THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Development of policies to increase headroom for innovation in Egypt and the Kingdom of Saudi Arabia

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Table of contents

1. Introduction 6

2. The importance of innovation 7

3. Analytical framework and methods 11

3.1. Aims and objectives 11

3.2. Analytical framework 11

3.3. Methods 14

3.3.1. Comparator countries 14

3.3.2. Literature review 14

3.3.3. Primary data collection 15

3.3.4. Simulation exercise 16

4. Results 17

4.1. Regulatory issues & policies 17

4.1.1. Generic and biosimilar medicines 17

4.1.2. Originator medicines 21

4.1.3. Medicine recalls including generic, biosimilar and originator medicines 28

4.2. Supply-side policies 29

4.2.1. Pricing 29

4.2.2. Reimbursement 33

4.2.3. Procurement 34

4.3. Demand-side measures 35

4.3.1. Generic and biosimilar prescribing 35

4.3.2. Generic and biosimilar substitution 36

4.3.3. Financial incentives for healthcare professionals 38

4.3.4. Non-financial incentives for healthcare professionals 40

4.3.5. Pharmaceutical industry activities 40

4.4. Simulation exercise: estimating potential savings 43

4.4.1. Methodology 43

4.4.2. Results 51

4.4.3. Sensitivity analysis 59

4.4.4. Limitations 59

4.5. Best practices promoting use and uptake of innovative medicines 61

4.5.1. Earmarking funds for innovative medicines 61

4.5.2. Allocating funds to innovative medicines 64

5. Discussion & recommendations 71

5.1. Step 1: Optimise access to innovative medicines 72

5.1.1. Intellectual property rights 73

5.1.2. Regulatory issues for innovative products 74

5.1.3. Pricing and reimbursement *76*
5.2. Step 2: Improve policies for generic and biosimilar products in Egypt and KSA 77
5.2.1. Regulatory issues *77*
5.2.2. Supply-side issues *79*
5.2.3. Demand-side issues *80*
5.3. Step 3: Earmark and allocate savings to innovative products 84
5.3.1. Earmarking funds for innovation *84*
5.3.2. Allocating funds to innovation *86*
5.4. Step 4: Monitor allocation of savings to innovative products to ensure a sustainable healthcare system 91
6. Roadmaps for Egypt and KSA 93
7. Conclusion 98
References 100
Appendix 1. Overview of best practice countries 122
Appendix 2. Policy and practice in Egypt 126
Appendix 3. Policy and practice in KSA 134
Appendix 4: Overview of clinical study requirements for biosimilars across global regions 147
Appendix 5: Simulation exercise results 148

Figures

Figure 1: Pricing structure in KSA....32
Figure 2: Pricing structure in Egypt....32
Figure 3: Originator vs generic prices and volumes (SU sold) of ACE1 inhibitors in Egypt, 2016-2020; values in USD and volumes in SUs....45
Figure 4: Lisinopril and amoxicillin+clavulanic acid prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020....46
Figure 5: Candesartan cilexetil and valsartan prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020....47
Figure 6: Pantoprazole and omeprazole prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020....48
Figure 7: Escitalopram and citalopram prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020....49
Figure 8: Rosuvastatin and atorvastatin prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020....50
Figure 9: Median generic prices per SU in study and comparator countries in 2016 and 2020; values in USD....51
Figure 10: Median originator and generic volumes market shares in the study and comparator countries in 2016 and 2020....52
Figure 11: Base case spending vs potential savings from optimal purchasing in Egypt and KSA in 2016-2020; values in USD....54
Figure 12: Base case spending vs potential savings from reduction in generic prices in Egypt and KSA in 2016-2020; values in USD....55
Figure 13: Base case spending vs potential savings from increase in generic market shares in Egypt and KSA in 2016-2020; values in USD....56
Figure 14: Docetaxel and imatinib prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, SP, DE) in 2016-2020....58
Figure 15: Base case spending vs potential savings from optimal purchasing in Egypt and KSA in 2016-2020 (generic market shares + 40% higher minimum generic price in comparator countries); values in USD. 60
Figure 16: Four concrete steps in working towards headroom for innovation in Egypt and KSA....71
Figure 17: The Egyptian Drug Authority (EDA)....127
Figure 18: Pricing rules for pharmaceutical products in KSA....139

Tables

Table 1: Indicators for the assessment of health system performance in generic and biosimilar policies and uptake of innovative medicines....13
Table 2: Generic/biosimilar market entry....20
Table 3: IP rights and data exclusivity....23
Table 4: Registration timelines for new molecular entities....27
Table 5: Pricing of generic/biosimilar medicines....31
Table 6: Reimbursement policies for generic medicines....34
Table 7: Presence and enforcement of generic and biosimilar prescribing and substitution regulation....37
Table 8: Financial and non-financial incentives for healthcare professionals for encouragement of generic and biosimilar uptake and use....41
Table 9: Roadmap for key priorities for Egypt....94
Table 10: Roadmap for key priorities for KSA....96
Table 11: Health insurance coverage in comparator countries....122
Table 12: Use of branded medicines in comparator countries....123
Table 13: Use of generic medicines in comparator countries....124
Table 14: Local production of generic and biosimilar medicines in comparator countries[1]....125
Table 15: Profit rates for pharmacists and distributors in Egypt....133

Abbreviations

ACEs	Angiotensin Converting Enzyme Inhibitors
AIFA	Italian Medicines Agency
ANDA	Abbreviated New Drug Application
ARBs	Angiotensin Receptor Blockers
ATU	Temporary Authorisation for Use
AUD	Australian Dollar
CCHI	Council of Cooperative Health Insurance (Saudi Arabia)
CDF	Cancer Drugs Fund
CIPM	Spanish Inter-ministerial Medicinal Products Pricing Committee
COO	Country of Origin
COVID-19	Coronavirus disease of 2019
CTD	Common Technical Document
CVZ	Dutch Healthcare Insurance Board
DE	Germany
DEN	Denmark
DKMA	Danish Medicines Agency
EDA	Egyptian Drug Authority
EEA	European Economic Area
EGY	Egypt
EMA	European Medicines Agency
EPF	Employee Provident Funds
ERP	External reference pricing
EU	European Union
FDA	Food and Drug Administration
GCC	Gulf Cooperation Council
GDP	Gross Domestic Product
GDP	Good Distribution Practices
GMP	Good Manufacturing Practice
GP	General Practitioner
HIO	Health Insurance Organisation
HTA	Health Technology Assessment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHSI	International Horizon Scanning Initiative
INN	International Non-proprietary Name
IP	Intellectual Property
IRP	Internal Reference Pricing
IT	Information Technology
IV	Intravenous Injections
KSA	Kingdom of Saudi Arabia
LCGP	Local Content and Government Procurement Authority (Saudi Arabia)

LOE	Loss of Exclusivity
LSE	London School of Economics and Political Science
MA	Marketing Authorisation
MENA	Middle East and North Africa
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MNGHA	Ministry of National Guard Health Affairs (Saudi Arabia)
MoH	Ministry of Health and Population (Egypt)
MYS	Malaysia
NED/NL	the Netherlands
NHS	National Health Service (UK)
NHSE	National Health Service of England
NICE	National Institute for Health and Care Excellence (UK)
NME	New Molecular Entity
NPRA	National Pharmaceutical Regulatory Agency (Malaysia)
NUPCO	National Unified Procurement Company for Medical Supplies (Saudi Arabia)
NZa	Dutch Healthcare Authority
OECD	Organisation for Economic Co-operation and Development
OOP	Out-of-Pocket
PAS	Patient Access Scheme
PBS	Pharmaceutical Benefits Scheme (Australia)
PD	Pharmacodynamic
PhRMA	Pharmaceutical Research and Manufacturers of America
PIS	Prescribing Incentive Schemes (UK)
PK	Pharmacokinetic
PLFSS	French Social Security Finance Bill
PMP	Price Maintenance Premium
PPIs	Proton Pump Inhibitors
PPRS	Pharmaceutical Price Regulation Scheme (UK)
QALY	Quality-adjusted Life Year
QOF	Quality and Outcomes Framework
RCT	Randomised Controlled Trial
RWE	Real World Evidence
SAIP	Saudi Authority for Intellectual Property
SFDA	Saudi Food and Drug Authority
SOCSO	Social Security Organisation (Malaysia)
SPA/SP	Spain
SPC	Supplementary Protection Certificate
SSRIs	Selective Serotonin Re-uptake Inhibitors
SU	Standard Unit
T1DM	Type 1 Diabetes Mellitus
TPE	Total Pharmaceutical Expenditure
TPPA	Trans-Pacific Partnership Agreement

TRIPS	Trade-Related Aspects of Intellectual Property Rights
UHC	Universal Health Coverage
UHIA	Universal Health Insurance Authority
UK	United Kingdom
UPA	Unified Purchase Authority
US	United States
USD	United States Dollar
VAT	Value-Added Tax
VPAS	Voluntary Pricing and Access Scheme (UK)
WHO	World Health Organisation
WoS	Web of Science
WTO	World Trade Organisation
ZonMw	Netherlands Organisation for Health Research and Development

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1. Introduction

Establishing an efficient and sustainable healthcare system with universal healthcare coverage is key in many settings, with the aim of balancing high-quality care, and improvements in the health of the population with efficiency of services without overburdening national budgets. These efforts face serious challenges, such as the burden of the continuous entry of new products into healthcare markets on health budgets.

