same facilities, due to risk of cross-contamination. Losing bidders for these products must usually shut down their facilities, which adds financial risk and may make it more likely for losing firms to exit these markets.

[25] There have been documented cases of medicine shortages in other countries which use medicine tenders, including the Netherlands [129] and New Zealand, [391] often owing to problems at manufacturing facilities and issues in sourcing drug ingredients.

4.3.3 Generic competition

The South African government adopted a so-called Bolar provision in 2002 to speed up the availability of generic drugs.[26] This provision permits generic firms to conduct clinical tests required for market authorization prior to the loss of market exclusivity for originator firms.

Yet there remain regulatory barriers to entry in South Africa. The registration process for the Medicines Control Council, the national agency in charge of evaluating medicinal products and granting firms marketing authorization, is often slow and laborious, largely due to lack of resources. [338] Applications for new drug registration can take up to four years, while amendments to existing registrations, such as notifying the NDoH of a difference source of an active ingredient, can take two years. There is little coordination of registration of key products, which results in some items being excluded from tenders, further weakening competition. The South African Health Products Regulatory Agency is expected to be introduced in 2017 as a replacement to the Medicines Control Council, which may result in more transparent, efficient regulatory processes. South African authorities may wish to consider other options, such as granting waivers to procure a medicine without marketing authorization if it has been approved in a country with a stringent regulatory authority. There are also regional marketing authorization initiatives to increase the number of approved medicines (eg, ZanZiBoNa in Southern Africa).

The issuance of voluntary licenses has sped up the availability of some generics. Notably, the increase in voluntary licensing agreements for antiretroviral drugs led to more competition in this tender, putting downward pressure on prices. Merck, Sharpe & Dohme, for instance, issued voluntary licenses for efavirenz to Adcock in 2007, and to Aspen, Cipla and Sonke in 2008. Similarly, in 2006 Gilead granted Aspen Pharmacare a license for tenofovir, which resulted in Aspen acquiring 70% of the tenofovir market and the price decreasing by 64%.

The pricing of therapies for HIV/AIDS and TB is highly politicized in South Africa, with non-governmental organizations and activists putting pressure on companies, lawmakers, and policymakers to keep prices low. There are ongoing discussions between governmental and non-governmental stakeholders about the role of voluntary and compulsory licensing in guaranteeing access to affordable medicines for patients.[27]

[26] The Patents Amendment Act of 2002 inserted a new section 69A in Act 57 of the original Patents Act of 1978 which included a Bolar provision.

[27] See Makgoba, [401] Geffen, [402] and Nattrass [403] for political overviews, and Ford, [404] Marc, [405] Bass, [406] Roffe, [407] and Collins-Chase [408] for discussion of compulsory and voluntary licensing battles between industry, government, and activist groups.

4.3.4 Limitations

This study has limitations. First, the procurement data ("RSA Pharmaceutical database") are self-reported by suppliers, without independent verification. The data are patchy and of variable quality, although the information relating to high-priority items, like antiretroviral therapies and anti-TB medicines, are more reliable. Still, the results highlight the large discrepancies between estimated and procured quantities for most products, even if the point estimates might not be exact.

Second, we did not examine within-contract price adjustments for exchange rate fluctuations due to lack of availability for many of the tenders. The results likely underestimate the actual prices paid by the South African government.

Third, the three types of price indexes apply different weights to reflect consumption patterns. The Laspeyres index uses quantities from the base period, whereas the Paasche index relies on period-specific quantities, leading to different estimates of price levels. The Fisher index is the geometric mean of the other two indexes. Each approach has its pros and cons. [409] Moreover, the sample sizes for some of the price indexes were small, given the need to track a common sample of products over time.

Finally, the HHI analyses may over or understate competition in some drug classes, since the results are presented at the tender-wide level. Moreover, the analyses of market concentration did not consider different licensing arrangements for antiretroviral therapies and other products.

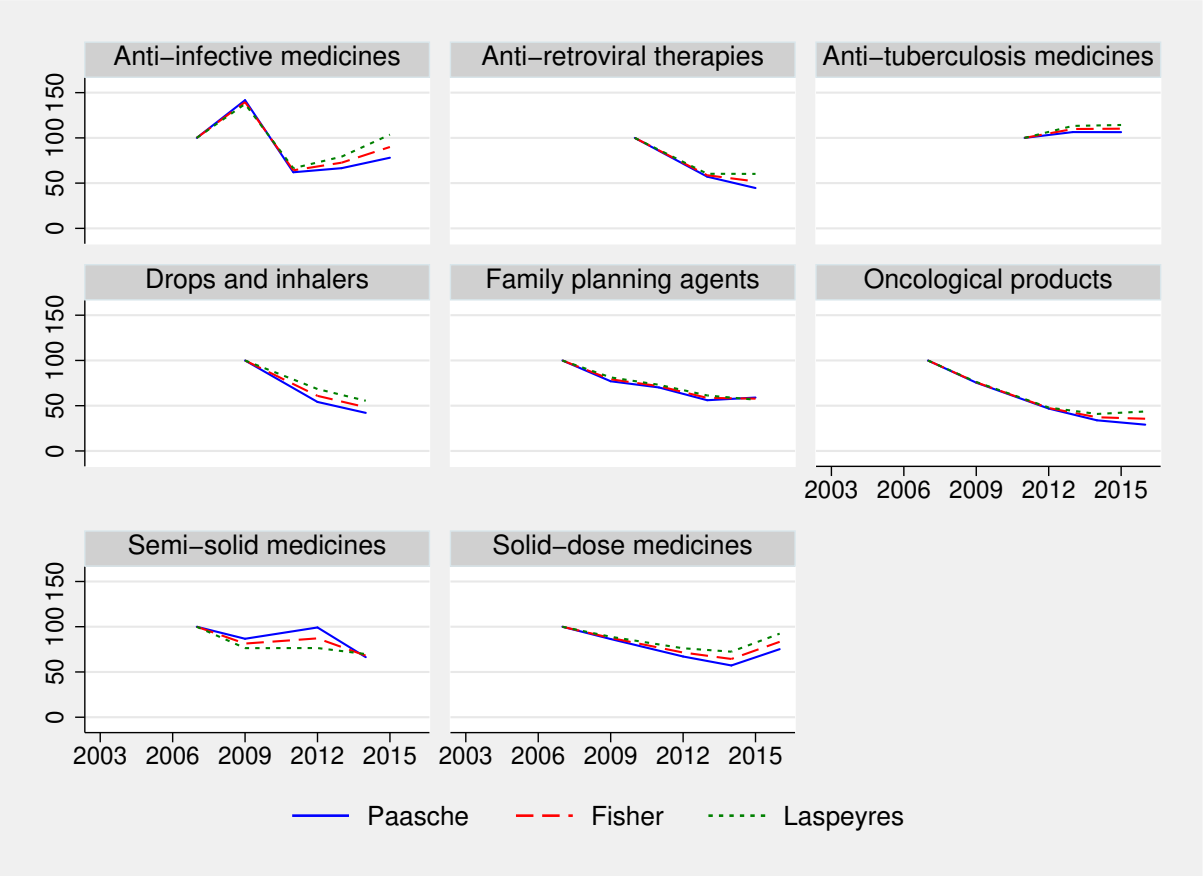
4.4 Conclusions

It is important to examine whether existing procurement processes in South Africa can secure adequate quantities of essential medicines, at cost-effective prices, both now and in the future. As it stands, the acceptable price premiums are capricious, and there is little agreement on an evidence-based balance between health and industrial priorities. Without agreement, tendering might simply turn into a means for short-sighted and, potentially, Pyrrhic victories.

In South Africa, disruptions occur occasionally due to unforeseen demand, manufacturing problems, provincial maladministration, supply-chain inefficiencies, and poor communication between the national health ministry, provincial health departments, and suppliers. Poor supply and logistics management at provincial level is a key cause of stock-outs. Countries which aim to introduce tendering systems should carefully manage these issues to guarantee supply of high-quality medicines at low prices.

Appendix A: Price index sensitivity analysis

Figure A. Price trends by medicine category (2003-2016) in a sensitivity analysis



The sensitivity analysis was based on a sample of 25 anti-tuberculosis medicines, 44 anti-infective medicines, 7 family-planning agents, 34 oncological products, 37 drops and inhalers, 42 semi-solid medicines, 142 solid-dose medicines, and 18 antiretroviral therapies.

Appendix B: Full results of sub-group analyses

In all tables, the gray cells indicate the year in which the first generic became available.

Table A. Changes in prices (ZAR per pack) of statins (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Atorvastatin	10	30	210.44	55.23	49.25	36.32	16.30	12.39	11.10
Atorvastatin	20	30	381.07	67.97	60.61	44.82	22.73	22.93	17.66
Atorvastatin	40	30	-	-	-	57.19	33.84	43.35	29.29
Atorvastatin	80	30	-	-	-	77.28	62.71	-	-
Fluvastatin	20	30	105.22	53.62	86.44	90.00	79.52	-	-
Pravastatin	10	30	301.94	288.74	119.54	27.92	18.75	14.90	-
Pravastatin	20	30	377.69	360.93	156.32	30.57	20.38	16.99	19.95
Simvastatin	10	30	50.92	12.41	7.74	5.44	4.16	4.46	6.00
Simvastatin	20	30	56.59	19.79	11.47	8.32	6.36	6.37	7.70

Table B. Changes in prices (ZAR per pack) of angiotensin receptor blockers (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Losartan	50	30	-	-	-	23.18	8.29	6.72	7.69
Losartan	100	30	-	-	-	-	-	13.44	14.91

Table C. Changes in prices (ZAR per pack) of proton-pump inhibitors (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Lansoprazole	30	14	-	-	-	-	-	4.26	6.95
Lansoprazole	30	30	-	-	-	58.98	-	7.12	12.18
Omeprazole	10	30	-	-	-	-	12.03	38.83	36.83
Omeprazole	20	30	152.31	45.23	23.71	14.22	8.91	-	-
Pantoprazole	40	30	350.13	371.58	201.65	146.57	-	-	-
Ranitidine	150	60	32.86	18.98	13.53	13.87	11.69	-	13.20
Ranitidine	300	30	32.42	22.99	16.41	14.91	-	9.48	-

Table D. Changes in prices (ZAR per pack) of selective serotonin reuptake inhibitors (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Citalopram	20	30	72.04	43.31	16.92	9.76	9.36	7.08	8.00
Fluoxetine	20	100	30.84	18.56	16.12	15.45	15.14	11.13	21.63
Fluoxetine	20	30	18.67	7.59	9.55	9.21	8.97	3.61	6.00
Fluvoxamine	100	30	272.32	307.30	221.61	186.71	-	-	-
Paroxetine	20	30	170.36	170.15	44.36	17.92	21.39	-	-
Sertraline	50	30	-	-	-	-	-	8.74	-

Table E. Changes in prices (ZAR per pack) of angiotensin-converting-enzyme inhibitors (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Captopril	12.5	100	31.13	26.23	23.46	-	-	-	-
Captopril	25	60	10.11	5.55	-	8.77	7.06	6.76	10.00
Captopril	50	60	14.11	8.63	-	19.36	-	-	-
Enalapril	5	30	5.40	3.98	3.21	3.36	2.99	2.94	3.13
Enalapril	10	30	6.66	4.41	3.60	3.68	3.18	3.74	4.57
Enalapril	20	30	10.50	7.01	6.16	4.64	4.24	4.92	7.08
Fosinopril	10	30	79.44	-	-	-	-	-	-
Fosinopril	20	30	104.39	-	-	-	-	-	-
Lisinopril	5	30	-	-	7.02	8.60	-	-	-
Lisinopril	10	30	-	-	8.18	10.70	-	-	-
Lisinopril	20	30	-	-	12.86	16.22	-	-	-
Perindopril	4	30	24.25	23.81	21.21	16.68	9.96	-	25.47
Quinapril	5	30	31.70	-	21.07	19.48	-	-	-
Quinapril	10	30	53.43	-	20.00	18.49	-	-	-
Quinapril	20	30	106.85	-	58.32	34.00	-	-	-
Ramipril	2.5	30	45.96	30.61	16.64	11.52	8.97	-	-
Ramipril	5	30	49.52	35.14	20.23	13.56	10.54	-	-

Table F. Changes in prices (ZAR per pack) of calcium-channel blockers (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Amlodipine	5	30	109.96	34.63	6.78	4.13	2.93	2.41	3.19
Amlodipine	10	30	252.15	92.65	26.67	6.77	3.88	3.44	4.23
Isradipine	2.5	60	72.10	59.27	215.17	224.91	-	-	-
Isradipine	5	30	56.52	41.25	47.25	46.37	-	-	-
Nifedipine	5	100	35.81	33.65	30.01	26.44	25.80	-	34.34
Nifedipine	10	100	44.44	-	-	-	-	50.87	55.76
Nifedipine	10	250	118.87	99.92	82.53	-	-	-	-
Nifedipine	30	30	47.79	45.61	24.83	14.68	12.84	-	23.70
Nifedipine	60	30	129.49	123.56	48.74	29.37	25.33	-	41.00
Nimodipine	30	100	1007.56	123.56	942.40	856.44	-	-	-

Table G. Changes in prices (ZAR per pack) of atypical antipsychotics (2003-2016).

	Strength (mg)	Pack size (tablets)	2003	2005	2007	2009	2012	2014	2016
Amisulpride	50	30	-	217.93	194.33	163.32	141.28	132.24	125.82
Amisulpride	200	30	-	483.46	431.10	362.31	313.41	293.38	279.20
Clozapine	25	100	183.77	103.12	84.57	46.15	39.92	34.29	36.10
Clozapine	100	100	463.26	268.12	219.88	143.12	123.81	110.38	115.60
Olanzapine	2.5	30	-	-	-	234.99	26.74	20.26	18.24
Olanzapine	5	30	-	-	503.71	469.55	40.11	30.39	24.73
Olanzapine	10	30	-	-	1007.42	939.54	60.16	39.33	30.94
Risperidone	0.5	30	-	-	-	-	9.78	7.33	8.21
Risperidone	1	30	-	-	321.84	12.36	7.84	4.51	4.79
Risperidone	2	30	394.59	402.90	377.22	17.00	10.76	5.01	5.59
Risperidone	3	30	591.85	604.31	565.80	20.09	12.35	8.15	7.70
Sulpiride	50	100	34.49	32.17	32.31	42.24	-	-	-
Sulpiride	200	50	136.60	136.86	108.23	94.91	-	-	-

Appendix C: Full results of analysis of procurement figures

Table A. Estimated and actual procurement figures for ACE inhibitors, ARBs, atypical antipsychotics, CCBs, PPIs, SSRIs, and statins in the 2012 and 2014 solid-dose tenders.

			2012 tender			2014 tender		
	Strength (mg)	Pack size (tablets)	Estimated volume	Actual volume	% difference	Estimated volume	Actual volume	% difference
Amisulpride	50	30	5,700	5,279	-7.39%	18,700	31,283	67.29%
Amisulpride	200	30	43,200	29,115	-32.60%	105,200	134,839	28.17%
Amlodipine	5	30	10,119,872	784,200	-92.25%	27,923,400	19,526,680	-30.07%
Amlodipine	10	30	2,032,900	367,424	-81.93%	3,228,100	7,117,977	120.50%
Atorvastatin	10	30	-	-	-	750,000	145,719	-80.57%
Atorvastatin	20	30	393,900	10,976	-97.21%	382,000	224,738	-41.17%
Atorvastatin	40	30	-	-	-	21,000	38,239	82.09%
Captopril	25	60	-	-	-	97,100	48,597	-49.95%
Citalopram	20	30	713,900	121,006	-83.05%	800,500	939,472	17.36%
Clozapine	25	84	-	-	-	73,100	79,226	8.38%
Clozapine	100	84	-	-	-	144,900	175,189	20.90%
Enalapril	5	28	1,262,900	2,043,530	61.81%	261,100	7,627,046	2821.12%
Enalapril	10	28	-	-	-	37,836,200	23,531,287	-37.81%
Enalapril	20	28	-	-	-	6,725,800	3,798,550	-43.52%
Fluoxetine	20	28	-	-	-	1,052,700	1,198,960	13.89%
Fluoxetine	20	30	806,800	468,255	-41.96%	-	-	
Fluoxetine	20	100	190,800	215,995	13.20%	126,000	247,710	96.60%
Lansoprazole	30	14	-	-	-	2,251,300	1,095,632	-51.33%

			2012 tender			2014 tender		
	Strength (mg)	Pack size (tablets)	Estimated volume	Actual volume	% difference	Estimated volume	Actual volume	% difference
Lansoprazole	30	28	-	-	-	3,734,400	2,672,970	-28.42%
Losartan	50	30	172,100	41,136	-76.10%	320,100	371,039	15.91%
Losartan	100	28	-	-	-	34,900	66,190	89.66%
Nifedipine	10	100	-	-	-	30,900	36,886	19.37%
Nifedipine	30	28	8,403,200	6,790,655	-19.19%	-	-	
Olanzapine	5	28	-	-	-	58,100	52,536	-9.58%
Olanzapine	10	28	-	-	-	85,600	181,979	112.59%
Olanzapine	2.5	28	-	-	-	11,400	18,520	62.46%
Omeprazole	10	28	9,100	1,630	-82.09%	-	-	
Omeprazole	20	28	2,201,400	4,378,223	98.88%	-	-	
Pantoprazole	20	30	-	-	-	20,000	46,436	132.18%
Paroxetine	20	30	40,600	2,340	-94.24%	-	-	-
Ranitidine	150	60	767,799	237,480	-69.07%	-	-	-
Ranitidine	300	30	-	-	-	1,049,400	238,913	-77.23%
Risperidone	0.5	30	15,000	10,125	-32.50%	69,200	135,018	95.11%
Risperidone	1	30	279,500	155,719	-44.29%	574,500	547,342	-4.73%
Risperidone	2	30	733,400	83,417	-88.63%	908,300	728,915	-19.75%
Risperidone	3	30	243,100	46,047	-81.06%	349,700	295,323	-15.55%
Sertraline	50	30	-	-	-	323,200	32,610	-89.91%
Simvastatin	10	28	3,244,900	637,187	-80.36%	26,347,200	8,088,499	-69.30%
Simvastatin	20	28	2,914,100	210,600	-92.77%	5,852,800	4,118,794	-29.63%

			2012 tender			2014 tender		
	Strength (mg)	Pack size (tablets)	Estimated volume	Actual volume	% difference	Estimated volume	Actual volume	% difference
Total			34,594,171	16,640,339	-51.90%	121,566,800	83,593,114	-31.24%

Table B. Estimated and actual procurement figures for anti-tuberculosis therapies in the 2013 tender.

			2013		
	Strength (mg)*	Pack size (tablets)*	Estimated volume	Actual volume	% diff.
Capreomycin	1 (g/ml)	1 (vial)	314,000	128,860	-58.96%
Ethambutol	400	100	202,200	93,532	-53.74%
Ethambutol	400	56	238,500	83,832	-64.85%
Ethambutol	400	84	250,800	104,601	-58.29%
Ethionamide	250	250	30,600	16,221	-46.99%
Ethionamide	250	28	42,700	19,767	-53.71%
Ethionamide	250	56	47,700	35,391	-25.81%
Ethionamide	250	84	164,000	125,602	-23.41%
Isoniazid	100	1000	20,000	10,754	-46.23%
Isoniazid	100	28	724,800	388,970	-46.33%
Isoniazid	100	84	260,800	137,407	-47.31%
Isoniazid	300	28	4,308,200	2,437,891	-43.41%
Kanamycin Sulphate	1 (g/ml)	1 (vial)	1,787,300	145,066	-91.88%
Levofloxacin	250	28	130,000	6,700	-94.85%
Levofloxacin	250	5	24,000	63,878	166.16%
Moxifloxacin	400	10	300,000	46,019	-84.66%
Moxifloxacin	400	28	319,470	310,825	-2.71%
Pyrazinamide	500	28	181,600	81,086	-55.35%
Pyrazinamide	500	56	164,600	106,422	-35.35%
Pyrazinamide	500	84	188,600	141,525	-24.96%

			2013		
	Strength (mg)*	Pack size (tablets)*	Estimated volume	Actual volume	% diff.
Rifampicin	150	100	18,700	15,724	-15.91%
Rifampicin	600	100	7,100	4,375	-38.38%
Rifampicin and Isoniazid	300/150	56	1,494,600	557,060	-62.73%
Rifampicin and Isoniazid	150/75	56	753,400	355,198	-52.85%
Rifampicin and Isoniazid	150/75	84	1,091,900	349,187	-68.02%
Rifampicin and Isoniazid	60/60	28	477,600	245,330	-48.63%
Rifampicin and Isoniazid	60/60	56	642,400	351,744	-45.25%
Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol	150/75 400/275	100	529,800	47,363	-91.06%
Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol	150/75 400/275	112	504,360	157,502	-68.77%
Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol	150/75/ 400/275	28	182,340	75,998	-58.32%
Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol	150/75 400/275	56	420,840	209,273	-50.27%
Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol	150/75/ 400/275	84	551,160	283,861	-48.50%
Terizidone	250	100	447,700	158,573	-64.58%
Total			16,821,770	7,295,537	-56.63%

* Unless otherwise stated

Table C. Estimated and actual procurement figures for antiretroviral therapies in the 2013 tender.

			2013		
	Strength (mg)*	Pack size (tablets)*	Estimated volume	Actual volume	% diff.
Abacavir	20 (mg/ml)	1 (vial)	2,600,000	1,924,842	-25.97%
Abacavir	300	56	900,000	1,654,869	83.87%
Abacavir and Lamivudine	600/300	28	500,000	504,364	0.87%
Atazanavir	150	56	2,000	7,823	291.15%
Darunavir	300	120	1,000	2,685	168.50%
Didanosine	100	60	130,000	60,082	-53.78%
Didanosine	250	30	20,000	36,304	81.52%
Didanosine	25	60	20,000	15,596	-22.02%
Didanosine	400	30	40,000	44,242	10.61%
Didanosine	50	60	70,000	26,463	-62.20%
Efavirenz	200	84/90	1,500,000	613,298	-59.11%
Efavirenz	50	28	2,000,000	1,921,826	-3.91%
Efavirenz	600	28	18,001,000	13,936,673	-22.58%
Etravirine	100	112	100	818	718.00%
Lamivudine	10 (mg/ml)	1 (vial)	1,000,000	1,253,964	25.40%
Lamivudine	150	56	20,000,000	10,125,812	-49.37%
Lamivudine	300	28	12,000,000	9,308,585	-22.43%
Lopinavir and Ritonavir	100/25	60	320,000	561,631	75.51%
Lopinavir and Ritonavir	200/50	120	2,000,000	2,663,767	33.19%
Lopinavir and Ritonavir	80/20 (mg/ml)	5 (vials)	500,000	450,355	-9.93%

			2013		
	Strength (mg)*	Pack size (tablets)*	Estimated volume	Actual volume	% diff.
Nevirapine	200	56	2,000,000	3,743,633	87.18%
Nevirapine	50 (mg/5ml)	1 (100 ml vial)	500,000	806,640	61.33%
Nevirapine	50 (mg/5ml)	1 (240 ml vial)	300,000	229,330	-23.56%
Raltegravir	400	56	600	3,137	422.83%
Ritonavir	100	84	15,000	27,517	83.45%
Ritonavir	80 (mg/ml)	1 (vial)	28,000	24,630	-12.04%
Stavudine	15	56	125,000	222,107	77.69%
Stavudine	1 (mg/ml)	1 (vial)	100,000	26,718	-73.28%
Stavudine	20	56	4,800,000	301,239	-93.72%
Stavudine	30	56	1,600,000	817,996	-48.88%
Tenofovir and Emtricitabine	300/200	28	100,000	567,414	467.41%
Tenofovir and Lamivudine	300/300	28	500,000	619,469	23.89%
Tenofovir	300	28	24,999,000	4,632,222	-81.47%
Tenofovir, Emtricitabine, and Efavirenz	300/200/60	28	30,000,000	40,687,273	35.62%
Zidovudine and Lamivudine	300/150	56	1,200,000	1,418,615	18.22%
Zidovudine	100	100	100,000	110,811	10.81%
Zidovudine	300	56	2,800,000	2,176,685	-22.26%
Zidovudine	50 (mg/5ml)	1 (vial)	100,000	267,142	167.14%
Total			130,871,700	101,796,577	-22.22%

* Unless otherwise stated

Appendix D: Full results of analysis of public versus private-sector prices

Table A. Public vs private-sector prices for calcium-channel blockers (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Amlodipine	10	30	6.77	107.42	1588%	3.88	99.79	2573.79%	3.44	65.56	1905%	4.23	72.69	1718%
Amlodipine	5	30	4.13	67.93	1646%	2.93	63.11	2154.40%	2.41	36.95	1532%	3.19	40.97	1284%
Isradipine	2.5	60	-	-	-	-	-	-	-	-	-	-	-	-
Isradipine	5	30	46.37	342.62	739%	-	-	-	-	-	-	-	-	-
Nifedipine	10	100	-	-	-	-	-	-	50.87	77.88	153%	55.76	84.72	152%
Nifedipine	10	250	-	-	-	-	-	-	-	-	-	-	-	-
Nifedipine	30	30	14.68	174.88	1191%	12.84	152.73	1189.30%	-	-	-	23.70	150.97	637%
Nifedipine	5	100	26.44	50.79	192%	25.80	48.19	186.79%	-	-	-	34.34	53.33	155%
Nifedipine	60	30	29.37	387.59	1320%	25.33	360.10	1421.48%	-	-	-	41.00	245.34	598%
Nimodipine	30	100	856.44	954.83	111%	-	-	-	-	-	-	-	-	-
Total			984.19	2086.06	212%	70.78	723.92	1022.74%	56.72	180.38	318%	162.22	648.02	399%

Table B. Public vs private-sector prices for angiotensin-converting-enzyme inhibitors (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Captopril	12.5	100	-	-	-	-	-	-	-	-	-	-	-	-
Captopril	25	60	8.77	16.73	191%	7.06	15.88	225%	6.76	18.44	273%	10.00	20.45	204%
Captopril	50	60	19.36	24.20	125%	-	-	-	-	-	-	-	-	-
Enalapril	10	30	3.68	44.43	1208%	3.18	44.08	1385%	3.74	41.57	1111%	4.57	48.74	1066%
Enalapril	20	30	4.64	61.81	1333%	4.24	74.64	1761%	4.92	73.33	1490%	7.08	82.56	1167%
Enalapril	5	30	3.36	30.46	906%	2.99	30.90	1033%	2.94	29.65	1009%	3.13	34.19	1093%
Fosinopril	10	30	-	-	-	-	-	-	-	-	-	-	-	-
Fosinopril	20	30	-	-	-	-	-	-	-	-	-	-	-	-
Lisinopril	10	30	10.70	23.96	224%	-	-	-	-	-	-	-	-	-
Lisinopril	20	30	16.22	23.96	148%	-	-	-	-	-	-	-	-	-
Lisinopril	5	30	8.60	23.96	279%	-	-	-	-	-	-	-	-	-
Perindopril	4	30	16.68	137.56	825%	9.96	84.96	853%	-	-	-	25.47	68.40	269%
Quinapril	10	30	18.49	53.72	290%	-	-	-	-	-	-	-	-	-
Quinapril	20	30	34.00	81.35	239%	-	-	-	-	-	-	-	-	-
Quinapril	5	30	19.48	70.12	360%	-	-	-	-	-	-	-	-	-
Ramipril	2.5	30	11.52	32.46	282%	8.97	89.65	999%	-	-	-	-	-	-
Ramipril	5	30	13.56	38.64	285%	10.54	135.62	1286%	-	-	-	-	-	-
Total			189.06	663.35	351%	46.95	475.73	1013%	18.37	162.99	887%	50.25	254.34	506%

Table C. Public vs private-sector prices for angiotensin-receptor blockers (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Losartan	100	30	-	-	-	-	-	-	13.44	86.79	646%	14.91	85.42	573%
Losartan	50	30	23.18	115.92	500%	8.29	86.20	1040%	6.72	-	-	7.69	107.84	1402%
Total			23.18	115.92	500%	8.29	86.20	1040%	20.16	86.79	431%	22.60	193.26	855%

Table D. Public vs private-sector prices for selective-serotonin-reuptake inhibitors (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Citalopram	20	30	9.76	41.72	428%	9.36	67.66	723%	7.08	67.56	954%	8.00	69.21	865%
Fluoxetine	20	100	-	-	-	-	-	-	-	-	-	-	-	-
Fluoxetine	20	30	9.21	25.48	277%	8.97	22.89	255%	3.61	21.43	594%	6.00	20.65	344%
Fluvoxamine	100	30	186.71	278.57	149%	-	258.99	-	-	258.50	-	-	286.60	-
Paroxetine	20	30	17.92	156.82	875%	21.39	148.81	696%	0.00	133.55	-	-	-	-
Sertraline	50	30	-	-	-	-	-	-	8.74	76.64	876%	-	-	-
Total			223.60	502.59	225%	39.72	498.35	1255%	19.44	557.68	2869%	14.00	376.46	2689%

Table E. Public vs private-sector prices for atypical antipsychotics (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Amisulpride	200	30	362.31	702.61	194%	313.41	666.71	213%	293.38	665.48	227%	279.20	686.36	246%
Amisulpride	50	30	163.32	207.14	127%	141.28	196.56	139%	132.24	196.20	148%	125.82	202.36	161%
Clozapine	100	100	143.12	852.85	596%	123.81	720.41	582%	110.38	695.86	630%	115.60	797.24	690%
Clozapine	25	100	46.15	302.18	655%	39.92	233.39	585%	34.29	232.95	679%	36.10	258.28	715%
Olanzapine	10	30	939.54	1,689.75	180%	60.16	618.45	1028%	39.33	507.85	1291%	30.94	281.46	910%
Olanzapine	2.5	30	-	-	-	26.74	306.49	1146%	20.26	224.80	1109%	18.24	134.26	736%
Olanzapine	50	28	-	-	-	-	-	-	-	-	-	-	-	-
Olanzapine	5	30	-	-	-	40.11	516.03	1287%	30.39	396.10	1303%	24.73	219.45	887%
Risperidone	1	30	12.36	159.35	1289%	7.84	303.30	3869%	4.51	172.83	3835%	4.79	196.08	4094%
Risperidone	2	30	17.00	578.14	3400%	10.76	510.81	4747%	5.01	369.51	7378%	5.59	420.66	7525%
Risperidone	3	30	20.09	845.30	4207%	12.35	746.85	6048%	8.15	572.14	7024%	7.70	520.00	6753%
Sulpiride	200	50	94.91	327.23	345%	-	-	-	-	-	-	-	-	-
Sulpiride	50	100	42.24	144.05	341%	-	-	-	-	-	-	-	-	-
Total			1,841.04	5,808.59	316%	776.38	4,819.00	621%	677.94	4,033.73	595%	648.71	3,716.15	573%

Table F. Public vs private-sector prices for proton-pump inhibitors (2009-2016).