Pharmaceutical expenditure in Middle East and North Africa (MENA)[1] region is reported to range between 11% and 49% of total health expenditure[2] [1], supplemented by an estimated out-of-pocket (OOP) spending burden for pharmaceuticals of 26.9% of total health expenditure in 2018, ranging from 6% in Oman to 62% of current health expenditure in Egypt [2]. In the context of constrained budgets and high overall healthcare costs, the appeal of using generic and biosimilar medicines as cost-effective alternatives, where possible, becomes significant for health care systems and purchasers or commissioners of services for cost-containment purposes. However, the achievement of healthcare savings and efficiency together with the availability of appropriate treatments for local healthcare systems lies in the balance of implementing effective policies which focus on both (i) the uptake and diffusion of low-cost generic and biosimilar medicines which meet high quality standards in terms of safety and bioequivalence/biosimilarity and the use of appropriate supply- and demand-side levers and (ii) the uptake of new and potentially innovative medicines through the reward of research and development efforts and establishment of efficient Intellectual Property (IP) protection and data exclusivity provisions.

[1] *The World Bank definition of the Middle East and North Africa (MENA) region includes Algeria, Bahrain, Djibouti, the Arab Republic of Egypt, the Islamic Republic of Iran, Iraq, Jordan Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, KSA, the Syrian Arab Republic, Tunisia, the United Arab Emirates, the West Bank and Gaza, and the Republic of Yemen.*

[2] *Health expenditure as a percentage of Gross Domestic Product (GDP) was an average of 6%, ranging from 2.32% in Djibouti to 8.66% in Iran* [317].

2. The importance of innovation

What is pharmaceutical innovation?

?

Pharmaceutical innovation is when new products create significant clinical benefit compared to existing treatment options (if any are available), in addition to other factors, such as value to society by improving patients' health, or improvements to safety or convenience of use compared to available alternatives, among others [3]. Pharmaceutical innovation is time dependent, meaning that the unique value of an innovation will change over the course of time due to competition and technological change [3].

Why is innovation important in healthcare?

Healthcare systems should seek to incorporate new and potentially innovative medicines into pharmaceutical offerings. Uptake of new pharmaceuticals has been associated with long-term improvements in health outcomes such as longevity, improved health status, and productivity [4]. Innovative medicines can also ensure better quality of life for patients and their families, and improve the efficiency, effectiveness, quality, safety, sustainability of a healthcare system [5]–[7].

According to evidence, innovative medicines[3] accounted for 73% of life expectancy gains in 30 high-income countries in the period 2000-2009 [8]. For example, in Canada, the premature cancer mortality rate decreased by 9% between 2000 to 2011 due to the introduction of relevant new pharmaceuticals in the preceding decades (1985 to 1996), where, in the absence of these pharmaceuticals, the mortality rate would have increased by 12.3% [9]. Another example of such gains is seen in evidence which shows that life expectancy at birth increased in Canada while hospital utilisation (i.e.: curative care hospital discharges per 100,000 population) decreased by 25% from 1995 to 2012, largely due to pharmaceutical innovation [4].

Innovative medicines may also play a role in reducing costs for the wider system. Pharmaceutical innovation may be perceived to be associated with high costs, but in practice innovation can lower the overall cost of treating diseases by reducing the use of health services (e.g. reducing hospitalisations and nursing home residence rate) [4]. For every $24 spent on new pharmaceuticals treating cardiovascular diseases between 1995-

[3] Innovative medicines are defined as those which were technologically advanced based on the year of their invention or first use by the author.

2004 in 20 OECD countries there was a saving of $89 in hospitalisation expenditure [10]. Looking across all diseases in the US, a reduction in hospital expenditure was estimated to be more than twice as large compared to the increase in pharmaceutical expenditure attributed to pharmaceutical innovation [4].

Encouraging pharmaceutical innovation is thus essential to create a sustainable healthcare system with better performance on health outcomes and service utilisation. To encourage the uptake of innovation in healthcare, better collaboration and knowledge exchange are needed across stakeholders [5] together with the optimisation of factors such as healthcare funding and policy and government regulations which reward innovation and improve access to these products [6].

How can headroom for innovation contribute to funding innovation?

Countries are faced with tough decisions on how to efficiently allocate scarce resources given the pressures of limited healthcare budgets combined with rising health spending due to factors affecting demand for and supply of health care, such as continuing and more expensive technological innovation, demographic change, and increasing consumer demand [11]. This is critical for achieving objectives around creating sustainable and affordable healthcare systems where high-quality care and population health improvements are balanced with efficiency of services, and where national budgets are not loaded with excessive burden.

Entry of new products into the market can place additional burden on health budgets, at least in the short-term, unless savings or recalibration can be taken elsewhere within existing expenditure in the pharmaceutical sector or healthcare system, or if overall budgets can be expanded. Therefore, important trade-offs need to be made which may include, among many others, the process of selecting which new and potentially innovative pharmaceuticals should be funded by the healthcare insurance or the introduction of cost-containment measures such as price controls which have proven to not to be a long-term solution [12]. However, evidence has shown that a concrete option for longer-term financial sustainability in healthcare systems may be to introduce higher levels of competition and uptake in the off-patent and generic/biosimilars market to free up financial resources to help pay for new products and relieve constrained budgets, creating *headroom for innovation* [13]. Overall, headroom for innovation encourages efficiency within the pharmaceutical sector by creating the financial ability for healthcare systems to access to new and innovative medicines of high clinical value in a sustainable way, while avoiding provision of larger budgets or obtaining funding outside of the pharmaceutical budget.

What is headroom for innovation?

Headroom for innovation suggests that the elimination of distortion, increase competition in the off-patent sector, and/or shift of consumption from in-patent products to off-patent products, where possible, can provide space for budget allocations to other segments of the pharmaceutical market, such as innovative products [14]–[19].

The concept of headroom for innovation was championed by the European Commission in the late 1990s, notably accepted as a suitable policy option through the 1997 Bangemann roundtable.

To action headroom for innovation, the right policy tools for generic/off-patent markets need to be leveraged across:

- regulatory policies, to ensure high quality[4] generic and biosimilar products come to market.
- supply-side interventions (pricing, reimbursement, and procurement), to contribute to lower prices for the purchaser.
- demand-side measures, to influence physician, pharmacist, and patient behaviours.

Policies which address these elements can be an essential cost-containment tool [17], [18] and a sustainable long-term solution for the funding of innovative pharmaceuticals [13].

What pre-requisites are necessary prior to creating headroom for innovation?

Before policies to promote headroom for innovation can be successfully implemented, there are a few pre-requisites health systems must have in place.

- *Intellectual property rights (IPR).* When regulatory bodies do not adhere to the TRIPS agreement or establish or enforce patent rights for innovative medicines, generic or copy-cat products may come to market immediately or at any point. This mitigates any efforts at rewarding innovation and the high cost of R&D, ultimately potentially disincentivizing pharmaceutical companies from registering and/or developing new products.
- *Time to access for innovative products*. Prior to redirecting savings to innovative products, countries may need to ensure that access to these novel medicines is optimised. Market access pathways can be long, delayed processes and policy reform aiming to improve time to patient access can support headroom for innovation efforts.

[4] High quality generics and biosimilars are those which have been tested for (i) safety and (ii) bioequivalence and biosimilarity, respectively, by competent regulatory authorities based on universally accepted guidelines.

- *Regulatory oversight.* There must also be sufficient regulatory oversight for generics and innovators to ensure high quality products are entering the marketplace. Low quality generics that do not have the same efficacy as branded medicines could undermine headroom for innovation efforts by harming individuals' health, fostering distrust amongst users, and creating greater demand for brand name medicines.

Addressing these issues can facilitate the transformation necessary for health systems to sustainably afford innovative medicines and engage in the creation of headroom for innovation.

3. Analytical framework and methods

3.1. Aims and objectives

The creation of headroom is crucial to allow resources to be spent as efficiently and effectively on issues where need is the greatest, such as newer and potentially more innovative pharmaceutical products. This study considers the potential to create headroom for innovation in the healthcare systems of Egypt and the Kingdom of Saudi Arabia (KSA) by identifying potential generic policy interventions which can contribute to cost-containment, exploring which policies could be implemented and strengthened to attract innovative products, and drawing on examples of best practices of allocating savings resulting from improved generic policies to innovative medicines. Delays to innovative medicines in Egypt and KSA are observed in different stages of the access resulting in difficulties in market entry and patient access for these medicines. In addition, uptake and diffusion of generic and biosimilar medicines, where these are available, in Egypt and KSA remain low compared to other markets across the world due to high originator brand loyalty [24]–[27]. In this context, the objectives of this report are fourfold:

- First, to identify gaps and issues in existing generic policies in both countries based on best practices from other countries.
- Second, to propose how to improve generic and biosimilar uptake and suggest potential policy reform to reducing inefficient healthcare spending on these products.
- Third, to quantify the potential savings associated with optimised spending on generics and biosimilars.
- Finally, to provide recommendations on how to create headroom for innovation by freeing up resources through generic and biosimilar policy change and how to redirect savings to reward innovation using examples of practices from other countries.

3.2. Analytical framework

To identify where gaps exist in current policies in Egypt and KSA and where healthcare savings could be generated for the potential creation of headroom for innovation, a conceptual framework was designed to capture critical pharmaceutical policy parameters across both generic and new and potentially innovative pharmaceuticals relevant for this assessment. By depicting the current policy landscape, the framework provided a structure to record current policies in both the originator and generic sector of these two countries, with the aim to identify possible policy gaps and areas of improvement to promote generic

and biosimilar use when clinically appropriate, increase levels of competition in the generic market, and promote market access, use and uptake of innovative medicines.

The design of the framework considered optimal policies in generic markets across supply- and demand-side measures and relevant policy tools for originator, branded generic/biosimilars and generic/biosimilar medicines. The framework comprises the following main themes: (i) health systems; (ii) pharmaceutical regulatory issues and measures; (iii) availability and use of medicines; (iv) supply-side policies for generics and biosimilars including pricing and reimbursement policies, and (v) demand-side policies for generics and biosimilars. Indicators for each endpoint were selected to enable comparisons across the study countries (Egypt and KSA) against best practice examples drawn from other settings. This comparative assessment was used to highlight possible gaps and areas of improvements. The themes and accompanying indicators are presented in Section 3.