			2009			2012			2014			2016		
	Strength (mg)	Pack size (tablets)	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.	Tender	SEP	% diff.
Omeprazole	10	30	-	-	-	12.03	150.50	1251%	38.83	141.96	366%	36.83	135.77	369%
Lansoprazole	30	14	-	-	-	-	-	-	4.26	244.91	5753%	6.95	234.24	3370%
Lansoprazole	30	30	58.98	138.66	235%	-	-	-	7.12	121.65	1709%	12.18	134.88	1107%
Omeprazole	20	30	14.22	46.37	326%	8.91	40.11	450%	-	-	-	-	-	-
Pantoprazole	40	30	146.57	315.30	215%	-	-	-	-	-	-	-	-	-
Ranitidine	150	60	13.87	52.73	380%	11.69	29.02	248%	-	-	-	13.20	32.10	243%
Ranitidine	300	30	14.91	30.91	207%	-	-	-	9.48	25.76	272%	-	-	-
Total			248.56	583.97	235%	32.63	219.63	673%	59.69	534.28	895%	69.16	536.99	776%

5

What is the price impact of tendering for medicines by therapeutic class? A difference-in-differences estimation

"Many people feel marginalized and powerless in the face of what seems like unbridled capitalism. The global movement for treatment access said: 'Hold on a minute, corporate entities have a social duty and responsibility.' But treatment activists and international NGOs tend to sulk too much if we don't get everything we want. We've made huge advances in bringing the price down. The medicines I take today were priced ten times higher before we started our campaign. ... That doesn't mean we've got everything, though. It's important to remain vigilant."

– Zackie Achmat, *South African activist (July 2004)*

Key messages

- Many new medicines offer little or no additional therapeutic benefit over existing therapies.
- Therapeutic tendering is one policy option to reduce spending on so-called me-too medicines.
- In South Africa, the introduction of therapeutic tendering was associated with an estimated 33% to 44% reduction in the prices of solid-dose drugs in 2014.
- The national health ministry saved an estimated ZAR 1.13 to 1.50 billion on solid-dose medicines in 2014 through therapeutic tendering.

Abstract

Context: Many new medicines offer little or no additional therapeutic benefit over existing therapies. One option to reduce spending on so-called me-too drugs, and to indirectly incentivise drug companies to develop truly innovative medicines, is for payers to tender for medicines by therapeutic class. Under a therapeutic tendering policy, the payer only buys the least expensive products in defined therapeutic classes. The aim of this study was to measure the association between implementation of therapeutic tendering and medicine prices and government spending in South Africa.

Methods: I carried out a retrospective observational study of changes in the pack prices of solid-dose medicines (n = 138) over an 11-year period (2003-2014) before and after the introduction of a national therapeutic tendering system in South Africa and compared the findings with changes over the same period for solid-dose medicines which were not subjected to the policy (n = 672). I ran various difference-in-differences models, with and without adjustments for product characteristics, to estimate the impact of the new policy on medicine prices and spending.

Findings: Compared to trends in the prices of solid-dose medicines not subjected to therapeutic tendering, implementation of therapeutic tendering was associated with a 33.0% (95% CI, 4.0%-53.3%) to 43.7% (95% CI, 20.7%-60.0%) reduction in the average price paid per medicine, depending on the statistical model used. Spending by the health ministry declined by an estimated 1.13 billion (95% CI, ZAR 138.01 million - ZAR 1.83 billion) to 1.50 billion rand (95% CI, ZAR 709.65 million - ZAR 2.06 billion) as a result of therapeutic tendering.

Conclusions: Therapeutic tendering was associated with large drops in the prices of solid-dose medicines, which likely saved the South African health ministry millions of rand in 2014.

MANY new medicines offer little or no additional therapeutic benefit over existing therapies. [57, 67][1] Data, mostly from high-income countries, highlight the potential for large savings on therapeutic substitutes, [250] as described in Chapter 2. To incentivise drug companies to develop truly innovative medicines, regulators in some countries have adopted policies to cut spending on so-called me-too medicines, such as therapeutic drug substitution and reference pricing. [116, 123][2]

Another option to reduce spending on me-too drugs is to tender for medicines by therapeutic class. [33] Pharmaceutical tendering refers to the bulk purchase of medicines from suppliers at agreed-upon prices over a contracted period. [2, 111, 140, 142, 143, 208, 224, 279, 317–319] Under a therapeutic tendering policy, a payer only buys the least expensive product in a defined therapeutic class.

Tendering by therapeutic class can generate greater savings than tendering by individual products in two ways. First, the prices of some products might fall due to increased competition, especially when one or more of the medicines in the therapeutic group are patent protected. Second, the average volume-weighted price per class might decrease after patients switch to the cheapest product in each class. In the latter case, the volume-weighted price can go down even if the price of the cheapest product did not change, or even increased.

In this study, I investigate the South African therapeutic tendering system. The country's national government has issued pharmaceutical tenders since 1982. In 2014, the national health ministry implemented a therapeutic tendering system for solid-dose medicines with a view to maximize savings on therapeutically-equivalent products. The aim of this study was to estimate the effect of the introduction of this policy on: (i) the prices of medicines subjected to the policy and (ii) the total spending on these products. Before describing the methods and dataset, I present basic theories underpinning pharmaceutical tenders.

[1] This chapter is being prepared for submission to a peer-reviewed journal.
[2] Refer to Chapters 1 and 2 for more information on reference pricing and substitution policies.

5.1 Theoretical background

Auction, agency, and contract theory are all helpful frameworks against which to analyze findings relating to pharmaceutical tenders. [321, 410, 411] Tenders are closely linked to the theory of auctions, one of the oldest forms of markets. [410–412] McAfee and McMillan (1987) define an auction as "a market institution with an explicit set of rules determinng resource allocation and prices on the basis of bids from the market participants." [411] A seminal paper by Vickrey [413] brought the topic into the field of economic research, with much having been written since. The present article will focus on the literature relevant to public tenders, but recent overviews by Milgrom [414] and Klemperer [410] offer useful insights into auction theory.

Theoretical studies have outlined basic models of first-price, sealed-bid reverse auctions for homogeneous products. The descriptions below were derived from work conducted by Milgrom and Weber, [415] McAfee and McMillan, [411] Huh and Roundy, [416] and Klemperer, [410] unless otherwise indicated.[3]

Consider a scenario in which there are at least two pharmaceutical firms which produce a generic product, say a 28-tablet pack of the cholesterol-reducing drug simvastatin (20 mg). Each simvastatin manufacturer i ($i = 1, 2, \cdots, n$) has a cost of production c ($c_i = c_1, c_2, \cdots, c_n$). A successful bidder earns a profit which is equal to its bid value, b_i, minus its cost of production, c_i.

There are four key assumptions to this model. First, bidders are risk neutral, meaning they are neither risk averse nor risk seeking. In other words, the bidding decisions of suppliers are not affected by the amount of uncertainty present in the bidding process. Second, manufacturers' production costs are independent of each other, and these costs are private knowledge. Third, profits are solely a function of a firm's bid. And, fourth, bidders possess symmetric information, meaning no firm has any advantage over another one due to additional knowledge about other firms or the tendering process. (There are several reasons why these assumptions may not hold, as discussed at the end of this section.[4])

Each firm assumes that the other firms follow a bidding rule, β, based on their costs of production. In other words, given a cost of simvastatin production c_i, a firm will always bid $\beta(c_i)$, which can also be written as b_i. β is a monotonically increasing function, meaning that a higher cost of production always results in a higher bid.

A firm's probability of winning corresponds to the probability that the lowest cost of production among all other bidders, c_j, is larger than its own. That is, $\beta(c_j) > b_i$.

[3] As described in Chapters 1 and 2, generic medicines can be assumed to be homogeneous products for most patients.

[4] Maskin and Riley [417] relax each of these assumptions in their analysis.

This probability can be expressed as

$$1 - F(\frac{1}{\beta(b_i)})^{n-1}$$

where F is the probability distribution function of production costs for the $n-1$ other firms. It is assumed that each firm tries to maximize expected profits, π_i, which can be written as

$$\pi_i = (b_i - c_i)(1 - F[\frac{1}{\beta(b_i)}]_i^{n-1})$$

The profits that firm i would earn if it won with bid b_i are multiplied by the probability of winning with this bid.

The profit maximization problem can be solved at a Nash equilibrium, in which each bidder is assumed to behave rationally and in a way that is consistent with the assumptions outlined above. Under such conditions, the optimal bid for supplier i results in a price that is close to the marginal cost of production. The solution corresponds to a situation in which bidder i is indifferent as to whether the tender is won or not. Interested readers should consult the relevant theoretical studies for the solutions to this Nash equilibrium problem, which is outside the scope of this thesis. [410,411,415,416]

This basic model is a useful starting point for analyzing tenders. It indicates that tenders should put downward pressure on prices of multi-source products. More specifically, the model suggests that a drug purchaser which issues a tender—and is able to attract a sufficient number of bids—would end up paying close to the marginal cost of production of the cheapest firm.

Yet there are many reasons why the results of this basic model may not hold. Importantly, in South Africa and elsewhere, there are often additional variables beyond best price which are used to determine the winners. These variables can either be written into the conditions of award or involve ad hoc decisions by the buyer, as described in Chapter 4. In other words, although auctions or tenders provide a forum for price competition, the buyer may select the final winner in response to non-price considerations specific to the circumstances and needs of the buyer. For example, the national health ministry in South Africa allows local manufacturers to match the lowest price for designated products. A local firm might therefore bid a higher price knowing they are likely to receive an opportunity to revise its offer. Moreover, part of the bid evaluation is based on broad-based black economic empowerment scores, and the health ministry regularly splits awards to reduce the risk of supply disruptions. Still, theoretical models suggest that when buyers award sizable market shares to the lowest bidders, reverse auctions should stimulate strong price competition. [418–422]

Moreover, the degree of risk aversion may differ between companies. For example, large-size firms which produce many products may be more willing to take risks than

small and medium-size ones, given that firms prepare bids based on their medicine portfolios (ie, joint probability of winning a number of contracts, rather than any one contract). There might be differences in risk perceptions between local and international companies. Also, repeat bidders might obtain useful insights about the tendering process which may affect their bidding strategy, resulting in firms possessing asymmetric information. For instance, a manufacturer might be reluctant to offer its best price if it experienced late payments or incorrect volume forecasts in previous tenders.

Therapeutic tendering, in theory, should make the system even more competitive by treating all products in a designated class as homogeneous. By increasing the number of potential bidders, the probability of the payer obtaining a lower bid increases. Yet, given the reasons above for why the basic theoretical assumptions may not always hold, it is important to assess empirically whether therapeutic tendering is associated with a reduction in prices and spending.

5.2 Methods

5.2.1 Institutional background

As described in Chapter 4, the national government in South Africa issues tenders to set the prices of essential medicines in the public health care system.[5] The National Department of Health (NDoH) divides medicines into fourteen categories (see **Box 4.1** in Chapter 4). The health ministry puts out a tender medicines in each category every two-to-three years. Tenders outline the quantity of each product that is needed, as well as other information like lead times. The NDoH accepts bids from national and international manufacturers with the right to sell a product in South Africa.

Before the implementation of therapeutic tendering, the national government issued tenders for each medicine listed on the country's standard treatment guidelines. For example, in 2012, the NDoH separately tendered for atorvastatin (10 mg), fluvastatin (40 mg), and simvastatin (10 mg). In 2014, in an effort to enhance price competition, the South African NDoH began tendering by therapeutic class for medicines which it considers interchangeable. The health ministry designated therapeutic classes in all of the categories shown in **Box 4.1**, with the exceptions of anti-tuberculosis medicines and large-volume parenterals.[6] For instance, in the tender for solid-dose medicines and transdermal patches, the NDoH views the cholesterol-reducing drugs atorvastatin (10 mg), fluvastatin (40 mg), lovastatin (20 mg), rosuvastatin (5 mg), and simvastatin (10 mg) as therapeutically equivalent. Under the new policy, the health ministry started only buying the least expensive product in this group (simvastatin, 10 mg, in 2014).

The NDoH stopped tendering by therapeutic class in 2016 due to concerns about patient adherence to therapy, since therapeutic tendering resulted in changes to treatment regimens for some patients. There is ongoing policy discussion at national level to reintroduce the policy.

5.2.2 Data sources

In this paper, I focus on tenders for solid-dose medicines and transdermal patches, which were awarded every two years between 2003 and 2009 and then every two years between 2012 and 2016; **Appendix A** lists the therapeutic classes for solid-dose medicines and transdermal patches. I focused on products in this category for three reasons. First, the tender category is by far the largest, accounting for roughly 40% of products on contract between 2003 and 2016 (3,294/8,655). Second, by restricting

[5]Between 2003 and 2011, the National Treasury issued tenders. The National Department of Health took over the tendering process in 2012.

[6]The health ministry did not designate therapeutic categories for diagnostic agents, contrast media, and pharmaceutical packaging materials, but none of these categories contain medicines.

the analysis to a single tender category, it allowed us to minimize any differences in the results which might have arisen due to variation in tendering procedures across categories. Third, it reduced confounding due to differences in the results attributable to medicinal forms (eg, liquids vs. powders vs. tablets vs. injections).

I obtained all tender contracts for solid-dose drugs procured in the public sector between 2003 and 2016. Tender contracts contain information on medicine prices, quantities, manufacturers, and lead times.[7]

The dataset contained 3,294 products, which were defined by active ingredient and indication (ATC level 4). The number of products per year ranged from 289 line items in 2016 to 508 in 2003, including split contracts. I excluded 359 products which belonged to one or more of the following categories: combination products with multiple active ingredients, products not on the country's "essential medicines list", minerals, vitamins, proteases, and saccharins. I also dropped the 2016 data from the analysis, since therapeutic tendering was halted in that year. I was left with 2,648 observations: 2,300 products which did not belong to a therapeutic tendering class (ie, control arm) and 348 products which belonged to such a class in 2014 (ie, treatment arm).

The prices per pack were adjusted for inflation based on consumer price indexes, [353] with all costs reported in 2016 rand. I calculated average volume-weighted prices for split awards.[8] I also calculated the average volume-weighted price per therapeutic class, since this is the outcome of interest.[9]

This product-level panel dataset consisted of five pre-intervention periods (2003, 2005, 2007, 2009, 2012) and one post-intervention period (2014). The panel dataset was unbalanced, since not all products were procured in each year and new products were added to the tender in each year.

I restricted the products to those available in all six tender years to account for the changing composition of the control and treatment groups over time, as done in other studies. This was done to limit selection bias, [423] since average prices are very susceptible to extreme prices. For example, if a larger number of new on-patent medicines enter the control arm each year—which are usually accompanied by higher price tags—then this would raise the average price in the control group. This could then potentially lead to the parallel trends assumption not being met as a result of the

[7] A lead time is defined by the health ministry as "the [maximum permissible] time from submission of order to supplier to time of receipt by the department as confirmed by the Proof of Delivery document". [352]

[8] For instance, if one firm was asked to supply 60% of the contracted volume at a price of 5 ZAR per pack, and another was asked to supply 40% of the volume at a price of 10 ZAR per pack, the weighted price was 7 ZAR (5*0.6 + 10*0.4). The method applied by the NDoH to split awards is outlined in the conceptual framework.

[9] For example, if a therapeutic class consists of two products, one priced at 10 ZAR (15,000 packs) and the other at 20 ZAR (5,000 packs), the volume-weighted price would be 12.5 ZAR (10*0.75 + 20*0.25).

changing composition of the control and treatment arms. Although this led to a smaller sample size and a loss of statistical power, the remaining dataset still consisted of 135 products with measurements at six points in time (i.e. 810 observations). This included 138 observations for the intervention group, and 672 in the control group.

Trends in medicine prices are influenced by market characteristics, such as the availability of new medicines, loss of exclusivity for branded medicines, and competition between brand-name and generic firms. [424] In order to estimate the impact of therapeutic tendering on the prices of medicines subjected to this policy, it is necessary to distinguish between the impact of the policy on the prices and the impact of underlying market factors. To control for the latter, I selected those medicines in the solid-dose tender which were not grouped into therapeutic classes as control groups.

5.2.3 Econometric model

I followed a similar identification strategy to that in Pavcnik (2002). [186] To address potential observed and unobserved confounding, I estimated the following multivariable difference-in-differences model

$$ln(p_{it}) = \alpha_i + \beta D_i + \gamma A_t + \delta D_i \cdot A_t + m_i + T_t + \epsilon_{it}$$

where p was the price (expressed as a natural logarithm) of product i at time t, D an indicator variable for products subjected to therapeutic tendering (ie, treatment group), A an indicator variable for post-treatment period, m a product fixed effect, T a time fixed effect, and ϵ an error term. The measurement of treatment effect was done using ordinary least squares.

The interaction term $D \cdot A$ was the main result of interest. This term captured the impact of the introduction of therapeutic tendering in 2014 on the weighted-average prices of drugs subjected to the policy. The prices were expressed as natural logarithms since the data were positively skewed. The use of log-transformed prices also allows for an intuitive interpretation of the results in terms of the relative price change.

All models included a product fixed effect to control for any individual characteristics of units–in both treatment and control arms—that affect price levels but do not vary over time. This includes time-invariant characteristics such as the therapeutic value of a medicine, form (eg, tablet vs. modified-release capsule vs. patient-ready pack), therapeutic class, and strength. Similarly, the time fixed effect controlled for any changes over time which affected prices, such as efficiency improvements in the tendering process as the Treasury or National Department of Health gained experience.

I ran various difference-in-differences models with and without adjustment the generic status of a medicine, ie, a dummy variable indicating whether a product was

off-patent or not [10]. The generic status of a medicine could change over time, ie, time-variant covariate. In each model, I clustered the standard errors by medicine (ie, robust standard errors) to account for potential heteroscedasticity or autocorrelation. [425] This corrects for any within-medicine correlation between repeated measures.

I calculated a supplementary model as a robustness check: I collapsed the time-series data from 2003 to 2012 into a single pre-treatment period (ie, average values for each product), and then re-ran the models. [425] By ignoring the time-series dimension of the data, this model addresses the potential for the standard errors to be underestimated due to serial autocorrelation. The results of a widely-cited simulation exercise found that this approach helps solve this issue. [425]

The methods outlined above adhere to guidelines on how to evaluate the impact of changes to pharmaceutical pricing policies. [426] All statistical tests were two-tailed and used a type I error rate of 0.05. The data were analyzed in Stata version 15.

5.2.4 Model assumptions

A difference-in-differences analysis compares changes in the outcome variable among units in a treatment group (ie, units subjected to a new policy or event) and units in a control group (ie, units not subjected to the intervention). The key assumption is that the trends in the outcome variable would have followed parallel paths in the post-intervention period had the intervention not occurred. Under such a scenario, the outcome in the control group can serve as a proxy for what would have happened in the treated group in the absence of treatment (ie, unobserved counterfactual). [427] Thus, by taking the difference in the pre- and post-treatment outcomes in the treated and control groups, and then taking the difference of these differences, the model eliminates the effect on prices of market-level factors that affected both groups. [424, 428] This accounts for both observed and unobserved heterogeneity between the two groups, as long as the trends then follow parallel paths.

To verify the parallel trends assumption,[11] researchers often plot the mean outcome values in the treatment and control groups to visually inspect whether the trends are parallel. However, medicines can go off-patent at various times, which may result in an unbalanced pattern if you do not control for the off-patent status of a drug (ie, whether it is still patent-protected or available in generic form). It is important to account for any relevant product characteristic that can change over time at different rates in the treatment and control groups and that is likely to impact prices.

[10] To determine the off-patent status of a product, I triangulated information contained in the "Private-Sector Database of Medicine Prices", "Republic of South Africa Pharmaceutical Database", and tender contracts.

[11] This assumption is sometimes referred to as the common trends assumption or parallel paths assumption. Wing and colleagues define it as: "[difference-in-differences designs] assume that confounders varying across the groups are time invariant, and time-varying confounders are group invariant". [428]

Therefore, to test for parallel trends, I adjusted the model above for the off-patent status of a product and included leads of the treatment in each of the other years (2003-2012). This was done by interacting the treatment indicator with the year variable.[12] [429] These are sometime referred to as "placebo tests". In other words, I controlled for the generic status of medicines and then examined the treatment effect in each year. If the parallel trend assumption were to hold, I would observe a statistically significant treatment effect in the intervention year ($D \cdot T$), but no significant effects in any of the earlier years when the policy was not yet in place.

There are three other assumptions underpinning difference-in-differences analyses. First, it is assumed that the intervention is unrelated to the outcomes at baseline. In other words, the allocation of medicines to treatment or control groups was not influenced by their starting prices.[13] This is unlikely to be the case for therapeutic tendering, since the inclusion or exclusion of products is due to their perceived therapeutic interchangeability. Second, the composition of the intervention and comparison groups must remain stable over time, which is part of the stable unit treatment value assumption (SUTVA). This was accounted for by restricting the analyses to those products observed in all study periods, as outlined in the section above on data sources. Third, SUTVA also requires that the intervention had no spillover effects on other units not subjected to treatment.

[12] I could not test for lags in the treatment since I only had one post-treatment observation.

[13] Bertrand *et al* explain that difference-in-differences estimation "is appropriate when the interventions are as good as random, conditional on time and group fixed effects". [425]

5.3 Results

5.3.1 Summary statistics in year prior to intervention

Table 5.1 shows summary statistics about the costs per pack and market shares of the most and least expensive products in each therapeutic class in 2012.[14] The table only displays information for those therapeutic classes with two or more therapeutically equivalent products on tender in that year.

These data highlight the rationale behind the introduction of therapeutic tendering in 2014. In 2012, the NDoH purchased multiple products in 15 out of the 34 therapeutic classes.[15] The median price difference between the lowest- and highest-priced product in each class was R 12.92 (range: R 1.27 - R 328.94). The median share of the highest-priced product in a class was 47.7% (range: 1.8% - 93.4%). In brief, sizable savings were lost in most therapeutic classes with multiple products on tender.

5.3.2 Parallel trends assumption

The products in the control group by definition differ from those in the treated arm, since therapeutic tendering cannot be applied to any product (ie, it is not possible to randomly apply the policy to any product). In other words, the products in the treated arm are likely to differ systematically from those in the control group in terms of observed and unobserved characteristics. Thus, it is important to examine the trends in prices of medicines in the treatment and control groups to see whether it is reasonable to assume that the medicines in the control group can be used to account for market-level factors which affect both groups.

To test whether the parallel trends assumption holds, I ran the model with leads in the treatment.[16] This was done by interacting the treatment indicator and time variables, to see whether the there was a significant treatment effect in any other year. A significant term would indicate that the trends differed between the products in the control and treatment arms in a given year, which would violate the parallel trends assumption. **Table 5.2** shows the estimated coefficients and standard errors, none of which are significant at the 5% level. These "placebo tests" indicate that the parallel trends assumption holds, since otherwise the results would have shown a significant treatment effect in other years. Thus, the difference-in-differences model should provide a reliable estimate of the true causal effect.

[14] As mentioned in the methods, all monetary values reported in inflation-adjusted 2016 rand, based on consumer price index data for South Africa (World Bank, 2017). Volume-weighted prices were calculated for split awards.

[15] Between 2003 and 2016, multiple therapeutic substitutes were purchased in 23 out of the 34 classes.

[16] As explained in the methods, I adjusted for the off-patent status of a product, which influences the parallel trends.

Table 5.1: Prices and market shares across therapeutic tendering classes (2012).

Drug class	ATC (Level 4)	Tender group	Quantity (no. of packs)	Price of drug in class (ZAR per pack)		Δ price (ZAR)	Share of drug in class (%)	
				Least expensive	Most expensive		Least expensive	Most expensive
Aminosalicylic acid and similar agents	A07EC		124,900	R 279.30	R 356.63	R 77.33	92.8%	7.2%
Sulfonylureas	A10BB	1	1,074,100	R 3.27	R 6.50	R 3.23	9.3%	90.7%
		2	3,718,400	R 3.78	R 12.13	R 8.35	2.7%	97.3%
Dihydropyridine derivatives (calcium-channel blockers)	C08CA	1	23,099,500	R 3.12	R 13.66	R 10.54	63.6%	36.4%
		2	2,876,000	R 4.12	R 26.94	R 22.82	70.7%	29.3%
ACE inhibitors	C09AA		25,716,200	R 3.38	R 10.59	R 7.21	47.7%	52.3%
HMG CoA reductase inhibitors (statins)	C10AA	1	3,590,900	R 4.42	R 17.34	R 12.92	90.4%	9.6%
		2	3,326,000	R 6.76	R 35.99	R 29.23	87.6%	11.8%
Drugs for urinary frequency and incontinence	G04BD		135,700	R 34.83	R 363.77	R 328.94	85.6%	10.8%
Alpha-adrenoreceptor antagonists (for benign prostatic hypertrophy)	G04CA		581,700	R 23.87	R 56.88	R 33.01	10.3%	28.0%
Ethers chemically close to antihistamines	N04AB		389,200	R 26.38	R 45.97	R 19.59	93.3%	6.7%
Serotonin-norepinephrine reuptake inhibitors	N06AX		102,800	R 53.84	R 313.69	R 259.85	1.8%	2.8%
Anti-inflammatory and anti-rheumatic products, non-steroids	M01AB	1	1,758,000	R 2.72	R 3.99	R 1.27	2.7%	97.3%
		2	1,074,800	R 2.67	R 5.24	R 2.57	47.0%	53.0%
		3	2,470,100	R 7.07	R 11.70	R 4.63	30.8%	69.2%

Table 5.2: Sensitivity analysis to test the common trends assumption.

	Coefficient (Standard error)
Treatment * 2005	-0.266 (0.144)
Treatment * 2007	-0.307 (0.163)
Treatment * 2009	-0.333 (0.183)
Treatment * 2012	-0.426 (0.215)
Off-patent status (covariate)	✓
Product indicator	✓
N	810

Robust standard errors, shown in parentheses, were clustered by product. 2003 is the omitted year indicator.

*** Significant at the 0.1% level.

** Significant at the 1% level.

* Significant at the 5% level.

5.3.3 Estimated impact of therapeutic tendering on prices

Table 5.3 shows the difference-in-differences estimator for each model. The results indicate that therapeutic tendering was associated with a large reduction in prices, with the estimated size of the reduction ranging from 33% in model 4 to 44% in model 1.[17]

In the basic model (1), which does not include any adjustments for covariates, the estimated size of the price decline was 44% ($p<0.001$), with a 95% confidence interval of 22% (-0.232) to 60% (-0.916).

In the second (2) model, a covariate was included to adjust for the off-patent status of a product (ie, whether it was available in generic form or not). The estimated price reductions ($p<0.01$) and standard errors were lower than in the basic model, and the R^2 value increased.

In the third model (3), I interacted the difference-in-differences estimator with

[17] These estimates are obtained by exponentiating the coefficients reported in the second row, since prices were expressed as natural logarithms in all models.

the off-patent status. The reasoning behind this was that the effect of the policy on medicines prices might differ depending on how long a product's been on the market and its price prior to the intervention. For example, a generic medicine which has been around for a long time and is very cheap in the year prior to the intervention cannot, in general, drop as much in price as a newer products which higher prices. In other words, there is bigger room for price drops for products which have gone off patent more recently. The triple interaction term was not significant (although the off-patent covariate was), and the difference-in-differences estimator provided similar results to the second model (2).

As expected, the standard error in the collapsed model (4) was larger than the others, since the model ignored most of the time series information. In this model, the average values in the pre-intervention periods were used, resulting in just one period before the intervention and one after. This robustness check is often conducted as part of difference-in-differences analyses due to concern that these analyses may understate standard errors due to severe autocorrelation in the outcome measure—usually highly positive serial correlation. The estimated price reduction in the collapsed model, in which the standard errors were also clustered by product, was comparable to those in models 2 and 3 and still significant at the 5% level, providing further support for the claim that therapeutic tendering had an effect on the prices of medicines in therapeutic clusters.

5.3.4 Estimated savings from therapeutic tendering

In 2014, the mean price among the medicines in the treated arm was R 20.16, meaning the introduction of therapeutic tendering was associated with an estimated average reduction in price of R 6.65 based on model 4 or R 8.87 based on model 1. By multiplying these values by 169,975,410—the number of packs of these medicines purchased in 2014 (ie, products subjected to therapeutic tendering)—the estimated savings ranged from R 1.13 billion (model 4, 95% CI: 138.01 million - 1.83 billion rand) to R 1.50 billion (model 1, 95% CI: 709.65 million - 2.06 billion rand), in inflation-adjusted 2016 values. This corresponded to a range of US$ 100.32 million (95% CI: US$ 12.23 - 161.95 million) to US$ 132.63 million (95% CI: US$ 62.88 - 182.18 million), based on the yearly average exchange rate (11.286) reported by the US Internal Revenue Service.

Table 5.3: The impact of therapeutic tendering on prices, by model (2014).

	(1)	(2)	(3)	(4)
Treatment * post	-0.574***	-0.451**	-0.428**	-0.401*
	(0.175)	(0.152)	(0.135)	(0.182)
95% confidence intervals (CI)	-0.916 to -0.232	-0.751 to -0.152	-0.696 to -0.161	-0.762 to -0.0411
Year indicators	✓	✓	✓	
Off-patent status (covariate)		✓	✓	
Off-patent status * treatment * post			✓	
Collapse pre-intervention periods				✓
Product indicator (fixed effect)	✓	✓	✓	✓
R-squared (overall)	0.0529	0.2213	0.2150	0.2329

Robust standard errors, shown in parentheses, were clustered by product. 2003 is the omitted year indicator. N is 810 in all models except the the collapsed difference-in-differences model (5), where N was 270 since there were only two time periods.

*** Significant at the 0.1% level.

** Significant at the 1% level.

* Significant at the 5% level.

5.4 Discussion

The results indicate that the introduction of therapeutic tendering in South Africa in 2014 for solid-dose medicines and transdermal patches was associated with a large drop in the volume-weighted prices of medicines grouped by therapeutic class. The estimated average size of this price decline ranged from 33% to 44%, depending on the model. The new tendering system is estimated to have saved the South African NDoH between ZAR 1.13 and 1.50 billion in 2014. Given that solid-dose medicines and transdermal patches only account for around 16% of total drug spending (Chapter 4), there is potential for even greater savings in other medicine categories.

Other studies have examined, using difference-in-differences models, the impact of internal reference pricing at ATC level 4—also called therapeutic reference pricing—on prices and spending for medicines included in therapeutic clusters. [128, 186, 424, 430–432] Under a therapeutic reference pricing scheme, a payer establish a maximum reimbursement level for medicines included in a therapeutic cluster, which can include both patent-protected and generic products (ie, both chemically- and therapeutically-equivalent drugs). Those studies generally found that therapeutic reference pricing was associated with a decline in the prices of medicines subjected to the policy, which offers further support for measures which aim to capitalize on the therapeutic substitutability of medicines to put downward pressure on prices.

More research is needed to determine the impact of therapeutic reference pricing on different medicines types (ie, non-solid dose forms) and medicines in other therapeutic areas (eg, oncology and anti-infective medicines) which are tendered for separately in South Africa. Also, it is important for future work to try to disentangle effect of greater competition (ie, increase in number of bidders) from the effect of an increase in the tendered quantity—both of which could account for part of observed change in price levels.