Indicators focusing on the regulatory setting, supply- and demand-side policies identify potential gaps on current practices on generic and biosimilar policies and examine whether there are provisions at regulatory level which could potentially promote the use of generics but also protect data exclusivity and intellectual property rights for originator products. These indicators focused on presence of regulatory-specific policies for generics/biosimilars and originator pharmaceuticals with an active patent, pharmaceutical pricing and reimbursement and the dynamic between these systems and, practices favourable to locally produced pharmaceuticals and interventions targeting physicians, pharmacists, and patients for better uptake of generics and biosimilars. Additional contextual indicators on health systems overview and on the use and diffusion of medicines including originator and generic/biosimilar medicines were selected for inclusion to, amongst other reasons, aid our understanding of the organisation of healthcare systems, areas of healthcare spending, the achievement or desire to achieve universal health coverage, the extent of generic and biosimilar market penetration, and the presence of local manufacturers.

Table 1: Indicators for the assessment of health system performance in generic and biosimilar policies and uptake of innovative medicines

Endpoints	Description	Indicators
Health systems	Organisation and financing of healthcare, and achievement of universal health coverage	- Universal healthcare coverage - Population health coverage - Service coverage index - Population with private/voluntary health insurance
Availability & use of medicines	Pharmaceutical spending, use of branded medicines, use of generic and biosimilar medicines, Local manufacturing industry, and uptake	- Total pharmaceutical spending - Spending on branded medicines - Degree of use/uptake of branded products - Spending on generic products - Spending on biosimilar products - Size of generic sales - Size of biosimilar sales - Value of generic sales - Value of biosimilar sales - Degree of use/uptake of generic products - Degree of use/uptake of biosimilar products - Number of local manufacturers - Types of products produced locally
Regulatory issues & policies	Interventions at regulatory level for optimal market penetration	- Presence of regulatory authority - Presence of abridged approval pathways - Use of Bolar provisions - Bioequivalence testing - Good manufacturing practices and quality assurance - Intellectual property rights and data exclusivity - New molecular entries - Time to market - Time to patient access - Medicine recalls for generics, biosimilars, and innovative products
Supply-side policies	Pricing and reimbursement policies	- Price regulation for generic and biosimilar products - Pricing mechanisms for innovative products after patent expiry - Preferential practices for local manufacturers in pricing - Reimbursement regulation - Preferential practices for local manufacturers in reimbursement - Presence of procurement bodies/organisations at national and local level - In-patient/out-patient market procurement - Preferential practices for local manufacturers in procurement
Demand-side policies	Financial incentives and non-financial controls or policies for health care professionals and patients for better generic/biosimilar use	- Presence & enforcement of generic and/or biosimilar prescribing - Presence & enforcement of generic and/or biosimilar substitution - Financial incentives for healthcare professionals - Non-financial incentives for healthcare professionals - Pharmacy and wholesaler renumeration strategies - Pharmaceutical detailing practices - Patient-level policies and behaviours
Uptake and diffusion of innovative medicines	Policies and initiatives for uptake and diffusion of and re-allocation of savings to new, potentially innovative medicines	- Pricing and reimbursement policies - Managed entry agreements - Incentive structures - Special funding - Horizon scanning - Shared values and commitment to real world evidence

3.3. Methods

This report avoids using the terms 'in-patent' and 'off-patent' for Egypt and KSA to reflect on the important differences in the existence and implementation of IP and data exclusivity policies in these two countries compared to the benchmark countries. When referring to the Egyptian and KSA markets, the terms 'originators', 'branded medicines' and 'generics' are used instead.

3.3.1. Comparator countries

Five high-income and emerging markets acted as benchmark countries for a comparative assessment with Egypt and KSA across policies for generics and biosimilar medicines and new and potentially innovative medicines. Denmark, the Netherlands, Malaysia, Spain, and the United Kingdom (UK)[5] were selected as case studies because of the significant size of their generic markets, their considerable experience in successfully addressing the challenges in the generic sector, and their efficient supply- and/or demand-side policies. The comparator countries have strong local generic manufacturing activities which enabled comparisons between health and industrial policy trade-offs, relevant in the context of Egypt and KSA. Detailed information on why these countries were chosen is discussed in Appendix 1. The conceptual framework described above was used to enable comparisons between best practice and study countries, and to aid in the identification of potential policy gaps.

In addition to the benchmark countries for generic and/or biosimilar policies, best practice examples of successful targeted efforts for the uptake and diffusion of innovative medicines and rewarding of research and development were also drawn from other countries including Australia, France, Italy, and Japan.

3.3.2. Literature review

Extensive desk research focusing on both peer-reviewed and grey literature was conducted to identify relevant information for the indicators in the conceptual framework. Keywords and phrases aligned with the indicators were utilised to identify information for the study and best practice countries. Evidence from peer-review and grey literature, including current regulatory, pricing and reimbursement legislation, identified during the desk

[5] *Information on the United Kingdom has been included where possible. Some information may pertain solely to England.*

research was extracted for each of the countries across each indicator in the conceptual framework.

The literature search was limited to English language results from 2015 onwards to capture the most recent developments in originator, generic and biosimilar markets, and policies. Databases searched including PubMed, Web of Science (WoS), Scopus and Google Scholar. The websites of competent authorities and agencies in all study countries were reviewed; the relevant websites in Egypt and KSA were examined by a native Arabic speaker. The websites of the World Health Organisation (WHO), the World Bank, and the Organisation for Economic Co-operation and Development (OECD) were reviewed to identify general information on healthcare systems and pharmaceutical markets of and policies in the study countries. Legislative documents and information on local initiatives were shared by local Pharmaceutical Research and Manufacturers of America (PhRMA) teams in Egypt and KSA.

3.3.3. Primary data collection

Primary data collection was performed to complement and validate findings from the literature, and to identify country-specific contexts and challenges, key trends in generic and biosimilar markets in the study countries, specifications on intellectual property rights and data exclusivity for originator medicines, and any current or planned policy interventions. The evidence from primary data collection was further used to inform recommendations on the creation of headroom for innovation in Egypt and KSA and to assess contextual factors which could have an impact on the feasibility of certain policies in these two settings.

Primary data collection was completed in two key phases. The first phase included semi-structured interviews with local key experts in Egypt, KSA and Spain, which was one of the best practice countries. Spain was included in the semi-structured interviews to validate, complement, and clarify some of our findings from secondary sources. Local stakeholders included government officials, representatives from regulatory authorities, insurance organisations, pharmacy departments, and procurement agencies. Experts in KSA were identified by the London School of Economics and Political Science (LSE), while experts in Egypt were identified with the help of the PhRMA Egypt team. All contacted experts in both countries were affiliated with the national regulatory agencies, the national procurement and purchasing bodies, the national government and health insurance, the local industry and academia. The Spanish expert is an academic identified through the LSE's network. Three experts (out of the five initially contacted) in KSA, two experts (out of the six initially contacted) in Egypt and one expert in Spain participated in the interviews. The semi-structured interviews took place using the Zoom platform from March to

September 2021. A general interview discussion guide was developed based on the thematic areas of the conceptual framework. The interview discussion guide was tailored to include targeted questions and points of discussion based on the expertise and affiliation of each interviewee. Targeting the content of the interviews to the expertise of the interviewee allowed for the opportunity to deep-dive into key thematic areas and obtain a better understanding of the status quo and future directions of the local markets. Evidence generated from the interviews was incorporated into the findings of the literature review.

The second phase of primary data collection involved consultation with local PhRMA teams in Egypt and KSA to provide feedback and comments and further provide additional material when evidence in the literature was lacking.

Evidence generated by these two phases is referenced in the text using two separate references. Primary evidence from the first phase is reported as 'local experts', while evidence form the second phase is reported as 'local industry'. In cases where minimal or outdated evidence was drawn from the literature review, primary evidence was prioritised and reported.

3.3.4. Simulation exercise

In Section 3.4 we pursue a simulation analysis of the savings that could be generated for Egypt and KSA in a number of genericised product markets by analysing price and market share differences between these two countries and a group of comparator countries that routinely achieve low prices and high generic market penetration for generics. The methodology pursued (i.e., data sources, product names, the relevant endpoints and sensitivity analysis) are discussed in detail in Section 3.4.1.

4. Results

This results section provides a comparative assessment of all indicators under the regulatory, supply-side, and demand-side themes of the conceptual framework (Sections 3.1, 3.2 and 3.3, respectively). More detailed country specific information on Egypt can be found in Appendix 2 and on KSA in Appendix 3. This section then presents the results from a simulation exercise estimating the potential savings from optimizing generic policies (Section 3.4) and key examples of how such savings can be earmarked and rerouted to spending on innovative medicines (Section 3.5).

4.1. Regulatory issues & policies

4.1.1. Generic and biosimilar medicines

Abridged approval pathways[6]*.* All comparator countries have abridged approval pathway practices for the approval of generic medicines and do not require full pre-clinical and clinical testing where bioequivalence testing demonstrate that the medicinal product is a generic of the reference originator product (**Table 2**). Biosimilars are subject to more restrictive regulatory requirements with regard to clinical studies in Denmark, the Netherlands, Spain and the UK [28]–[31], while Malaysia follows the EMA principles for the assessment of biosimilars for marketing authorisation [32]. Both Egypt and KSA have processes for abridged approvals for products approved and marketed by the Food and Drug Administration (FDA) in the United States (US) and the European Medicines Agency (EMA) [33], [34]; in Egypt this process is used for both imported originator and generic medicines with a submitted common technical document (CTD), while in KSA it is applied only to innovative products (**Table 4**) [33].

Additionally, the new Decree 645 in Egypt has been implemented to facilitate the registration process for generic medicines. Under this decree, the Egyptian Drug Authority (EDA) accepts registration requests above the official number allowed in a box of similar pharmaceuticals to facilitate generic registration. Primary evidence states that under this pathway, generic registration occurs in 12 to 18 months [33].