Policymakers aiming to implement therapeutic tendering must consider potential issues which may arise. First, therapeutic tendering is only applicable to groups of medicines which can reasonably be considered perfect or near-perfect substitutes, ie, no significant differences in efficacy, safety, or side effect profiles. It is important to obtain buy-in from pharmacists and physicians on designated therapeutic classes to avoid disagreements over the perceived substitutability of medicines those classes. For therapeutic tendering to be more widely practiced, as with therapeutic substitution or reference pricing (see Chapter 2), the relevant authorities should disseminate and enforce guidelines to ensure the buy-in of physicians, pharmacists, and insurers.

Second, the achievement of low prices through therapeutic tendering is not sufficient on its own to guarantee the availability of medicines at these prices. It is also important to put in place safeguards to prevent supply disruptions, which might be more likely

to occur if a single firm is asked to supply a larger quantity of medicines (ie, satisfy the entire patient demand within a therapeutic cluster). To this end, it may be important for payers to split the awards of a therapeutic tender between two or more firms to minimize the risk of shortages.

Third, it is possible that patient adherence may decline if the reason for a therapeutic switch is not well explained, especially since medicines can have different shapes, sizes, and colors. This might be particularly problematic for chronically ill patients who consume a large number of medicines (ie, polypharmacy). Physicians and other health stakeholders need to communicate such changes to patients to promote continued adherence to treatment.

5.4.1 Limitations

This study has several limitations.

First, the model suffers from potential endogeneity issues. For example, tender prices are not necessarily independent: what happens in another tender category (ie, **Box 4.1** in Chapter 4) could affect solid-dose prices. It was also not possible to determine whether there were any spillover effect on the prices of other medicines (eg, in the private sector). Moreover, there was no way to tell whether products in the treated arm were selected because they were thought to be products which were particularly well-suited for therapeutic tendering (ie, selection bias). [425] However, since this policy cannot be randomly allocated to any unit, it is reasonable to assume that the products were selected only based on therapeutic interchangeability—as opposed to any other reason which might have influenced prices—which was confirmed through discussions with health ministry officials. It is also impossible to determine definitively that nothing other than the policy changed in 2014, and that we can attribute the entire treatment effect only to the introduction of therapeutic tendering, although, again, this was confirmed qualitatively through discussion with ministry officials.

Second, I only had one post-intervention observation, and was thus unable to determine any change in underlying trends of prices. Thus, the results are only a point estimate of the immediate impact of the policy change on prices and spending. Tender outcomes, however, are categorically different from drug utilization rates or drug prices set in a free market. In such cases, utilization rates sometimes only stabilize several months after the intervention, which, in turn, leads to delays before the full impact on prices and expenditures can be observed. In addition, there might be cyclical trends in utilization, such as seasonal variation in prescribing, which can only be captured with a large set of post-intervention observations. This is less of a concern with tendering: one would expect that companies have assessed the implications of the policy change and changed their bidding strategy in the first tender. Instead, pre-intervention observations

are more important in this case.

Third, I was unable to distinguish between quantity and competition effects, due to lack of data on the number of bidders. It is possible that either the larger quantities obtained through pooling procurement in therapeutic tenders or an increase in the number of bids was the driver behind the observed price reductions. Future analyses should explore the relationships between quantities and prices, as well as number of bids and prices.

Fourth, as an additional robustness check, I would ideally have used propensity-score matching to control for product mix, quantity, number of bids, year, product type, therapeutic class, off-patent status, number of products in a class (ATC level 3), and product age. These are all factors which influence price levels, based on empirical studies (Chapter 1). Propensity-score matching is meant to create balanced groups as per randomization and improve the precision of estimates, although estimates are still vulnerable to unobserved confounding. However, I did not have data on all of the relevant variables mentioned above. For instance, I had no data on how long product has been off patent (ie, age of a molecule). Also, as the sample size was small, pruning the data through propensity-score matching would have likely decreased the statistical power considerably.

Finally, the effect of therapeutic tendering is dependent on when the policy is introduced (ie, "status quo" prior to implementation). Point estimates may differ if the policy is introduced after tendering is used for years, as in South Africa, or immediately introduced without tendering having been used previously.

5.5 Conclusions

Policymakers should promote the use of less expensive, therapeutically-equivalent medicines, preferably generics, whenever possible. Therapeutic tendering is a potentially important policy lever to cut spending on more expansive therapeutic substitutes, especially patented products which face limited market competition. Therapeutic tendering is associated with a large decline in the volume-weighted average prices of medicines included in therapeutic clusters, and the introduction of this policy can generate sizable savings.

Appendix A: List of therapeutic categories

Table A. Solid-dose medicines included in therapeutic classes and groups (2014).

Class	Group	ATC-4	Medicine	Strength	Pack size
1	1	A02BC	Lansoprazole	15 mg	28 capsules
			Omeprazole	10 mg	28 tablets/capsules
			Pantoprazole	20 mg	28 tablets
			Rabeprazole	10 mg	28 tablets
	2	A02BC	Esomeprazole	20 mg	28 enteric-coated tablets
			Lansoprazole	30 mg	28 capsules
			Omeprazole	20 mg	28 capsules
			Pantoprazole	40 mg	28 enteric-coated tablets
			Rabeprazole	20 mg	28 tablets
	3	A02BC	Esomeprazole	20 mg	14 tablets
			Lansoprazole	30 mg	14 capsules
			Omeprazole	20 mg	14 tablets
			Pantoprazole	40 mg	14 enteric-coated tablets
	4	A02BC	Esomeprazole	40 mg	28 enteric-coated tablets
			Lansoprazole	30 mg	28 capsules
			Omeprazole	40 mg	28 capsules
			Pantoprazole	40 mg	28 enteric-coated tablets
			Rabeprazole	20 mg	28 tablets

Class	Group	ATC-4	Medicine	Strength	Pack size
	5	A02BA	Ranitidine	150 mg	56 film-coated tablets
			Ranitidine	300 mg	28 film-coated tablets
2	1	A07EC	Mesalazine	400 mg	90 tablets
			Mesalazine	500 mg	90 tablets
			Sulphasalazine	500 mg	100 tablets
3	1	A10BB	Gliclazide	80 mg	28 tablets
			Glimepiride	1 mg	28 tablets
	2	A10BB	Gliclazide	80 mg	56 tablets
			Glimepiride	2 mg	28 tablets
	3	A10BB	Gliclazide	80 mg	112 tablets
			Glimepiride	4 mg	28 tablets
4	1	C02CA	Doxazosin	4 mg	30 modified-release tablets
			Prazosin	5 mg	30 tablets
	2	C02CA	Doxazosin	1 mg	30 tablets
			Prazosin	1 mg	100 tablets

Class	Group	ATC-4	Medicine	Strength	Pack size
5	1	C08CA	Amlodipine	5 mg	28 tablets
			Felodipine	5 mg	30 tablets
			Lercanidipine	10 mg	28 tablets
			Nifedipine	30 mg	28 modified-release tablets
	2	C08CA	Amlodipine	10 mg	28 tablets
			Felodipine	10 mg	30 tablets
			Lercanidipine	20 mg	28 tablets
			Nifedipine	60 mg	28 modified-release tablets
	3	C09AA	Enalapril maleate	10 mg	28 tablets
			Fosinopril	20 mg	30 tablets
			Perindopril	4 mg	28 tablets
			Quinapril	20 mg	28 tablets
	4	C09AA	Enalapril maleate	10 mg	56 tablets
			Enalapril maleate	20 mg	28 tablets
			Fosinopril	40 mg	30 tablets
			Perindopril	8 mg	28 tablets
			Quinapril	40 mg	28 tablets
6	1	C10AA	Atorvastatin	10 mg	28 tablets
			Fluvastatin	40 mg	28 capsules
			Lovastatin	20 mg	28 tablets

Class	Group	ATC-4	Medicine	Strength	Pack size
			Rosuvastatin	5 mg	28 tablets
			Simvastatin	10 mg	28 tablets
	2	C10AA	Atorvastatin	20 mg	30 tablets
			Atorvastatin	40 mg	30 tablets
			Rosuvastatin	20 mg	28 tablets
			Simvastatin	20 mg	28 tablets
7	1	G04BD	Darifenacin	7.5 mg	28 tablets
			Flavoxate HCl	200 mg	84 tablets
			Oxybutynin chloride	5 mg	84 tablets
			Tolterodine-l-tartrate	4 mg	28 modified-release tablets
8	1	G04CA	Alfuzosin	10 mg	28 tablets
			Doxazosin	4 mg	30 modified-release tablets
			Tamsulosin HCl	0.4 mg	28 sustained-release capsules
			Terazosin	5 mg	28 tablets
9	1	B01AC	Aspirin	80 mg	28 dispersible tablets
			Aspirin	81 mg	28 enteric-coated tablets
			Aspirin	100 mg	28 tablets
			Aspirin	300 mg	14 soluble scored tablets
10	1	N04AB	Biperiden HCl	2 mg	28 tablets

Class	Group	ATC-4	Medicine	Strength	Pack size
			Orphenadrine HCl	50 mg	28 tablets
			Trihexyphenidyl HCl	2 mg	28 tablets
	2	N04AB	Biperiden HCl	2 mg	56 tablets
			Orphenadrine HCl	50 mg	56 tablets
			Trihexyphenidyl HCl	2 mg	56 tablets
	3	N04AB	Biperiden HCl	2 mg	84 tablets
			Orphenadrine HCl	50 mg	84 tablets
			Trihexyphenidyl HCl	2 mg	84 tablets
11	1	G02CB	Pramipexole	0.125 mg	100 tablets
			Pramipexole	0.25 mg	100 tablets
			Pramipexole	1 mg	100 tablets
			Bromocriptine	2.5 mg	28 tablets
			Bromocriptine	5 mg	28 tablets
			Ropinirole HCl	0.25 mg	84 tablets
			Ropinirole HCl	0.5 mg	84 tablets
			Ropinirole HCl	1 mg	84 tablets
			Ropinirole HCl	5 mg	84 tablets
12	1	N06AX	Bupropion HCl	150 mg	56 tablets
			Sertraline	50 mg	30 tablets/capsules
			Venlafaxine	37.5 mg	28 tablets

Class	Group	ATC-4	Medicine	Strength	Pack size
			Venlafaxine	75 mg	28 modified-release capsules
			Venlafaxine	150 mg	28 modified-release capsules
13	1	N06AB	Citalopram	20 mg	28 tablets
			Escitalopram	10 mg	28 tablets
14	1	M01AB	Diclofenac sodium	25 mg	15 enteric-coated tablets
			Ibuprofen	400 mg	15 coated tablets
			Naproxen	250 mg	10 tablets
	2	M01AB	Diclofenac sodium	25 mg	30 enteric-coated tablets
			Diclofenac sodium	50 mg	15 enteric-coated tablets
			Ibuprofen	400 mg	30 tablets
			Naproxen	250 mg	20 tablets
	3	M01AB	Diclofenac sodium	25 mg	84 enteric-coated tablets
			Ibuprofen	400 mg	84 tablets
			Naproxen	250 mg	56 tablets
	4	M01AB	Diclofenac sodium	25 mg	100 enteric-coated tablets
			Ibuprofen	400 mg	100 tablets
			Naproxen	250 mg	100 tablets
15	1	P02CA	Albendazole	200 mg	2 tablets

Class	Group	ATC-4	Medicine	Strength	Pack size
			Albendazole	400 mg	1 tablet
16	1	R06AE	Cetirizine dihydrochloride	10 mg	28 tablets
			Desloratadine	5 mg	28 tablets
			Loratadine	10 mg	28 tablets
17	1	C09CA	Candesartan	8 mg	28 tablets
			Losartan	50 mg	28 tablets
			Valsartan	40 mg	28 tablets
	2	C09CA	Candesartan	16 mg	28 tablets
			Losartan	100 mg	28 tablets
			Valsartan	80 mg	28 tablets

6

Transitioning to a national health system in Cyprus: A stakeholder analysis of pharmaceutical policy reform

"I like maxims that don't encourage behavior modification."
– Bill Watterson, *Calvin and Hobbes (19 Jan. 1991)*

Key messages

- Cyprus is one of the few high-income countries in the world that has yet to establish a national health system which covers a basic set of health care services for all legal residents.
- There are issues in the country's pharmaceutical sector, notably underuse of generic medicines, high medicine prices, and high out-of-pocket drug spending.
- The national government will need to adapt its tendering system and other pharmaceutical policies as it transitions to a national health system in 2017.
- A key challenge is how to raise awareness among patients, physicians, and pharmacists about the benefits of greater generic drug use.

Abstract

Context: Cyprus intends to introduce a national health insurance scheme in 2017. The aim of this study was to review the pharmaceutical sector in Cyprus in terms of the availability and affordability of medicines and to explore pharmaceutical policy options for the national health system finance reform.

Methods: We conducted semi-structured interviews in April 2014 with senior representatives from seven key national organisations involved in pharmaceutical care. The captured data were coded and analysed using the predetermined themes of pricing, reimbursement, prescribing, dispensing, and cost sharing. We also examined secondary data provided by the Cypriot Ministry of Health; these data included the prices and volumes of prescription medicines in 2013.

Findings: We identified several key issues, including high medicine prices, underuse of generic medicines, and high out-of-pocket drug spending. Most stakeholders recommended the national government review existing pricing policies to ensure medicines within the forthcoming national health system are affordable and available, introduce a national reimbursement system and incentivize the prescribing and dispensing of generic medicines. There were disagreements over how to (i) allocate responsibilities to governmental agencies in the national health system, (ii) reconcile differences in opinion between stakeholders and (iii) raise awareness among patients, physicians, and pharmacists about the benefits of greater generic drug use.

Conclusions: In Cyprus, if the national health system is going to provide universal health coverage in a sustainable fashion, then the national government must address the current issues in the pharmaceutical sector. Importantly, the country will need to increase the market share of generic medicines to contain drug spending.

In 2013, Cyprus had a population of about 858,000 and a gross domestic product (GDP) of about 16,500 euros (€) per capita. [433, 434][1] The country's health system consists of a public and a private sector. Individuals with annual incomes of no more than € 15,400, the chronically ill and civil servants—together representing about 83% of the population—are eligible for public-sector coverage. [435] The government pays for public-sector health care while patients and private health insurers pay for private-sector health care. Total health expenditure is about 7.3% of the GDP. [344] About 43% and 57% of health spending is publicly and privately funded, respectively. [433] In 2010, pharmaceutical expenditure—€ 322 per capita—accounted for 19.8% of total health expenditure in Cyprus. [433]

In 2013, Cyprus agreed to a memorandum of understanding with creditors from the European Commission, European Central Bank, and International Monetary Fund and introduced an economic adjustment programme to address the country's financial, fiscal, and structural challenges. [436] The memorandum calls for the introduction of a national health system finance reform to allow free choice of provider, social equality and solidarity, financial sustainability, and universal coverage of a minimum benefit basket. [437] Initially, the memorandum called for the introduction of a national health system by mid-2016. The implementation of this health system is now expected to take place in 2017.

In the forthcoming system, the government will pay for all health care services in the benefit basket—subject to cost sharing—and supplement current tax revenues with other sources of funding, including taxes on employers, employees, and pensioners. [438] The reform will bring major changes in financing, coverage, provider payment, and data collection and monitoring. [435] The government still needs to decide which drugs to cover, which pricing and reimbursement policies to apply and what type of cost sharing to introduce.

Given the lack of research on the Cypriot pharmaceutical system, [144, 439–442] the aim of this study was to review the current system of pharmaceutical care in the private and public sectors in terms of the availability and affordability of medicines. We also wanted to explore how the public and private markets could be efficiently merged in the national health system and to assess the key barriers to the implementation of the new system.

[1] This chapter was published: Wouters OJ, Kanavos PG (2015). Transitioning to a national health system in Cyprus: A stakeholder analysis of pharmaceutical policy reform. *Bulletin of the World Health Organization*, **93**(9): 606-613.