Bioequivalence and biosimilarity testing. Bioequivalence testing for generic medicines and biosimilarity testing for biosimilar medicines are present across Egypt, KSA and the

[6] *Abridged approval pathways refer to processes which are shortened or lighter for products already assessed by other regulatory agencies, such as the EMA or the FDA. Examples of this are the verification reviews and abridged evaluations discussed for Egypt and KSA. Accelerated approval is a process which provides a fast track for products based on the perceived importance of the medicines for public health, used in Europe and the US for in-patent originator medicines.*

comparator countries (Denmark, the Netherlands, Malaysia, Spain, and the UK).

The regulatory environments for generic and biosimilar medicines in Denmark, the Netherlands, Spain, and the UK are similar: there are no country-specific requirements for market entry and all national regulations follow standard guidance by the EMA (**Table 2**). KSA [35], [36] and Malaysia [37] have both adopted the EMA principles of biosimilar regulation, though in the former clinical study requirements are more lenient than the requirements in the European Union (EU) (see Appendix 4). In Egypt, biosimilar approvals rely on biosimilarity testing and sometimes pharmacovigilance risk mitigation plans for new forms and concentrations [33].

Bolar provisions. The existence of Bolar amendments, which allow generic manufacturers to develop the relevant information needed to submit for regulatory approval of generics and biosimilars while the relevant originator or biologic is still under patent to encourage the immediate launch of generics and biosimilars after patent expiry of originators and biologics, is prevalent across both Egypt and KSA as well as the comparator countries. However, the use of these provisions in Egypt remains unclear since generics can be registered and launched during patent protection of originators due to lack of a well-established link of intellectual property rights and patent protection [33].

Good manufacturing practices (GMP). Both Egypt and KSA have implemented guidelines and regulation for generic and biosimilar medicines at regulatory level: KSA has developed GMP guidelines based on the US FDA guidelines, while Egypt has adopted the WHO GMP standards as a reference.

Pharmacovigilance. All comparator countries have implemented regulations with a special focus on the pharmacovigilance of biologic and biosimilar medicines. In Egypt, the manufacturer must submit a pharmacovigilance plan which aligns with guidelines after which site visits take place [38]. Both Egypt and KSA do not have any form of naming strategies specific to biosimilars products where the brand name of the biologic is included in addition to the international non-proprietary name to facilitate pharmacovigilance, accurate identification and increase trust in these medicines. However, KSA has proposed a policy in this direction [39].

Time to market. Time to generic entry differs across countries, often due to the time taken to assess marketing authorisation (MA) applications. As presented in **Table 2**, time delay to generic entry, defined as the proportion of patent expired sales with generic entry (%) at 24 months, is 91.6% in Denmark, 88.6% the UK, 76.3% in Spain and 64.3% in the Netherlands [18]. In Malaysia, the mean time to entry was approximately 396 days [40].

No evidence was found on actual delays to generic entry in Egypt and KSA. However, considering the official timeline of 165 working days for the registration of generic medicines in KSA and the actual observed time of 10 to 12 months, delays in the registration process can be assumed [41]. In Egypt, one to two years are observed for the registration of generic medicines [41]. In comparison, a full evaluation in Malaysia takes 210 working days and an abridged evaluation takes 116 (single active ingredient) or 136 days (two or more active ingredients) [42], while European countries are given a timeframe of 210 working days for a full evaluation and 150 working days for accelerated assessments based on EMA guidelines [43].

Local producers experience far shorter product registration times than foreign producers in KSA, as the registration process often takes years for imported products compared to as little as three months for locally manufactured pharmaceuticals [44]. This large difference in market access times between local and foreign producers has not been noted in the comparator countries.

Further, the time to market for biosimilar medicines is the longest in KSA (**Table 2**) where the process is reported to take 18 months [24]. In comparison, a timeline of zero to five months in the Netherlands and the UK, five to eight months in Denmark and eight to eleven months in Spain from EMA approval to first biosimilar sales are reported [45]. In Egypt, the timeline for biosimilar market access is eight to ten months, similar to timelines seen in Spain (**Table 2**).

Table 2: Generic/biosimilar market entry

	EGY	KSA	DEN	MYS	NED	SPA	UK
Use of abridged approval procedures	Yes[1]	Yes	Yes	Yes	Yes	Yes	Yes
Bioequivalence testing	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Regulation/policies for market entry of biosimilars	Minister decree 297/2009[2] Biosimilar Decree no. 150/2015	Developed by guidance from EMA and ICH	EMA guidelines	Adopted EMA guidelines	EMA guidelines	EMA guidelines	Based on the EMA guidelines
Bolar provisions	Yes[3]	Yes	Yes	Yes	Yes	Yes	Yes
Proportion of patent expired sales with generic entry (%) at 24 months	([4])	No evidence	91.6%	No evidence	64.3%	76.3%	88.6%
Availability of generic alternative (% of molecules with generic launched up to 24 months after patent expiry)	([4])	([5])	45.5	([6])	43.4	32.1	46.7
Time to market (biosimilars)	8-10 months	18 months	5–8 months	([7])	0-5 months	8–11 months	0-5 months
Note:	Bolar provisions allow generics manufacturers to develop a drug and submit regulatory approval information before the patent officially expires. [1] Abridged approval of pharmaceutical products (including biological medicines) approved and marketed by the EMA and the FDA, along with a separate route for applications in CTD format. [2] WHO, ICH, EMA and US FDA guidelines are used as reference. [3] Use of Bolar provisions is unclear in Egypt since the lack of a well-established link between intellectual property rights and patent protection of originators [33]. [4] Generics can be launched before originator. [5] There is no evidence available, yet some shortage incidents take place especially after long time following loss of exclusivity, dropping the price significantly. [6] Fatokun et al. [40] found that, for the twelve best-selling prescription drug products which lost patent protection between 2001-09, a total of 154 generics entries occurred over the eight year period they studied. The mean time to entry was approximately 396 days. According to the authors, the time to generics entry was significantly delayed after patent expiration of the equivalent innovator product. [7] Malaysia has signed the TPPA, a clause of which outlines that biosimilar medicine applications cannot be accepted by the NPRA for the period that the data exclusivity of the reference originator product is valid [46]. As a result, the registration of biosimilars is delayed.						
Abbreviations:	CTD: Common Technical Document; DEN: Denmark; EGY: Egypt; EMA: European Medicines Agency; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; NPRA: National Pharmaceutical Regulatory Agency; SPA: Spain; TPPAA: Trans-Pacific Partnership Agreement; UK: United Kingdom; US FDA: United States Food and Drug Administration; WHO: World Health Organisation						
Source:	Use of abridged evaluation procedures: [33] (EGY); [33], [34] (KSA); [28] (DEN); [29] (NED); [42] (MYS); [30] (SPA); [31], [47] (UK). Bioequivalence testing: [48] (EGY); [49] (KSA); [28], [50], [51] (DEN); [52] (NED); [42], [53] (MYS); [30], [54] (SPA); [55] (UK). Regulation/policies for market entry of biosimilars: [56] (EGY); [57] (KSA); [28] (DEN); [28] (NED); [37] (MYS); [58] (SPA); [59] (UK). Bolar provisions: [60] (EGY); [60] (KSA); [61] (DEN); [61] (NED); [61] (MYS); [61] (SPA); [61] (UK). Time delay to generic entry: [33] (EGY); [18] (DEN); [18] (NED); [18] (SPA); [18] (UK). Availability of generic alternative: [33] (EGY); [33] (KSA); [18] (DEN); [18] (NED); [18] (SPA); [18] (UK). Time to market: [24] (EGY); [24] (KSA); [62] (DEN); [62] (NED); [62] (SPA); [62], [63] (UK).						

4.1.2. Originator medicines

IP and data exclusivity

The study countries and the comparator countries are members of the World Trade Organisation (WTO) and national regulation on IP rights is developed in accordance with the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreements [64].

Egyptian law (Law No. 82 of 2002) sets out pharmaceutical patents are valid for 20 years with no possibility of extension beyond this period [65]. While there are currently no specific laws for pharmaceutical patents in KSA, the main national law related to patents (Law No. 159) provides pharmaceuticals with patent protection for 20 years [66], [67]. Unlike Denmark, the Netherlands, Spain and the UK, there are no provisions for extension of the patent beyond the patent term of 20 years in KSA and Egypt. Moreover, in contrast to the comparator countries, patentability of additional medicines indications beyond first indication is not possible under Egyptian and KSA patent law or the Gulf Cooperation Council (GCC) Patent Office's laws [65] [68].

KSA and Egypt are ranked among the countries with the lowest overall scores of the 2020 US Chamber International IP index[7] (39.44% and 30.18%, respectively) compared to countries such as Japan, France, Germany, the UK and the US which achieved the highest scores (more than 90%) [69]. In KSA, IP infringements have been documented where some generic medicines have been authorised and procured while patents for originator products were in place [70]. However, ongoing efforts by Saudi Authority for Intellectual Property (SAIP) to set up a mechanism to protect IP and move towards patent linkage (please refer to Appendix 3 for further information) may prevent IP infringements by strengthening patent protection depending on how effective the mechanism being devised will be [33].

In KSA regulatory data protection[8] is five years from the date of approval, while there is no specific guidance on such protection periods in Egypt [65], [67], [68]. The data exclusivity periods in Denmark, the Netherlands, Spain, and the UK are eight years with a two-year market protection period. The comparator countries also offer an additional one year of market exclusivity if a new indication is registered within the first eight years. Neither KSA nor Egypt have specific provisions for market exclusivity protection periods

[7] *The index evaluates the IP framework in each economy using indicators which represent economies with the most effective IP systems. The index includes 50 indicators across nine categories of protection (i.e. patents, copyrights, trademarks, design rights, trade secrets, commercialisation of IP assets, enforcement, systemic efficiency, and membership and ratification of international treaties)* [69].