6.1 Methods

To collect primary data, we conducted interviews in April 2014 with senior representatives from seven national organizations **(Box 6.1)**. [443] The interviewees represented all but one of the organizations involved in pharmaceutical care in Cyprus. The exception was the Cyprus Medical Association, whose representatives were unavailable to meet. The interviewees were jointly selected by the researchers, the World Health Organization Regional Office for Europe, and the Cypriot Ministry of Health. We met with the representatives from each organization separately over three days and each interview lasted between 30 minutes and two hours. All interviews were held at the headquarters of the health ministry's department of pharmaceutical services, in Nicosia. At least three members of this department were present at each interview.

Box 6.1: National organizations represented by interviewees, Cyprus (2014).

1. Cyprus Association of Pharmaceutical Companies, representing Cypriot drug importers and distributors
2. Cyprus Association of Research and Development Pharmaceutical Companies, representing research-based manufacturers
3. Cyprus Pharmaceutical and Chemical Manufacturing Company, representing Cypriot manufacturers of generic drugs
4. Cyprus Pharmaceutical Manufacturer Association, representing Cypriot pharmacists
5. Health Insurance Organization, the government agency in charge of implementing the national health system reforms
6. Pancyprian Federation of Patients Associations and Friends, representing Cypriot patients
7. Ministry of health's department of pharmaceutical services, the government department in charge of national pharmaceutical policies

The interviews were semi-structured (**Box 6.2**) but the discussions varied based on the roles of each organization. One of the researchers and a ministry of health employee took notes during each interview, and these notes were discussed with health ministry officials after each meeting, to confirm our understanding of the data. We followed the consolidated criteria for reporting qualitative research checklist [444] and used NVivo 10 (QSR International, Melbourne, Australia) to organize, code, and analyse the interview data.

The department of pharmaceutical services also provided secondary data to help us understand the current policies and features of the pharmaceutical markets. These data included the prices and volumes of all prescription medicines used in the public and private sectors in 2013, relevant legislative documents and internal ministry of health reports. The quantitative data were analysed using Excel 2007 (Microsoft, Redmond, United States of America).

Box 6.2: Semi-structured interview template used to assess the Cypriot pharmaceutical market.

1. What are the strengths and weaknesses of the pharmaceutical policies in the public sector?
2. What are the strengths and weaknesses of the pharmaceutical policies in the private sector?
3. Which pharmaceutical policies should be changed before the introduction of the national health system reforms?
4. Which pharmaceutical policies should be applied in the national health system?
5. What are the key barriers to the successful implementation of the national health system reforms?

6.2 Results

6.2.1 Current pharmaceutical policies

6.2.1.1 Public sector

Public-sector drugs, which are freely available to patients with public health insurance, are procured centrally by the ministry of health through two types of tenders: open invitations and negotiations. [144, 441]

In an open invitation, which is used for about 75% of the drugs consumed in the public sector, the ministry of health issues a request for a quantity of drugs and invites confidential bids from manufacturers worldwide. The manufacturer that offers the lowest price is then asked to supply the entire market for two years. A tender category usually includes a single molecule—ie, the originator brand drug and generic drugs with the same active ingredient—but may also include all drugs that treat the same condition—eg, the class of cholesterol-reducing drugs known as statins. The invitation process lasts about eight months—excluding drug delivery time—and accounted for € 54.5 million of government expenditure in 2013. The remaining 25% of drugs used in the public sector, which are mostly on-patent, are procured through negotiations and accounted for € 50 million of government expenditure in 2013. Once a tender price has been accepted by both the ministry of health and the manufacturer, it is legally binding and cannot be changed.

The public-sector tender prices of generic drugs are usually 20-70% lower than the private-sector wholesale prices. In extreme cases, prices in the private sector may be more than 30-fold higher than in the public sector (**Table 6.1**). For on-patent drugs, however, the public-sector prices are usually only 5-10% lower than the private-sector prices.

For all tenders, the government buys the stock in three to four installments and distributes the drugs to the 11 hospital and 34 retail pharmacies in Cyprus, which together represent one public pharmacy for every 15,500 public-sector patients. Public-sector pharmacists receive a government salary. The annual storage, distribution, and dispensing costs for drugs sold in retail pharmacies total about € 6.3 million.

Table 6.2 summarizes the drug expenditure in the public sector for the year 2013; the ten and 50 highest-selling products accounted for 17.6% and 44.0% of expenditure, respectively. In the same year, there were 18 foreign research-based manufacturers that each had over € 1 million in public-sector drug sales in Cyprus—together representing 56.0% of all such sales. All foreign manufacturers sell their drugs in Cyprus via about 45 importers. These importers serve as wholesalers and handle national pharmacovigilance requirements. There are three Cypriot generic drug manufacturers, which export as much as 93% of their output to foreign markets.

Table 6.1: Anonymised tender results for three selected medicines, Cyprus (2013).

Product, condition, bid	Quantity, packs	Bid price, € /pack	Budget impact, € [a]	Private-sector wholesale price, € /pack
Product A (hypertension)				
Bid 1 (winner)	36,000,000	0.0189	678,857	0.35
Bid 2		0.0223	804,000	
Bid 3		0.0225	801,000	
Bid 4		0.0239	861,428	
Bid 5		0.026	936,000	
Bid 6		0.0333	1,200,000	
Bid 7		0.0411	1,478,571	
Bid 8		0.0463	1,668,215	
Bid 9		0.15	5,399,999	
Product B (osteoporosis and other bone disease)				
Bid 1 (winner)	5,000	12	60,000	208.02
Bid 2		29.29	146,450	
Bid 3		29.5	147,500	
Bid 4		29.85	149,250	
Bid 5		33.97	169,850	
Bid 6		38.9	194,500	
Bid 7		50.09	250,439	
Bid 8		105	525,000	
Bid 9		129	645,000	
Product C (colorectal cancer)				
Bid 1 (winner)	2,800	9.12	25,536	50.00
Bid 2		12.00	33,600	

€, euros.

[a] Actual budget impact may vary due to rounding.

Source: Data provided by the Department of Pharmaceutical Services, Ministry of Health, Nicosia, Cyprus.

All drugs sold in the Cypriot public sector are listed in a national formulary, which included 1,767 products in 2013. Nearly all of the drugs used in Cyprus for the treatment of cancer, haemophilia, hepatitis B, hepatitis C, and human immunodeficiency virus are sold exclusively in public pharmacies because all patients with these illnesses are eligible for public coverage. There is a co-payment plan, with an annual budget of € 600,000, that allows public-sector patients to buy medicines only available in the private sector.

Table 6.2: Drug expenditure in the public and private sectors, Cyprus (2013).

Category	Expenditure (millions of euros)[a]	
	Public sector	Private sector
Prescription drugs[b]	98.5	80.6
Inpatient	59.5	9.7
Outpatient	39	70.9
On-patent originator brand	7.7	8.4
Off-patent originator brand	10.8	46.6
Generic	19.3	11.4
Vaccines and others	1.2	4.5
Over-the-counter drugs	5	14.3
Total drug expenditure	**103.5**	**94.9**

[a] Excluding value-added tax.

[b] Inpatient and outpatient drugs are sold in hospital and retail pharmacies, respectively.

Source: Data provided by the Department of Pharmaceutical Services, Ministry of Health, Nicosia, Cyprus.

6.2.1.2 Private sector

Private-sector drug prices are set by the health ministry based on the recommendations of a pricing committee. For on-patent products, this committee bases the Cypriot wholesale price on the mean of the wholesale prices in one high-price country—ie, Sweden, two medium-price countries—ie, Austria and France, and one low-price country—ie, Greece. If a medicine is not available in one of these countries, the committee uses the price in a pre-selected alternate country. To account for the cost of importing the drug into Cyprus, the committee adds a 3% mark-up to the derived mean price. The committee recalculates the prices of most drugs every two years. It revises the price of each newly launched product annually for the first two years. The private-sector prices in Cyprus are among the highest in Europe, [445] largely because

this pricing system captures the official prices in the reference countries and does not take into account confidential discounts.

After patent expiry, originator brand drugs continue to be priced through international price referencing. Generic drugs must be priced at least 20% below the price of the originator brand at the time of patent expiry. Consumption of generic drugs in the private sector is low, partly because pharmacists are forbidden by law to substitute such drugs for any originator brand drugs prescribed by physicians (**Box 6.3**).

In 2013 there were 481 private pharmacies in Cyprus—ie, about one for every 300 private-sector patients. The pharmacy price of a drug includes the pharmacist's mark-up and a value-added tax of 5%. The mark-up is determined by the wholesale price of the drug pack and is set at 37%, 33%, and 25% for packs that cost no more than € 50, between € 50 and € 250, and more than € 250, respectively. Private-sector pharmacists also charge a flat fee of € 1.00 per prescription.

Table 6.2 summarizes the 2013 drug expenditure in the private sector. The ten and 50 highest-selling products accounted for 11.5% and 34.5% of private drug spending, respectively. About 87% of the total health expenditure within the Cypriot private sector was out-of-pocket while private health insurers paid the rest. [344] Only 2,054 of the 5,241 products registered for sale in the private sector were available in 2013—mostly because of insufficient demand for the other products.

Box 6.3: Current issues in the Cypriot pharmaceutical market (2014).

1. The private-sector prices are among the highest in Europe, largely because international price referencing does not capture confidential discounts in other countries.
2. On-patent drugs in the public sector are expensive. As public-sector prices are published online—and may therefore influence prices in countries that use the Cypriot prices for reference—manufacturers are not willing to provide large discounts to the ministry of health. The national association for research-based manufacturers has confirmed this observation.
3. There is underuse of generic drugs in the private sector and generic substitution by pharmacists is forbidden. Over 77% of spending in private retail pharmacies is on branded products—ie, on-patent and off-patent originator brands.
4. Although there is a national list of approved pharmaceutical products, the government does not disseminate any prescribing guidelines and

there are no information systems to monitor or control prescribing behaviour.

5. There are few limits on the financial relationships between physicians and manufacturers, which may lead to conflicts of interest.
6. Private-sector patients pay for drugs almost entirely out-of-pocket. This could expose patients to undue financial risks or deter some from seeking beneficial treatment.

6.2.2 Policy options

We investigated pharmaceutical policy options for the national health system, dividing the main feedback and suggestions of the stakeholders into the categories of pricing, reimbursement, prescribing, dispensing, and cost sharing. Below, to contextualize the stakeholders' statements, we have added references to relevant studies.

6.2.2.1 Pricing

The consensus was that reviewing the current pricing policies to facilitate the transition to the national health system was important. To decrease the prices of on-patent drugs in the public sector, the association representing research-based manufacturers recommended the ministry of health keep price discounts confidential—thus limiting the spill-over effect on markets that use Cypriot prices for reference. The health ministry representatives agreed to investigate legal options that could be followed to strike confidential agreements on drug prices. To reduce private-sector prices, the ministry of health offered to adjust its system of international price referencing—eg, it could apply the lowest price paid in the reference countries.

Stakeholders held differing views about which pricing policy to follow. The national associations for drug importers, local generic drug manufacturers, pharmacists, and research-based manufacturers each noted that there is a possible trade-off between low prices and the availability of medicines. As Cyprus is a small market, these groups posited that, if prices drop too low, the manufacturers of originator brand and generic drugs might not sell their products in Cyprus—because it would produce insufficient returns on the manufacturers' investments and/or adversely affect prices in other markets that use Cypriot prices for reference. The same groups urged the Cypriot government to use international price referencing in any future national health system and to apply a reimbursement system to receive confidential discounts. Other things being equal, however, a small population size does not appear to be associated with a relatively low market penetration by generic drugs. [8]

The ministry of health claimed the current wholesale prices of drugs in the private sector would be unaffordable in a national health system and that tendering could be used more widely. The health insurance organization suggested the prices of drugs in the national health system should be set somewhere between the current public- and private-sector prices, but did not elaborate further.

6.2.2.2 Reimbursement

All stakeholders were in favour of introducing a national reimbursement system. The health insurance organization intends to create a new national formulary and a reimbursement committee to manage it. Formularies can be used to specify the medicines eligible for reimbursement and—alongside prescribing guidelines—encourage the rational use of medicines. [446]

The health insurance organization and ministry of health are working independently on criteria for the admission of new products to a future formulary. The ministry of health suggested that, to guide the inclusion or non-inclusion of drugs in a national formulary, the government should monitor, collect, and analyse all relevant clinical and economic evidence from health technology assessment bodies in other countries. The government could ask manufacturers to adapt foreign data on the cost-effectiveness of drugs to local conditions.

The association for research-based manufacturers favoured the use of risk-sharing schemes in the national health system. Such schemes could be applied to hedge against uncertainties—at the time of a drug's entry to the Cypriot market—regarding the drug's budget impact, clinical effectiveness, and cost-effectiveness. These schemes grant manufacturers favourable reimbursement rates in return for achieving financial or outcome targets. The health insurance organization is considering the use of risk-sharing schemes. Although such schemes are widely used in Europe, they require appropriate performance measurement and enforcement. [447,448]

Finally, the health insurance organization noted that widespread tendering in a unified national market could create supply disruptions, drive some generic drug manufacturers out of business and lead to higher generic drug prices over time. The organization proposed instead to use internal reference pricing and to tender selectively if such pricing does not achieve adequate price reductions for some products. Internal reference pricing sets a reimbursement ceiling based on the prices in a basket of drugs—eg, the mean price of all drugs with the same active ingredient. If the price of a drug exceeds the reference price, the patient usually has to pay the difference. Systematic reviews have consistently found that such a policy can reduce drug prices and generate savings. [116,123,125] The federation representing patients supported offering patients the choice between a generic drug and an originator brand version at a higher price.

6.2.2.3 Prescribing

Prescribing guidelines can have a beneficial impact on prescribing, when enforced appropriately. [449–451] The Cypriot Ministry of Health plans to develop such guidelines for conditions with a high budget impact. When appropriate, the ministry might adapt guidelines published in other countries.

The interviewed representatives of the ministry of health, health insurance organization and pharmacy association suggested the government enforce the prescribing of generic drugs in the national health system. The health insurance organization aims to introduce an electronic prescribing system to examine prescribing patterns and to improve the quality of medicine use. The organization is reviewing other options to encourage cost-effective prescribing, such as pay-for-performance schemes. It remains unclear, from the evidence collected in other countries, whether pay-for-performance schemes often achieve their intended goals. [452]

The Cypriot Ministry of Health believes there should be appropriate limits on drug advertising and on the gifts and contributions given to physicians by drug manufacturers. One survey has found that, for Cypriot physicians, pharmaceutical sales representatives are one of the most important sources of information on the safety and efficacy of medicines. [453]

6.2.2.4 Dispensing

In some countries, if a physician prescribes an originator brand drug despite the availability of a cheaper generic equivalent, pharmacists can override the physician's decision and dispense the generic drug instead. Depending on the country, such generic substitution can be mandatory, [155] voluntary [115] or, as in Cyprus, forbidden. In our interviews, both the ministry of health and health insurance organization favoured mandatory generic substitution, which can speed up the market entry of generic drugs and reduce pharmaceutical spending. [10] The federation representing patients opposed such substitution, however, and stated that all treatment decisions should be made by physicians.

Most sales (81.3%) in the Cypriot private sector in 2013 were for drug packs with a wholesale price of no more than € 50 per pack. These packs were subject to one of the highest pharmacy mark-ups in Europe, of 37%. [295] The ministry of health and health insurance organization stressed that pharmacy mark-ups needed to be reduced and revised in Cyprus to encourage the dispensing of generic drugs. However, the interviewees from the association representing pharmacists expressed concern about the poor macroeconomic conditions in Cyprus and, consequently, the financial viability of pharmacies if the remuneration system were to change in any way that would reduce the income of pharmacists.

6.2.2.5 Cost sharing

The health insurance organization is exploring various cost-sharing options—ie, deductibles, co-insurance or co-payments or any combination of these. The organization is also considering whether to apply exemption criteria and cost-sharing caps to protect patients financially. It may remove co-payments for conditions where compliance is an issue, such as some psychiatric conditions. The interviewees from the federation representing patients stressed the importance of limits on cost sharing to protect vulnerable groups like the chronically ill. The interviewees from the ministry of health stated that the current out-of-pocket burden on private-sector patients was too high and that this burden needed to be reduced in the national health system.

6.2.3 Barriers

We identified four key barriers to the successful implementation of a comprehensive drug-benefit plan in the forthcoming national health system reforms.

First, it appeared difficult to obtain the buy-in of all stakeholders for the health care reform. Notably, there was disagreement over whether the prices of prescription medicines in the future system should be the current private-sector or public-sector prices or lie somewhere between the two. Other disputes might arise, such as physicians resisting the monitoring of prescribing habits. To resolve such disputes, it is important to involve all stakeholders in the reform process.

Second, the governmental stakeholders—ie, the health insurance organization and ministry of health—need to clarify their roles in the forthcoming system, particularly regarding who will be in charge of reimbursement. Clear and transparent rules are needed to allocate responsibilities. Since its inception, the Cypriot Ministry of Health has been solely in charge of national pharmaceutical policies. Although the health insurance organization was established in 2001, [438] it has only been actively engaged in discussions with the ministry of health for the last few years.

Third, most of the proposed policy changes would need to be accompanied by legislative changes, which may be time-consuming. Although the memorandum of understanding provided a broad timeline for the implementation of a national health system—including deadlines for key legislative changes—it allowed little time for consensus-building and preparation.

Finally, the patient association stated that many patients—especially in the private sector—do not perceive generic drugs to be as good as the originator drugs in terms of safety and efficacy. It is possible that in Cyprus some physicians and pharmacists also exhibit loyalty to brand name medicines. This may explain why generic substitution has been forbidden in the Cypriot private sector. The government could launch a public education campaign to promote the use of generic drugs. [150]

6.3 Discussion and conclusions

Pharmaceutical policies should reflect national priorities for health and industrial policy, including cost containment, employment, innovation, and trade promotion. [454] In many countries, the main objectives of pharmaceutical policies are to ensure equitable access to—and the good quality and rational use of—effective drugs. [23] The findings of this study are meant to inform the ongoing policy deliberations in Cyprus. They can also be used to inform discussions in other countries aiming to establish a comprehensive drug-benefit plan under universal health coverage.

This study has some limitations. First, personal bias is unavoidable in interviews. To minimize the risk of such bias, both interviewers closely followed an interview template. Second, no representatives of the Cyprus Medical Association were available for an interview during the study visit. Members of this association could have provided valuable input on the prescribing environment. Finally, although this study looked at reform in the pharmaceutical sector, a holistic analysis is needed to understand the full impact of national health system reforms in Cyprus.

Over the next few years, there is a need to update the legislative and institutional framework in Cyprus and to acquire data, through pilot studies and simulations, on how health care might operate under the new system. There is a further need to build capacity and to address issues before and after reforms are introduced. The government should work to eliminate each of the four barriers identified. The Cypriot authorities should also prepare for unforeseen problems that inevitably accompany large-scale changes to health systems. Once new policies are implemented, the government should continue to monitor the results.

7

Conclusion

"What are you after?" ... "Well," said Zaphod airily, "It's partly the curiosity, partly a sense of adventure, but mostly I think it's the fame and the money ..."

– Douglas Adams, *The Hitchhiker's Guide to the Galaxy*

Key messages

- It is important for policymakers and other health stakeholders to regularly monitor the functioning of generic drug markets to quickly catch and address problems, such as shortages or large price hikes.
- Policymakers can calculate price indexes to get a sense of whether they are overpaying for generic medicines or not, although it is important to recognize the methodological pitfalls of such comparisons.
- Tendering is potentially one of the most efficient tools for governments or health care bodies to procure medicines, but there is a lot of room for errors and unintended issues with a system as complex as tendering.
- Therapeutic tendering is a seemingly effective policy to cut spending on so-called "me-too" medicines.

A mix of factors, including aging populations, slowing economic growth, and rising costs of new drugs and medical technologies, have put pressure on governments to contain health care spending.[1] Given these severe cost pressures on health care budgets globally, some nations are reassessing, reforming, and restructuring their models of health system financing. In this context, most health policy analysts view generic medicines as a vital component of any strategy to improve access to medicines and promote universal health care in both developed and developing economies.

Substituting generic medicines for more expensive brand name versions is likely among the most cost-effective interventions in health care systems. [14, 15, 71–73, 455, 456] Generic medicines are bioequivalent replicas of brand name drugs, containing the same active ingredients and with identical quality, safety, and efficacy profiles. A generic can be sold for a fraction of the price of the brand name drug as it is relatively inexpensive to bring to market. Access to high-quality, low-cost generic medicines is especially important at a time when many high-income countries have cut public health care spending since the global economic downturn in 2008. [457, 458] In poorer countries seeking to increase access to health care, the availability of generic medicines can improve financial protection, reduce out-of-pocket spending, and enhance health care quality and efficiency.

Yet there is wide disparity in access to generic drugs across high- and middle-income countries, which has important economic and equity implications. The findings of this thesis contribute to the evidence base on how to encourage generic drug use and to stimulate price competition among generic drug companies, with a view to improve access to medicines. The five Ph.D. studies present evidence which can be used to inform generic drug policy reform in high- and middle-income countries aiming for universal health coverage.

As discussed in Chapter 1, generic drug markets could, in theory, operate efficiently under certain conditions. First, consumers must have access to information about the price and quality of medicines to make informed decisions. It is often difficult or impossible for patients to obtain these data. [459, 460][2] For a generic drug market to operate efficiently, patients must be able to easily choose between interchangeable products (ie, brand-name drugs and their generic counterparts) based on price[3], which

[1] Some of the text in this chapter was published: Wouters OJ, Mckee M (2017). Private financing of health care in times of economic crisis: A review of the evidence. *Global Policy*, **8**(S2): 23-29.

[2] It could be argued that greater efforts should be made to systematically collect and disseminate easy-to-understand data to patients, physicians, and pharmacists about the price and quality of medicines. However, it would be important to determine the administrative costs this would entail, whether it is even feasible given the complexities of health care decision-making, and whether all shortcomings inherent to generic drug markets could be adequately addressed.

[3] This assumes all generic drugs are bioequivalent to their brand-name counterparts, which is not always the case in low- and middle-income countries.

should incentivise companies to compete on costs. However, consumers are often insulated from the prices of medicines because of comprehensive drug insurance, making them less cost-conscious. This issue is exacerbated by the fact that treatment decisions are often taken by physicians, pharmacists, or insurers on behalf of patients. As a result, traditional economic laws of supply and demand do not always hold.[4] Second, patients, physicians, and pharmacists must hold evidence-based views and perceptions about generic medicines, which, as explained in Chapter 2, is not always the case. In reality, many patients and health care professionals view generics as being less safe and effective than their brand-name counterparts.

In summary, although standard economic theory might predict that little or no government regulation should be needed in generic drug markets to achieve low generic drug prices and high usage rates, [116] empirical results from this thesis and other studies reveal major failures in generic drug markets. Many commentators therefore argue that these markets should be regulated to some extent—even if just to prevent large price hikes for generic drugs—although the scale and nature of such regulation are rarely specified. Indeed, generic drug markets in many countries are heavily regulated. Yet governments in some countries, like the US, take a largely laissez-faire approach to governing off-patent pharmaceutical markets.

These issues and contradictory approaches have fuelled debates about how to regulate generic drug markets to achieve low prices and high usage rates on a sustainable basis. Although these debates are sometimes ideological, reflecting different views about the relationship between the individual and the state with respect to government intervention in free markets, they need to be evidence-based. The main aim of this thesis was to examine issues relating to generic drug prices, usage rates, and policies.

This thesis focused on generic drug markets, given key differences between generic and biosimilar products. As the US Food and Drug Administration explains [461]

> A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.

Generic and biosimilar drugs differ in terms of pricing, reimbursement, prescribing, and dispensing, and cost sharing regulation. [462] There is ongoing debate over the interchangeability and substitution of biological and biosimilar products, due to concern that substitution may increase immunogenicity. [463] In the EU, substitution policies for biological and biosimilar products are set at the national level. There is therefore a

[4] There have also been documented cases of generic drug firms colluding to fix the prices of generics, as mentioned in Chapter 2. [220, 269]

need to analyse generic and biosimilar markets separately.

7.1 Summary of key findings and contributions to the literature

The main research question posed in this thesis was: what are features of an efficient generic drug market? This broad, overarching topic was broken down into five sub-questions, each of which was addressed in one of the studies comprising this thesis.

1. How do generic drug prices, policies, and utilization rates compare across selected high-income countries? (*Article 1*)
2. What are the methodological challenges to comparing generic drug prices across countries? (*Article 2*)
3. What is the effect of pharmaceutical tendering on prices and competition over a 15-year period? (*Article 3*)
4. What is the price impact of tendering for medicines by therapeutic class? (*Article 4*)
5. What are features of a sustainable tendering system for generic drugs under universal health coverage? (*Article 5*)

As a starting point for this thesis, I compared how generic drug prices, spending, market shares, and policies compared across a wide range of high-income countries. Chapters 2 and 3 (Articles 1 and 2) provide empirical evidence and methodological guidance for generic drug price comparisons. These chapters also benchmark variation in generic drug prices between countries against differences in pricing and reimbursement policies for generics. A take-away message was that countries which relied on tendering or tender-like systems in 2013 seemed to have among the lowest prices among the countries included in the studies. This served as a starting point for more in-depth analysis of tendering.

Chapters 4, 5, and 6 (Articles 3, 4, and 5) provide data on the short- and long-term effects of tendering. There are few published data on tendering, despite it potentially being one of the most efficient policies for high- and middle-income countries to procure medicines. Given that tenders are currently under consideration in many settings, it is important to study existing systems to outline best practices.

Here I outline the key findings and empirical contributions to knowledge of each study.[5]

[5]Parts of the text in the following subsections, like description of study objectives and results, appear in the relevant sections of each chapter.

7.1.1 Article 1

This study found that there are missed opportunities for significant savings from generic drugs in Europe and the US.[6]

Shifting patients from branded to less expensive generic medicines is an important way to contain health care costs. Yet the prices and prescription rates of generics vary widely across Europe, resulting in missed opportunities for cash-strapped health systems and patients. Policymakers in Europe and the U.S. should do more to break down the barriers preventing timely access to affordable generic drugs for patients. The study highlights the patchwork of policies in place in Europe and the US.

The study analysed 2013 data on the list prices[7] and market shares of more than 3,000 generic drugs in 13 European countries and found the prices charged by manufacturers in Switzerland are, on average, more than two and a half times those in Germany and more than six times those in the United Kingdom, based on one commonly used price index. The proportion of prescriptions filled with generics ranges from 17 per cent in Switzerland to 83 per cent in the United Kingdom, among the countries included in the study. By contrast, roughly 9 out of 10 prescriptions are filled generically in the U.S. Having patients consume generic drugs instead of their more expensive brand name counterparts is among the most cost-effective interventions in health care, with potentially hundreds of millions of euros currently being wasted.

Based on a comprehensive literature review, this study identified numerous barriers to the use generic drugs, including misperceptions among patients about the quality of generic medicines and the lobbying powers of special interest groups. The article analysed how regulators and policymakers in both Europe and the U.S. can (i) make it easier for generic drugs to reach the market, (ii) stimulate price competition among generic drug makers, and (iii) increase generic drug use.

These proposals come at a time when health systems worldwide are under financial pressure. Notably, the U.S. has in recent years experienced a series of widely-criticized price hikes for generic drugs. For example, the price of pyrimethamine (Daraprim), an off-patent anti-infective medication used by HIV/AIDS patients, rose from $13.50 a tablet to $750 overnight in 2015, despite having been around for decades at low cost in the U.S.

[6]Some of the text in this subsection also appears in a summary of the paper I wrote for the London School of Economics website (http://www.lse.ac.uk/News/Latest-news-from-LSE/2017/09-September/Generic-medicine).

[7]List prices are official prices before discounts. The data does not reflect confidential rebates and discounts.

7.1.2 Article 2

In this study, I calculated all commonly used price indexes, using the same dataset as in the first article, to highlight methodological challenges to comparing generic drug prices across countries. I restricted the analysis to seven countries in order to increase the sample size and to only include countries for which both ex-manufacturer and retail data were available.

Consistent with the findings of Article 1, I observed large differences in generic drug prices between these seven countries. However, the results varied, sometimes dramatically, depending on the choice of index, base country, unit of volume, method of currency conversion, price level (ie, ex-manufacturers vs. retail), and therapeutic category.

Price indexes are one of the main statistical techniques that policymakers, regulators, and other health stakeholders have at their disposal to gauge differences in price levels between countries. In an era of ever-escalating drug prices, policymakers should regularly benchmark prices in their own countries against those of neighboring countries—or countries with similar income levels—to ensure they are not over-paying for generic drugs. This is especially important in resource-constrained settings, where generic medicines can generate savings and free up budget space.

However, health policy analysts applying these methods should be aware of the many methodological pitfalls which can influence the results of such analyses. When concerns about price levels in a country exist, drug price indexes should ideally be supplemented by quantitative analyses of drug policies, price analyses of individual products, and qualitative analyses to understand the nature and potential causes of observed issues.

7.1.3 Article 3

This study found that tendering can be an effective policy to procure essential medicines at low prices, based on analysis of data from South Africa.

The average prices of antiretroviral therapies, anti-infective medicines, small-volume parenterals, drops and inhalers, solid-dose medicines, and family-planning agents dropped by roughly 50% or more over this period in the country, based on price index calculations. Moreover, many tender contracts in South Africa remained competitive over time, based on Herfindahl-Hirschman results, with some notable exceptions. This offers important counter-evidence against claims made by some commentators that tendering systems are likely to lead to higher prices in the long-run, among other disadvantages. There remains concern that tendering might drive companies out of business, [325] so more work is needed to study the impact of centralised procurement systems on market structures. Indeed, the number of firms winning contracts decreased

steadily in most South African tender contracts between 2003 and 2016.

Tendering is potentially one of the most efficient platforms for setting medicine prices and purchasing products in bulk. As a centralised procedure, tendering allows national governments—or sub-national bodies, if tendering is done at a regional level—to achieve economies of scale and scope, realize administrative savings, and improve price transparency. Health policy analysts attribute the large savings observed in existing analyses of tendering systems to the ability of a monopsony (eg, a single purchaser of medicines on behalf of a large number of patients) to drive prices down aggressively for the products and services it covers.

Yet there is a lot of room for errors and unintended issues with a system as complex as tendering. Notably, there were large discrepancies between the drug quantities the South African health ministry estimated it would need to meet patient demand and the quantities the ministry went on to procure during tender period. The number of different firms winning contracts decreased over time in most tender categories, a situation which the health ministry should continue to monitor to prevent any future price hikes or supply disruptions.

There is also growing anecdotal and empirical evidence indicating that product shortages occur regularly in south Africa. The effects of stock-outs are significant: apart from the cost implications for the government of buying off-contract—often at a substantial premium—it may reduce patient trust in the system and can threaten treatment adherence.

7.1.4 Article 4

This study found that the introduction of therapeutic tendering in South Africa in 2014 was associated with large drops in the prices of solid-dose medicines, which likely saved the South African health ministry millions of rand in that year.

Given the rapidly increasing prices of many new medicines and the proliferation of me-too medicines, it is important for payers and regulators to incentivise drug firms to produce medicines which provide additional therapeutic benefit. One challenge is to stimulate price competition when medicines are protected by patents or other forms of market exclusivity, which grant firms monopoly pricing powers. In these cases, a policy option is to tender for medicines by therapeutic class.