[8] *Regulatory data protection (RDP) provides manufacturers with protection for the data from the pre-clinical and clinical trials generated during the marketing authorisation process. Once the RDP term has expired, generic manufacturers can use these data to apply for marketing authorisation approval.*

for orphan medicines used to treat rare diseases, in contrast to Denmark, the Netherlands, Spain, and the UK.

Generic and biosimilar medicines can be registered before originators in the Egyptian market and a weak link between the patent office and the EDA seems to have resulted in cases where IP rights are not implemented and preserved accordingly [33]. The SFDA have also approved locally manufactured generics during the 5-year RDP term in some cases where products were not patent-protected in Saudi Arabia or the GCC and relied exclusively on the RDP term [70].

Both Egypt and KSA have compulsory licensing provisions that go beyond TRIPS flexibilities. SAIP regulations on compulsory licensing provide for an excessively broad opportunity to grant a compulsory license three years after the patent has been granted and without prior notice to the patent holder [70]. In Egypt, compulsory licensing is permitted in certain cases; for example, for public benefit, such as maintaining national security and health when dealing with emergencies or circumstances of extreme necessity, or in support of national targeted efforts to support important sectors which can promote economic, social and technological development [65], [71]. For medicinal products specifically, compulsory licensing can be granted upon the request of the healthcare minister when existing patented medicines: (a) are unable to meet the needs of the country; (b) are of low quality; (c) have an unusual increase in price; d) are medicines for critical, chronic, incurable or endemic diseases, or medicines to prevent these diseases [71].

New molecular entities

The number of new molecular entities (NMEs) registered in the MENA region demonstrates an increasing trend over the years [41]. This trend is seen in KSA, where compared to only one NME registered between 2010-2012, eleven were registered between 2012-2014, 37 were registered between 2014-2016 and 45 were registered between 2016-2018 [41]. In Egypt, six NMEs were registered between 2012-2014, 28 were registered between 2014-2016 and 16 were registered between 2016-2018 [41]. The number of NMEs registered by the EMA was 38 between 2016-2018; comparatively, the number of NMEs registered at the same period is lower in Egypt, but higher in KSA [41]. Interestingly, while the number of registered NME is increasing, registration for medicinal products occurs later in the MENA region than equivalent registration in the EMA or the FDA [41]. However, lag time between approval in FDA/EMA and local submission in Egypt has improved under the abridged pathway due to the elimination of the one-year marketing condition in the reference country [33].

Table 3: IP rights and data exclusivity

	EGY	KSA	DEN	MYS	NED	SPA	UK
National authority issuing patents	The Egyptian Patent Office at the Academy of Scientific Research and Technology, Ministry of Scientific Research	Saudi Authority for Intellectual Property	The Danish Patent and Trademark Office	Patent Registration Office of the Intellectual Property Corporation of Malaysia	The Netherlands Patent Office	The Spanish Patent and Trademark Office	UK Intellectual Property Office[1]
Legislation on patents	Law No. 82 of 2002	Law No. 159 on the Protection of Patents, Layout-Designs of Integrated Circuits, Plant Varieties, and Industrial Designs	Patent Act (Consolidated Act no. 90 of 29 January 2019)	Patents Act 1983; Patent Regulations 1986	Dutch Patent Act 1995	Law 24/2015 of 24 July	Patents Act 1977
Extension of patent beyond the patent term of 20 years[2]	No provision	No provision	Can be extended under the supplementary protection certificate (Medicinal Products SPC Regulation (EC) *469/2009):* -up to 5 years	No provision	Can be extended under the supplementary protection certificate (Medicinal Products SPC Regulation (EC) *469/2009):* -up to 5 years -additional 6 months for products authorised for paediatric use	Can be extended under the supplementary protection certificate (Medicinal Products SPC Regulation (EC) *469/2009):* -up to 5 years -additional 6 months for products authorised for paediatric use	Can be extended under the supplementary protection certificate (Medicinal Products SPC Regulation (EC) *469/2009):* -up to 5 years -additional 6 months for products authorised for paediatric use

	EGY	KSA	DEN	MYS	NED	SPA	UK
Regulatory data protection (data and marketing exclusivity) periods	No specific regulatory data protection periods	-Regulatory data protection period of 5 years from the date of approval	-Data exclusivity period of 8 years -Additional 2 years of marketing exclusivity -Additional 1 year of marketing protection where a new indication is approved for the same product within the 8-year data exclusivity period	-Data exclusivity for up to 5 years for new medicines containing a new chemical entity. Data exclusivity for up to 3 years for registered medicines approved for a second indication[4]. -Under the TPPA, exclusivity is extended to both data and market exclusivity.	- Data exclusivity period of 8 years -Additional 2 years of marketing exclusivity -Additional 1 year of marketing protection where a new indication is approved for the same product within the 8-year data exclusivity period	-Data exclusivity period of 8 years -Market exclusivity period 10 years -Additional 1 year of marketing protection where a new indication is approved for the same product within the 8-year data exclusivity period	Data exclusivity period of 8 years -Additional 2 years of marketing exclusivity -Additional 1 year of marketing protection where a new indication is approved for the same product within the 8-year data exclusivity period
Marketing exclusivity protection periods for orphan medicines	No provisions	No provisions	Marketing exclusivity period of 10 years[3] for medicinal products that qualify as orphan drugs under the Orphan Medicines Regulation (EC) *141/2000*	No provisions	Marketing exclusivity period of 10 years[3] for medicinal products that qualify as orphan drugs under the Orphan Medicines Regulation (EC) *141/2000*	Marketing exclusivity period of 10 years[3] for medicinal products that qualify as orphan drugs under the Orphan Medicines Regulation (EC) *141/2000*	Marketing exclusivity period of 10 years[3] for medicinal products that qualify as orphan drugs under the Orphan Medicines Regulation (EC) *141/2000*
Note:	[1] Alternatively, an applicant may follow the European Patent's Office centralised procedure to apply for a patent in the UK [72]. [2] In accordance with the TRIPS agreement, the patent protection lasts for a minimum of 20 years in WTO member states [64]. [3] Exclusivity period can be shortened to six years if, at the end of year five, the medicinal product: a) no longer meets the criteria laid down for granting the orphan designation in the first place, or b) is sufficiently profitable not to justify maintenance of market exclusivity. [4] In this case, exclusivity applies only for the data relating to the second indication.						
Abbreviations:	DEN: Denmark; EEA: European Economic Area; EGY; Egypt; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; SPC: Supplementary Protection Certificate; TPPA: Trans-Pacific Partnership Agreement; TRIPS: Trade-Related Aspects of Intellectual Property; UK: United Kingdom; WTO: World Trade Organisation.						
Source:	[65] (EGY); [34], [67], [68] (KSA); [73] (DEN); [74] (NED); [75]–[77] (MYS); [78] (SPA); [79] (UK).						

Time to market and abridged approval pathways

As presented in **Table 4,** Egypt has the shortest official timelines for the registration of NMEs (105 working days) [41] compared to the study countries followed by the EMA (210 working days) [43], Malaysia (245 working days) [80] and KSA (290 working days) [41]. Despite the official timelines, the average observed time for a medicinal product to get approved is found to be longer in Egypt, KSA, and Malaysia.

In practice, these timelines are often exceeded. In Egypt, timelines for imported products and small molecules are one to two years, and registration of biologics and vaccines is reported to be two to three years [33] [81] [41]. However, registration timelines depend on the regulatory pathway followed: official timelines from the Ministry of Health and Population set out that pharmaceutical products and biologics which submit a CTD should be registered within six months, while products approved by the FDA and the EMA should be registered within one month, or, when approved by just one of these agencies, in two months [82]. In KSA, which has the longest official timeline, registration of NMEs is reported to take 16 to 20 months [41]. A recent study suggests that, even though NME registration timelines in KSA have improved over time, they still remain high compared to other Middle Eastern countries [83]. Some of the comparator countries have similar findings: In Malaysia, the median registration time for all medicines approved in 2017 was 515 days [84], while the overall median approval time for NMEs by the EMA in 2018 was reported to be 436 days[9] [85].

To aid with the registration of NMEs, accelerated processes are used by the EMA in Europe and in Malaysia. The EMA accelerated assessment scheme (also implemented in the UK) is designated for medicinal products that are considered to be of major interest for public health and therapeutic innovation and reduce the review time from 210 days, which is the official timeline for the assessment of a standard marketing authorisation, to 150 days [86], [87]. In practice, the overall median approval time for accelerated assessments by the EMA was an average of 249 days [85]. In Malaysia, lifesaving medicines, or medicines intended for a condition for which there is no alternative treatment available (e.g., rare disease), or medicines expected to tackle a public health threat may be processed through the priority review/fast track review for registration, referred to as Path I [84] in Malaysia, reducing the review time to 120 days. Five priority medicines designated as Path I in 2017 were approved in half the time compared to medicines processed through a standard review as the National Pharmaceutical Regulatory Agency (NPRA) [84].

[9] *Including clock-stops.*

KSA applies a priority review[10] for (i) medicines used to treat serious or life-threatening conditions and/or address unmet medical needs, (ii) medicines under the SFDA exempted list or (ii) medicines considered as first or second generic for an innovated product [263]. The official timeline for medicinal products under priority review in KSA is reduced by 40% [41]. Both Egypt and KSA[11] implement abridged approval pathways for medicinal products that are already approved and marketed by the FDA and the EMA [33] [41]. In both Egypt and KSA, these pathways aim to reduce the target timelines to 30 working days (if the medicinal product is approved and marketed by both the FDA and the EMA) or 60 working days (if the medicinal product is approved and marketed by either the FDA or the EMA) [41]. Despite the similar design of these pathways in both Egypt and KSA, registration of products in KSA requires only an FDA/EMA approval letter, while in Egypt a legalised certificate of the pharmaceutical product is required from the FDA/EMA [33]. There is no publicly available evidence for either country on how much the abridged pathway has improved standard registration timelines in practice.

Time to patient access

Based on data from 2010 to 2018, the average time to market access, defined as the time taken from dossier submission to approval by local authorities, was found to be approximately 3 to 3.25 years and 2.25 to 2.5 years in Egypt and KSA, respectively [41]. In comparison, the mean time to patient access, defined as the days between EMA marketing authorisation and the date of availability[12] to patients, between EMA marketing authorisation to availability to patient based on data from 2015 to 2018 was reported to be 154 days in Denmark, 252 days in the Netherlands, 349 days in the UK and 414 days in Spain [45].

Furthermore, when the lag time between first registration by the FDA or the EMA to registration in KSA and Egypt is considered, patient access is found to be 17 and 15 quarters of a year[13] in Egypt and KSA, respectively, but is reported to be decreasing over the years [41], [83]. On the other hand, time from registration to reimbursement seemed to have become shorter in both Egypt and KSA [41], [83].

No evidence was found on time to patient access to NME in Malaysia, however, it can be assumed that patient access is likely to be later than that of EMA as a lag time, defined as

[10] *Priority review by SFDA indicates that the review process will be expedited without altering any of the scientific standards and quality of evidence required for approval.*
[11] *The abridged approval pathway mentioned in this sentence refers to verification and abridged registration, which is only applicable for FDA or EMA approved medicines and provides considerable reduction in approval timelines.*
[12] *The point at which products gain access to the reimbursement list*
[13] *This accounts for a lag time of 4.25 years and 3.75 years in Egypt and KSA, respectively.*

the time between first market approval anywhere in the world to submission in the country, of 206 days is reported [88].

Table 4: Registration timelines for new molecular entities

	EGY	KSA	DEN	MYS	NED	SPA	UK
Official registration timelines of NMEs	105 days[1]	290 working days	210 working days (EMA centralised procedures)	245 working days	210 working days (EMA centralised procedures)	210 working days (EMA centralised procedures)	100 working days (rolling review) 210 working days[2] (EC decision reliance procedure)
Observed registration timelines	1-2 years (small molecules)	6-20 months (standard)	The overall median approval time 423 days	515 days	The overall median approval time 423 days	The overall median approval time 423 days	The overall median approval time 423 days
Abridged & accelerated approval pathways	30 days for NMEs and new biologics registered by US FDA and EMA (verification process) 60 days for NMEs and new biologics registered by US FDA or EMA (abridged process)	40% reduction for priority review 30 Working days for products approved and marketed by BOTH FDA and EMA (verification process) 60 Working days for products approved and marketed by either FDA or EMA (abridged process)	150-days (EU accelerated assessment)	120 days (Path I[3])	150 days (EU accelerated assessment)	150 days (EU accelerated assessment)	150 days (National accelerated assessment)
Note:	[1]105 days refer to the expected total number of days for registration of NME [2] 210 working days refers to the time to CHMP (Committee for Medicinal Products for Human Use) opinion. [3] Priority review/fast track review for lifesaving medicines, or medicines intended for a condition for which there is no alternative treatment available (e.g., rare disease), or medicines expected to tackle a public health threat.						
Abbreviations:	DEN: Denmark; EC: European Commission; EGY: Egypt; EMA: European Medicines Agency; EU: European Union; FDA: Food Drug Administration; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; NME: New Molecular Entity; UK: United Kingdom; US: United States.						
Source:	Official registration timelines for NMEs (for MA): [41] (EGY) (KSA); [43] (DEN) (NED) (SPA); [80] (MYS); [87] (UK). Observed registration timelines: [41] (EGY) (KSA); [85] (DEN) (NED) (SPA) (UK); [84] (MYS) Accelerated approval pathways: [41] (EGY) (KSA); [86] (DEN) (NED) (SPA); [84] (MYS)						

4.1.3. Medicine recalls including generic, biosimilar and originator medicines

A total of 84 medicine recalls were made by the SFDA between January 2010 to January 2019, 52 of which were generic medicines [89]. The main causes behind these recalls were contamination, lack of compliance with manufacturer's specifications, and failure to prove bioequivalence [89]. In addition, four medicine recalls have been reported on the SFDA website between February 2019 and April 2021 [90]. In Egypt, no summary statistics were found on drug recalls of either generics or originators.

Evidence from the benchmark countries includes aggregate data with no breakdown between generics and originators. The EMA issued 203 medicine recalls from 2010 to 2019 [91], [92], [93]. 42 recalls were issued in the period between 2018 and 2019, eleven of which were made due to product label issues, ten due to product packaging issues, eight due to manufacturing laboratory control issues, seven due to product physical issues and six due to product contamination and sterility issues [91], [92]. Out of the 203 recalls made by the EMA between 2010 and 2019, 38 recalls were classified as Class 1[14] recalls, 96 as Class 2[15] recalls and 69 as Class 3[16] recalls [91], [93]–[95]. The annual reports by the EMA does not report how many of these recalls were for generic medicines.

Similarly, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) issued 240 medicine recalls/notifications between January 1, 2010 and April 30, 2021 [96]. Of these, 200 are recalls and 40 are alerts for medicines. Common reasons behind these recalls include negative benefit-risk balance, potential contamination, poor manufacturing practices, poor packaging, incorrect labelling [97]. No information on the total number of recalls on generic medicine in the UK was found.

In Malaysia, two medicine recall notifications were identified on the NPRA website[17]: one was recalled in May 2016 [98] and the second one was recalled in April 2020 [99]. The reasons for these recalls were negative benefit-risk balance and safety concerns on the risk of liver injury, respectively. Moreover, in early 2019 it was reported on the news that some generic versions of a medicine used to treat high blood pressure were recalled by the Ministry of Health due to contamination [100].

[14] *Class 1 recall: the defect presents a life-threatening or serious risk to health.*
[15] *Class 2 recall: the defect may cause mistreatment or harm to the patient or animal but is not life-threatening or serious.*
[16] *Class 3 recall: the defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons, such as non-compliance with the marketing authorisation or specification.*
[17] *No further information available in English on the website.*

4.2. Supply-side policies

4.2.1. Pricing

Please refer to **Figure 1** and **Figure 2** for an illustration of the pricing structure in KSA and Egypt, respectively.

Originators. External reference pricing (ERP) is used in Egypt to set the prices of approximately 95% of originators, which are consequently used to calculate the price of generics [27]. Value-based pricing is used rarely when manufacturers appeal on the prices set by the pricing committee based on ERP. In this case, EDA uses value-based pricing to set up the prices of these medicines [27]. In KSA, prices of all medicines are set based on a list of rules, including the price in the country of origin (see **Figure 18** in Appendix 3). A review of the use of ERP in the Middle East concluded many of the countries, including Egypt and KSA, have room for improvement of ERP design and implementation when compared to best practice principles for ERP [101].

Generics. Both Egypt and KSA regulate prices of generics using price capping with managed competition based on sequential entry[18]. ERP is used by KSA for locally manufactured generics when the originator medicine is not available in the local market. None of the comparator countries use similar practices of managed competition based on sequence of entry for pricing of generics. The closest practice is seen in Spain: ERP is used to set the price of originators, which is subsequently used to set generic prices through price capping: a price cap of 40% below the initial price of the originator is applied to generic medicines entering the market, but the price cap does not change with sequential entry [102].

Pricing policies for generic pharmaceuticals for the remaining comparator countries are either free pricing (Denmark, Malaysia and the UK) or ERP, used in the Netherlands to set prices of medicines regardless their patent status [52]. Free pricing can either be uncontrolled or controlled indirectly. For example in Malaysia, prices of pharmaceuticals in the private sector are entirely dependent on market forces and competition [103]. While manufacturers in the UK are free to set the price of unbranded generic medicines[19], within the constraints of the Voluntary Pricing and Access Scheme (VPAS)[20] which imposes profit (based on rate of return) and sales growth caps [104].

[18] *Under this pricing mechanism, prices are set at a fixed percentage below the price of the originator and additional specific price reduction are applied based on order of market entry* [1].
[19] *The reimbursement price is subsequently set by the government's Drug Tariff based on information regarding revenues received and volumes supplied and is revised every three months* [104], [118].
[20] *Applies to all branded medicines, both patent-protected and not patent-protected.*

Biosimilars. Biosimilar medicines are priced using a price capping system with managed competition in KSA [33]. They are priced 70% below the biologic for the first entrant and 60% below the biologic for subsequent entrants [33]. However, sometimes a negotiation process is used to decide whether or not the biosimilar will be treated as a specialised medicine [33]. Biosimilars are also priced based on a price capping system in Egypt, with prices set 70% below the biologic for the first entrant, and 60% below the biologic for subsequent entrants [27], [33]. With the exception of Denmark, whose pharmaceutical industry association follows a price capping agreement for prescription only medicines [105], the comparator countries do not set biosimilar prices based on price capping. However, prices of biosimilars in these countries are lower than the price of the originator: evidence shows biosimilar (list) prices are around 25 to 30% below the originator biologic in Spain [63] and 10% to 25% in the UK [106]. The comparator countries used free pricing (Denmark), free pricing with indirect controls (Malaysia, UK), or tendering (the Netherlands).

Pricing of originators post generic entry. Mandatory price reductions of originator medicines upon entry of generics are applied in KSA [33]. Prices of originator medicines in KSA are reduced by 25% upon entry of a generic to the market, and biologics are reduced by 20% upon entry of a biosimilar (**Table 5**). In Denmark, a 20 to 30% reduction in the price of biologic medicines occurs upon biosimilar entry [63]. Spain applies price reductions for originator products only in cases where the originator has no generic or biosimilar competition at loss of exclusivity, and not upon generic entry.