To the best of my knowledge, this is the first quasi-experimental study of the impact of therapeutic tendering on medicine prices and spending. The South African health ministry introduced such a system for a solid-dose medicines in 2014, the largest tender category in the country. I ran various difference-in-differences regression models, with and without adjustments for covariates, to estimate the impact of the new policy on drug prices and spending. I also ran robustness checks (ie, placebo tests and collapsed

pre-intervention data) to examine the reliability of the results.

The findings consistently showed that the policy was associated with large declines in the prices of medicines subjected to the policy, ranging from an average of 33% to 44%, depending on the model. The findings suggest that such a decline likely led to savings of more than ZAR 1 billion for the health ministry in 2014 for these products.

Future studies should re-examine the South African therapeutic tendering system once data from more post-intervention periods are available, possibly using other research designs like interrupted time-series models (ie, segmented regression analysis). It is important to determine whether the findings in this thesis can be replicated, and whether they hold for other types of medicines (eg, injectables).

7.1.5 Article 5

This study outlined a blueprint for how Cyprus can move from a fragmented health care system—one in which there are parallel public and private systems—to a single-payer one, using tendering as the basis for a comprehensive drug-benefit plan.[8]

Cyprus is one of the few high-income countries in the world that has yet to establish a national health system that covers a basic set of health care services for all legal residents. At the time of the study, the government was aiming to introduce a national health system by 2017, and needed to decide which drugs to cover in the forthcoming health care system, which pricing and reimbursement policies to apply, and how much patients would have to pay for medicines.

To collect primary data, we conducted a four-day study visit to Cyprus in April 2014. During the visit, we interviewed senior representatives from seven national organizations involved in pharmaceutical care in the country. These organisations represented various stakeholders, including research-based and generic drug manufacturers, pharmacists, patients, and relevant government agencies. The health ministry's department of pharmaceutical services also provided secondary data on the prices and volumes of prescription medicines in 2013.

We identified several key issues, notably the underuse of generic medicines in the private sector, high medicine prices in both sectors and high out-of-pocket drug spending in the private sector. We also analyzed pharmaceutical policy options—based on the feedback and suggestions from the interviewees—to inform the ongoing reform process. The article also discussed likely barriers to the introduction of a comprehensive drug-benefit plan in the forthcoming national health system. Barriers include how to reconcile disagreements between stakeholders over which policies to adopt in the new

[8]Some of the text in this subsection also appears in a case study I wrote for the London School of Economics website (http://www.lse.ac.uk/researchAndExpertise/researchImpact/caseStudies/kanavos-wouters-enabling-health-care-reform-in-the-Republic-of-Cyprus.aspx).

system, as well as how to raise awareness among patients, physicians and pharmacists about the benefits of greater generic drug use.

7.2 Policy implications

7.2.1 Generic drug prices, usage, and policies

Following the worst global economic downturn since the Great Depression in the 1930s, there is renewed pressure on governments and health stakeholders to control health spending and to obtain good value for money in health care systems. Between 2008 and 2015, several European governments implemented generic drug policies to help control costs. [149, 224, 464, 465] During this period, Slovakia introduced voluntary generic prescribing, which was previously forbidden. Belgium, Estonia, Greece, Portugal, and Spain made generic prescribing compulsory. Greece and Portugal made generic substitution compulsory. And Finland introduced internal reference pricing.

Yet the results of the first and second articles suggest that many countries need to do a better job of obtaining lower prices from generic drug firms and more effectively control the distribution chain for pharmaceuticals. There remain large differences between countries in generic drug prices and rates of generic drug usage. An immediate priority is to persuade more physicians, pharmacists, and patients that generic drugs are bioequivalent to branded products, although this may take time. In the meanwhile, much could be achieved by requiring generic prescribing and substitution where such policies are not yet in place.

The regulatory environment for generic medicines and the structure of health care systems vary widely across countries. Therefore, it is unlikely that there is any one-size-fits-all solution to regulate generic drug markets. Instead, it is possible that a particular form of a policy might play a beneficial role in a specific setting but not in another. Thus, given the current state of knowledge, any calls to implement a particular pharmaceutical policy should, ideally, be accompanied by robust evidence, such as real-world pilot studies. Moreover, as the designs of generic drug policies are heterogeneous, it is necessary to assess the strengths and weaknesses of individual systems. Also, because different interventions are often implemented at the same time, it is sometimes difficult to disentangle the contribution of each policy change. It is therefore important to pay attention to the context in which these reforms are implemented before generalising findings from one setting to another.

Price indexes are one of the most useful statistical tools at the disposal of policy-makers to gauge how price levels compare across countries. Yet medicines differ within and between countries in strengths and formulations, as well as other factors (see Chapter 3). There is a trade-off between matching all these variables and the sample

size. The second study in this thesis illustrates how price-index calculations can differ dramatically depending on the choice of method. This offers insights for policymakers wishing to apply such methods. Another approach would be to compare the prices of individual "reference" products for various active ingredients. However, there is no obvious way to choose a strength-form combination to look at, and not all combinations will be available internationally, so researchers might end up with a small sample size. In short, while price indexes are a useful tool to assess how prices vary across countries, it is important to interpret the results with caution given these limitations.

7.2.2 Tendering and joint procurement

The thesis gives some of the first evidence internationally on how a tendering system influences medicines prices and competition over a period of ten years or longer. This is timely given that a growing number of countries in Europe and elsewhere are considering using such systems. [129, 140] Moreover, the research on the Cypriot tendering system can inform the ongoing health care reforms in the country. [466]

The results of these studies show that while tendering can achieve low prices in both the short- and long-term, it is important to recognize and proactively address issues which may arise, such as supply disruptions and mis-estimates of required quantities. It is important for policymakers aiming to introduce tendering to examine what role strategic procurement can play in the drug sector, and how to best leverage purchasing power to improve efficiency. As outlined in Chapter 4, policymakers should consider trade-offs between obtaining the lowest possible prices for medicinal products and other policy objectives (eg, industrial growth, split contracts to reduce the risk of supply disruptions, etc.).

Therapeutic tendering is potentially a very effective tool to reduce spending on patent-protected products which offer little additional therapeutic value (ie, "me-too" drugs), as shown in Chapter 5. To increase the cost savings from tendering, policymakers should promote competition between companies by facilitating generic market entry. It is important for government agencies or other bodies advertising tenders to attract bids from as many local and international manufacturers with marketing authorization as possible.

Moreover, there is growing interest in joint pharmaceutical procurement between countries with similar income levels and disease profiles (eg, Nordic countries; Belgium, Luxembourg, and the Netherlands). [33, 467] This is sometimes referred to as regional group or pooled procurement of medicines. Tendering might be a suitable platform for such procurement, which requires "shared political will, sharing of information and experience, capacity-building, and harmonization". [33] It is increasingly important for national governments to cooperate to get the best possible deals for their patients given

the spiraling costs of many medicines.

Group purchasing of medicines and other health technologies can create economies of scale and reduce transaction costs. It can potentially take place in public or private sectors, and at any level of health care systems. [468] Successful examples include the Pan American Health Organization's Revolving Fund, which purchases 46 vaccines (eg, polio, measles, yellow fever, rotavirus, and human papillomavirus vaccines) on behalf of governments in 41 countries and territories in Latin America and the Caribbean, [469–471] and the Gulf Cooperation Council Group Purchasing Program, which purchases essential medicines and medical supplies for governments in six Middle Eastern countries. [472] The EU has successfully issued tenders for some health products, including gloves and Bacillus Calmette-Guérin (BCG) tuberculosis vaccines. There is also interest in issuing tenders at EU level for new, expensive hepatitis C medicines. [33] Yet in Europe, despite harmonization of rules for public procurement (eg, EU Public Procurement Directive 2014), there is a need for more operational research and transparency to implement joint procurement.

7.3 Key limitations

In each of the five articles presented in this thesis, I outlined specific limitations which may have impacted the results of each paper. Here I elaborate on three cross-cutting limitations which affected most of the studies in this thesis. These issues are important for researchers on generic drug markets to consider in future studies.

7.3.1 List prices

The data in the first two articles did not reflect confidential discounts, which can be sizable for generic drugs in some countries. [294]

The lack of reliable data on confidential discounts is an issue which plagues most drug price comparisons and analyses, often leaving researchers with no choice but to rely on list prices. Drug firms regularly use this caveat to argue in regulatory filings that the findings of such analyses are flawed and do not reflect the actual prices they are offering to payers. [473, 474] However, without better access to such data—which drug firms usually keep confidential, stating they are commercially sensitive in nature—it is difficult for health policy researchers to get a better idea of how medicine prices compare across countries. With the prices of medicines in many therapeutic areas rising rapidly, it is more important than ever for health policy analysts, governmental bodies, and other stakeholders to promote price transparency in drug markets. Otherwise, drug firms hold a strong advantage when negotiating prices in different countries.

7.3.2 Price indexes

All drug price indexes suffer from important limitations, which is why I explored the methodological issues inherent to such analyses in the second article.

Laspeyres indexes answer the following question: if the base country paid the same prices for a sample of drugs as a comparator country, what would happen to drug spending? An index value of 120 for a foreign country, for example, indicates that expenditure in the base country would rise by 20% if it paid the prices found in the foreign country, assuming consumption remained constant. Another way to say this is that prices are, on average, 20% higher in the foreign country for the sample of drugs. Conversely, an index value of 80 suggests that the base country would reduce spending by 20% if it paid the same prices as the foreign country. Paasche indexes are interpreted similarly, but under the assumption that demand in the base country would look like that of each comparator country given the same prices. In most cases, Laspeyres and Paasche indexes can be thought of as lower- and upper-bound estimates, respectively, of potential savings in the base country. [206] Fisher indexes is the geometric mean of the Paasche and Laspeyres indexes, so Fisher results lie between the other two.

Uncertainty around the true underlying price elasticity—as well as the relative impact of other factors which influence demand, such as standards of care, disease prevalence rates, prescription drug coverage, and patient preferences—make it difficult to determine which index is most appropriate. This issue is compounded by the fact that there is no perfect measure of quantity for price indexes, there is uncertainty around whether purchasing power parities or exchange rates are more appropriate for currency conversions, and the choice of base country affects the results of Laspeyres and Fisher indexes.[9]

7.3.3 External validity

There are important threats to the external validity (ie, generalizability) of the findings in the last three articles on tendering systems.

It is important to examine the generalizability of the findings across countries: while the tendering models in Cyprus and South Africa may be suitable for those settings, they may be less effective—or even have adverse consequences—if used by policymakers in other countries. The results of these studies cannot necessarily be used to justify the use of tendering elsewhere. As a general rule, it is not advisable to transplant pharmaceutical policies from one country to another without careful consideration of the local regulatory and pharmaceutical environment.

[9]The latter issue is arguably less important for policymakers in individual countries, since the home country is usually chosen as the base.

Similarly, the results of the fourth article on therapeutic tendering should be interpreted with caution. The study only examined the impact of therapeutic tendering on solid-dose medicines, so the results may not hold for other types of products (eg, injectables and liquids). Also, because I only had data from one post-intervention period, it was not possible to determine any changes in the underlying price trends. The effect of therapeutic tendering is also dependent on when the policy is introduced (ie, "status quo" prior to implementation). Point estimates are likely to differ if the policy is introduced after tendering is used for years, as was the case in South Africa, or immediately introduced without tendering having been used previously.

In summary, it is difficult to extrapolate the findings in the last three articles to other tendering systems, given the unique features of the South African and Cypriot systems (eg, broad-based black economic empowerment scheme). Data from more countries are needed to validate these findings.

7.4 Ideas for future research

There are a number of possible extensions to the empirical evidence presented in this thesis.

First, more research is needed to better understand the drivers of differences in generic drug prices between countries. Future studies could conduct regression analyses to examine the association between generic drug policies (**Table 1.2**) and prices. I chose not to do this in the first two articles of this thesis for several reasons. Most importantly, I did not have information about some potential confounders, such as the time since patent expiry or loss of data exclusivity (whichever happened last), the drug indications, and the number of competitors on the market. I would not have been able to control for these factors. Moreover, I only had data for a single year, and it would be difficult to make causal inferences with a cross-sectional study design. Also, a sample size of ten countries would have been too small to conduct meaningful analyses with fixed effects. For example, the UK was the only country in 2013 that allowed free pricing with no other supply-side measures besides regulation of the distribution chain (**Table 1.2**). In such a case, it would be unclear whether a dummy variable for free pricing would capture the effect of the policy on generic drug prices, or the effect of unobserved country characteristics which are correlated with generic drug prices. Future research could conduct these types of analyses using longitudinal data from a larger sample of countries.

Second, additional work is needed to improve procurement procedures and supply management in tendering countries. It is important to study the most appropriate use of tendering in a particular setting. In some countries, national or regional bodies

buy drugs centrally and then supply health care institutions; elsewhere procurement is decentralised at the health institution or facility level. In some jurisdictions, it is possible that tendering should serve a back-up role as a strategic measure when other pharmaceutical policies do not deliver appropriate prices. In such cases, however, it would be important to clearly define what threshold should trigger the use of tendering. In summary, variation in reimbursement processes and administrative structures across jurisdictions may mean that a particular form of tendering is most appropriate in a given setting.

Third, it is important to study which factors and enablers are necessary for joint pharmaceutical procurement models to succeed. There is growing interest in such schemes, which require regional or sub-regional collaboration. For instance, national governments in several countries might band together to facilitate access to costly new medicines.

Fourth, data from more countries, especially low- and middle-income ones, are needed to determine which features of tendering systems are associated with lower prices. Additional research should examine the relationship between the quantities, number of bidders, and prices achieved through tendering. Researchers should analyse whether it is the quantity being tendered for or the number of bidders which is important for achieving large price reductions. It might be also be relevant to consider the size of suppliers (eg, in terms of number of products or market value), since smaller companies might be the first ones to disappear from the market if they are unable to cope with high levels of competition.

Fifth, future studies should re-examine the South African therapeutic tendering system once data from more post-intervention periods are available, possibly using other research designs like interrupted time-series analyses (ie, segmented regression model). A key limitation in the fourth article was that I only had access to one post-intervention observation, meaning I was unable to determine any change in the underlying price trends. Instead, I calculated a point estimate of the immediate impact of the policy change on prices. Also, similar analyses should be conducted for other medicine categories to examine the generalizability of the findings to other medicine forms (ie, non-solid dose drugs) and to specific therapeutic areas.

Finally, more research is needed to examine pricing and reimbursement issues in biosimilar drug markets. Biosimilar products are a recent innovation: the European Medicines Agency and US Food and Drug Administration approved their first biosimilar products in 2006 and 2015, respectively. [463] Yet in recent years, a number of insurers and health care systems have begun exploring whether biosimilars can be considered perfect substitutes to the originator biological products. [87] As more data become available, it is important to understand the impact of different supply- and demand-side policies on biosimilar drug prices and usage rates.

7.5 Final thoughts

Generics can generate large savings, especially for widely-consumed pharmaceuticals. This is particularly important at a time when many governments worldwide are facing budgetary pressures and are struggling to finance public health care. Under such conditions, payers and other health stakeholders should aim to minimise the prices and maximise the volume market shares of generic drugs.

It is widely acknowledged that market failures contribute, at least in part, to high generic drug prices and low generic drug use in some countries. As shown in this thesis, the prices and market shares vary dramatically across many countries. Given market failures in generic drug sectors, policymakers should consider implementing regulation to try to correct some of these failures.

The empirical evidence presented in this thesis points to tendering being an effective measure to stimulate price competition on a sustainable basis and to increase generic drug use—if coupled with mandatory generic substitution. Still, governments seeking to implement new pharmaceutical policies, such as tendering, should ideally test their proposals in real-world pilot studies.

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