Preferential practices for local manufacturers. KSA tries to promote local manufacturing by utilising supply-side interventions favouring local over imported medicines [24]. A recent price premium initiative was introduced in KSA by the Local Content and Government Procurement Authority (LCGP). The LCGP offers up to a 30% price premium[21] (10% premium from previous regulations and an additional 20% from the recent Price Premium Initiative) to nationally produced products listed in the initiative's list. The list includes 208 national products, 41 of which are products in the medicine and pharmaceutical sector [107]. The initiative also supports locally manufactured active pharmaceutical ingredients with an additional 10% price premium, regardless if the product is included in the initiative's list [107]. Preferential practices for local manufacturers in pricing favouring locally produced products were, until recently, in use in Egypt [108]. However, these types of preferential pricing policies for local manufacturers are not present in the selected comparator countries.

[21] *The premium is added to prices for foreign products equivalent to the products in the national list in government tenders.*

Table 5: Pricing of generic/biosimilar medicines

	EGY	KSA	DEN	MYS	NED	SPA	UK
Price regulation for generic medicines							
Price capping	Yes	Yes	Yes[1]	No	No	Yes	No
ERP	Yes	Yes[2]	No/Yes [3]	No[4]	Yes	Yes	No
Free pricing	No	No	Yes	Yes	No	No	Yes[5]
Price reduction for originator products after patent expiry	N/A[6]	25%[7]	No	No evidence	No	15%[8]	No evidence
Price regulation for biosimilar medicines							
Pricing mechanisms	Price capping	Price capping	Free pricing and price capping[9]	Free pricing Indirect price control through bulk purchase in the public sector	None; Price set through tendering	None, usually priced 25-30% lower than the reference product [10]	Free pricing governed by the VPAS[12]
Prices of originators post generic entry							
Price reduction for originator products after patent expiry	N/A[6]	25% (on generic entry), 20% (on biosimilar entry)	20–30% (on biosimilar entry)	No evidence	No	No[13]	No
Note:	[1] All pharmaceutical companies that are member of Danish Association of the Pharmaceutical Industry are obligated to follow the price cap agreement for prescription-only medicines. [2] Only for locally manufactured generics where the originator is not available in the local market. [3] ERP was expected to be re-introduced to the system around 1st of January 2020 for hospital-reserved medicines and 1stof July 2020 for eligible prescription drugs. [4] ERP is expected to be introduced by the end of 2020, but the first phase will involve only single-source or originator drugs. The next stage of rollout (over a 3–4-year timeframe) of the price controls programme is likely to be extended to other drug categories, including generic medicines, but will stay focused on the public sector. [5] Manufacturers are free to set the price of unbranded generic medicines. The reimbursement price is subsequently set by the government and is revised every three months. The price of branded generic medicines is regulated through either the Voluntary Scheme or the Statutory Scheme. [6] Egypt does not have well-defined implemented IP policies. [7] Price reduction occurs only after the first generic entry, not just upon patent expiry. [8] Medicinal products that do not have generic or biosimilar medicines but have lost exclusivity are subject to a 15% reduction in price. [9] All pharmaceutical companies that are member of Danish Association of the Pharmaceutical Industry are obligated to follow the price cap agreement for prescription-only medicines. [10] There are no publicly available pricing rules for biosimilars, but biosimilars are found to be usually priced 25-30% lower than the reference product. [11] High-tech generics are those which are considered to require rare production lines and are distinguished by a list published quarterly by the High Committee of Inspection upon Pharmaceutical Manufacturing. [12] The voluntary scheme imposes a limit on the reasonable profits that can be made by the manufacturer. [13] Spain applies a 15% price reduction for originator products only in cases where the originator has no generic or biosimilar competition at loss of exclusivity, not on generic entry.							
Abbreviations:	DEN: Denmark; EGY: Egypt; ERP: External reference pricing; IP: Intellectual Property; KSA: Kingdom of Saudi Arabia; LOE: Loss of exclusivity; MYS: Malaysia; NED: Netherlands; SPA: Spain; UK: United Kingdom; VPAS: Voluntary Pricing and Access Scheme.						
Source:	Price regulation for generic medicines (price capping / ERP / free pricing): [109]–[112] (EGY); [113] (KSA); [105] (DEN); [103], [114]–[117] (MYS); [102] (SPA); [118], [119] (UK). Price mechanism for originator products after patent expiry: [33] (EGY); [33], [113] (KSA); [120] (SPA). Price regulation for biosimilar medicines (pricing mechanisms): [33] (EGY); [113] (KSA); [28] (DEN); [121] (NED); [103] (MYS); [121], [63] (SPA); [63], [106], [118], [122] (UK). Pricing mechanisms for originator products after patent expiry: [33] (EGY); [113], [123] (KSA); [121] (DEN); [121] (NED); [120] (SPA); [63] (UK).						

Figure 1: Pricing structure in KSA

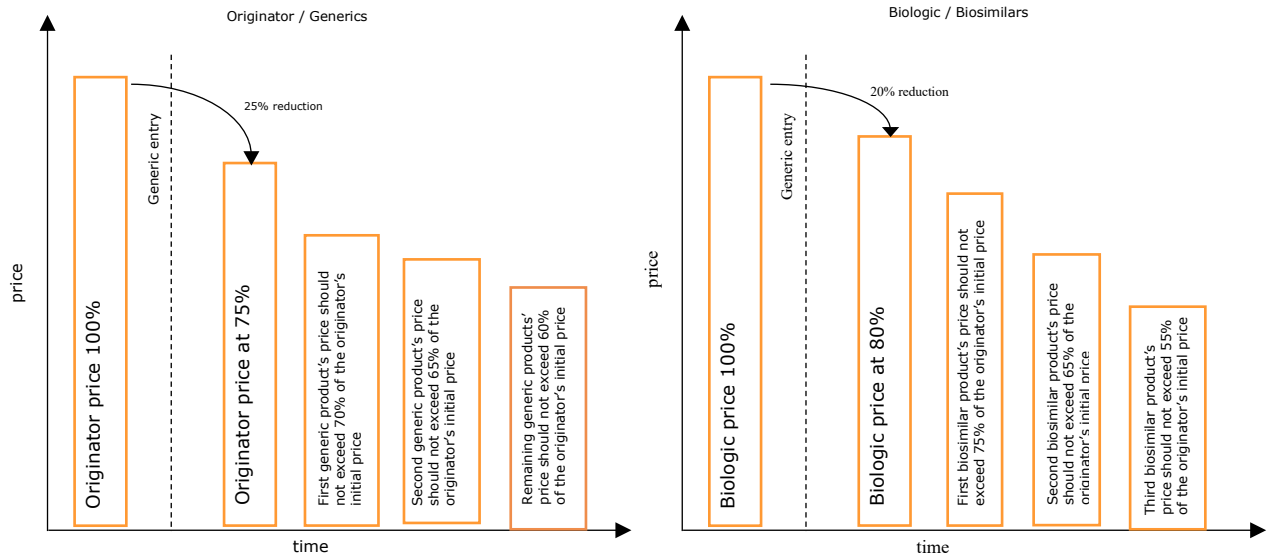
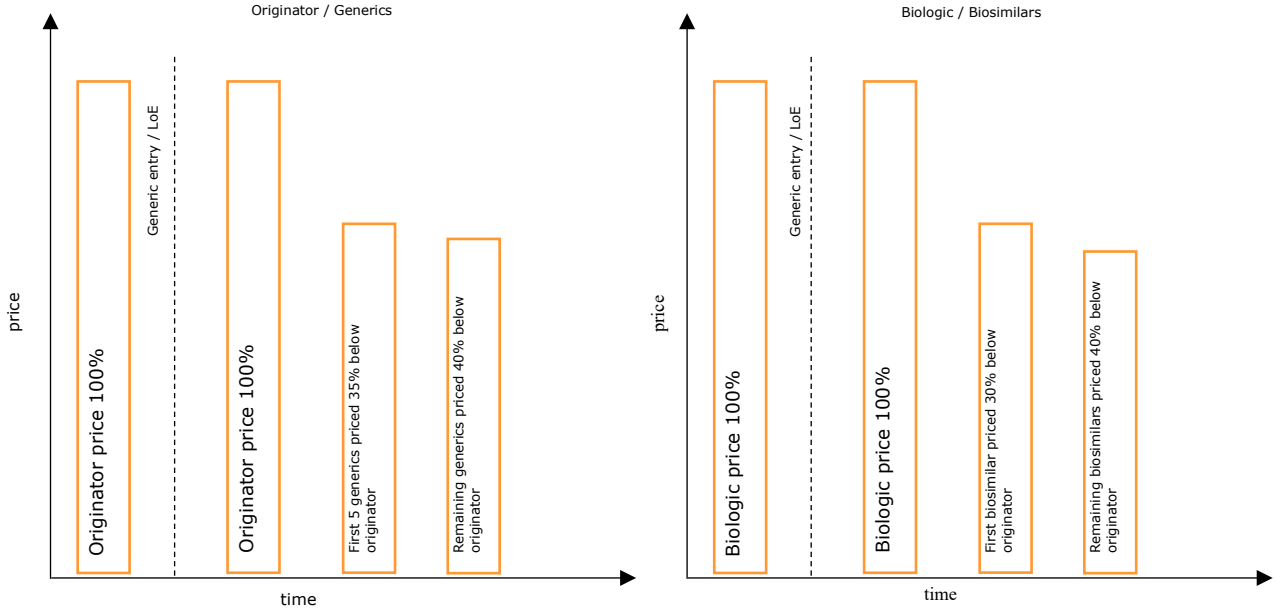


Figure 2: Pricing structure in Egypt



Note: The price of high-tech generics/biosimilars is based on the public price available reduced by 30% for the generics imported from reference countries and 35% for the generics imported from non-reference countries [33].

LoE: Loss of exclusivity

Source: The Authors.

4.2.2. Reimbursement

Box 1 Preference Policy Scheme in the Netherlands

The preference policy is a system of drug reimbursement used by many health insurers in the Netherlands. Under this scheme, health insurers can designate 'preferred' products that are eligible for reimbursement across a certain cluster of medicines with the same active ingredient and mode of administration [124]. Only manufacturers whose products are the most inexpensive are able to contract with health insurers [124]. This policy aims to increase price competition between manufacturers. While this policy was initially operated jointly by health insurers, since 2008 health insurers apply the preference policy individually [125]. The range of products under the preference price policy, as well as the designation period, vary between health insurers [125].

Internal reference pricing (IRP) and tendering are used in all comparator countries for the reimbursement of generic medicines **(Table 6)**; tendering is the predominant method of reimbursement for biosimilar medicines.

IRP is a key cost-containment tool by which reimbursed prices of generic medicines are subject to a ceiling [126]. Denmark, the Netherlands, and Spain apply IRP at molecular level, clustering medicines with the same active substance to define the reference price, while in Malaysia IRP is applied at therapeutic level, clustering medicines used to treat a particular condition to calculate the reference price. IRP is only used occasionally in KSA to price imported generics, while IRP is not used in Egypt.

Formulary management is implemented in KSA for both generics and biosimilars. This tool is also used in Malaysia, Spain, and at regional level in the UK for generics. This concept has been adapted in the Netherlands, where competition in the market is maintained through the preference policy (**Box 1**). The preference policy implemented in the Netherlands currently serves as best practice example for KSA; according to primary evidence, the Council of Cooperative Health Insurance (CCHI) is trying to implement a similar approach [33].

Tendering is a mechanism widely used across the five comparator countries for the purposes of procurement and reimbursement of generics, as well as in Egypt and KSA **(Table 6)**. Tendering is also used across Egypt, KSA, and the comparator countries for reimbursement of biosimilars [38], [127], [128]. In the UK, public tendering is used in the inpatient sector for generics (national and regional tenders) [119] and biosimilars (regional tenders) [122]. The majority of National Health Service (NHS) tenders are evaluated based on quality and price, awarding contracts to bidders who promises to deliver the best mix of these two dimensions (i.e. the most economically advantageous tender) [129].

Table 6: Reimbursement policies for generic medicines

	EGY	KSA	DEN	MYS	NED	SPA	UK
Internal reference pricing (molecular)	No	Yes[1]	Yes	No	Yes	Yes	No
Internal reference pricing (therapeutic)	No evidence	Yes[1]	No	Yes[2]	No	No	No
Tendering	Yes	Yes	Yes	Yes	Yes	No	Yes
Formulary Management	Sometimes	Yes	No	Yes	No	Yes	Yes [3]
Note:	Internal reference pricing: practice of applying a common reimbursement level or reference price for a cluster of interchangeable medicines. Internal reference pricing (molecular): Medicines with the same active substance (ATC-level 5) are grouped to define the reference price. Internal reference pricing (therapeutic): All drugs that are used to treat a particular condition or medicines that have a comparable therapeutic effect (ATC-level 3) are grouped to define the reference price. [1] According to current pricing regulations, pharmaceutical products must be priced considering prices of treatment alternatives registered in KSA. This is also the case for generic products. However, it is not clear to what degree this mechanism is applied. According to the previous pricing regulation, imported generics were priced in accordance with their therapeutic significance and the price could not exceed the lowest price of similar registered products. [2] For multisource products. [3] There are regional lists which include medicines that cannot be prescribed (negative list).						
Abbreviations:	DEN: Denmark; EGY: Egypt; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; UK: United Kingdom.						
Source:	Internal reference pricing (molecular): [33] (EGY); [113], [130] (KSA); [105] (DEN); [124] (NED); [131], [132] (MYS); [105] (SPA); [105], [133] (UK). Internal reference pricing (therapeutic): [33] (EGY); [113], [130] (KSA); [28] (DEN); [124] (NED); [131], [132] (MYS); [105] (SPA); [105], [133] (UK). Tendering: [33] (EGY); [24] (KSA); [134] (DEN); [135] (NED); [136], [137] (MYS); [106] (SPA); [119], [122] (UK). Formulary management: [33] (EGY); [24] (KSA); [138] (DEN); [139] (NED); [140] (MYS); [141] (SPA); [119] (UK).						

Preferential practices for local manufacturers. In KSA, preferential practices for locally produced products are present in formulary listing and the tendering process, while, until recently, similar mechanisms favouring local manufacturers as lower requirements for winning a tender for locally produced medicines were also in use in Egypt. However, as the system in Egypt has been revised, it is currently unclear whether these preferential policies for local manufacturers will remain in the new system under the Unified Purchase Authority (UPA).

4.2.3. Procurement

Tenders are being used for procurement of generics and biosimilars medicines used in both the in-patient and out-patient sector in Egypt and KSA. Procurement systems in both Egypt and KSA have been moving towards more centralised systems, with the introduction of the UPA in Egypt [33] and the National Unified Procurement Company for Medical Supplies (NUPCO) in KSA [108]. Since June 2020, Egypt has implemented an IT system for procurement for public hospitals under the auspices of the UPA [33].

In-patient medicines. In Denmark, Malaysia and the UK, national agencies are responsible for the procurement of generic and biosimilar medicines for the in-patient public sector [140], [142]–[145]. Spain implements initiatives for national procurement, but regional

authorities can also join procurement agreements with other regions [120], [146]–[148]. In addition to national procurement systems, Denmark and Spain have national procurement agreements with neighbouring countries: Denmark with Norway and Spain with Portugal [149], [150]. There is no national procurement body in the Netherlands: hospitals purchase from and negotiate with manufacturers or wholesalers either as individual purchasers, or as a group of hospitals [133].

Out-patient medicines. For outpatient medicines, all the countries purchase medicines directly from manufacturers and wholesalers [33], [125], [140], [142]–[145], [151]–[153]. In Malaysia, retail pharmacies buy the largest share of their medicines (70%-80%) from independent distributors and the remaining proportion (20%-30%) are purchased directly from local manufacturers, importers, and wholesalers [140]. There are examples of pharmacy buying groups in both Denmark and Spain which procure together medicines to increase their negotiation power [151], [152]. Procurement in the out-patient sector is present in KSA through the Wasfaty service, KSA's e-prescribing programme. In Egypt, all pharmaceuticals and medical devices used in the public sector are procured by the UPA [27].

Preferential practices for local manufacturers. Among the comparator countries, only Malaysia has preferential procurement practices in place to promote the local manufacturing industry. The government supports the local manufacturing industry as the largest buyer of locally produced generic medicines [131]. Priority for public procurement contracts is given to local manufacturers of generics over international suppliers through government procurement policies [131]. Where local generic medicines are not available, procurement for the public sector is made up of imported generics (19% of total quantity) and originator products (12% of total quantity) [131].

4.3. Demand-side measures

Presence and enforcement of generic/biosimilar prescribing and substitution interventions vary among the study countries. Demand-side efforts to encourage generic and biosimilar uptake and use across study and comparative countries are summarised in **Table 7**.

4.3.1. Generic and biosimilar prescribing

Generics. International non-proprietary name (INN) prescribing has been mandatory in KSA since 2017 [154], while in Egypt there is no current policy on INN prescribing and physicians choose whether to prescribe the generic or the originator product [27], [33]. The Universal Health Insurance Authority (UHIA) works closely with physicians on

prescribing by INN but this system is still in the process of being established [27]. Branded prescriptions dominate the private sector in Egypt [33].

Generic prescribing is allowed in Denmark, Malaysia, and Spain, while it is mandatory in the Netherlands and the UK. Egypt is the only country among those studied that has only very recently launched the first out of four phases of an information technology (IT) system to enable and target generic prescribing [27].

Biosimilars. In all countries except for Egypt, where differences are observed across different institutional settings, biosimilars are prescribed by physicians using brand names. INN prescribing for biologic medicines is not allowed in any of the countries, with the exceptions of the Netherlands and the Egyptian state fund where all products are prescribed by INN. In the Netherlands, this practice is allowed in retail pharmacies but not in hospitals [122]. Insurance companies in the Netherlands occasionally impose limits on the prescription of the original biologic product once a biosimilar becomes available on the market [155]. In the UK there are recommendations in place encouraging physicians to start treatment with the cheapest option available stimulating the use of biosimilars as these products are likely to be the most cost-effective options compared to biologics [156].

4.3.2. Generic and biosimilar substitution

Generics. Generic substitution is allowed in KSA and Egypt. In Egypt, substitution can be performed in the retail market only in cases when the prescribed product is not available. In the public system, pharmacists must dispense the product covered by the public tender, which might include both generics and originators [9]. An alternative can only be dispensed if the tendered product is not available [27]. Generic substitution policies exist in all comparator countries. Generic substitution is allowed in the Netherlands, Malaysia, and the UK, while it is mandatory in Denmark and Spain. In the Netherlands, insurance preference policies only reimburse generic medicines (see **Box 1**), resulting in high substitution at pharmacy level [21], [157].

Biosimilars. Among the study countries, automatic substitution by pharmacists is legally allowed for biological medicines only in the Netherlands. A physician is able to prescribe a biosimilar, and biologic substitution by pharmacies is allowed only if the route of administration and indication are the same as of the original biologic [158]. However, switching at pharmacy level is not common practice [159].

Table 7: Presence and enforcement of generic and biosimilar prescribing and substitution regulation

	EGY	KSA	DEN	MYS	NED	SPA	UK
Is there a generic prescribing policy in place?	No [1]	Yes	Yes	Yes	Yes	Yes	Yes
Is generic prescribing allowed?	Allowed [2]	Mandatory	Allowed	Allowed	Mandatory	Allowed	Mandatory [3]
Is there a generic substitution policy in place?	No	Yes/No	Yes	Yes	Yes	Yes	Yes
Is generic substitution allowed?	Allowed [4]	Allowed	Mandatory	Allowed	Allowed	Mandatory	Allowed [5]
Is there a biosimilar prescribing policy in place?	No [6]	Yes	Yes	Yes	Yes	Yes	Yes
Is prescribing biological medicines by INN allowed?	[7]	Not allowed [8]	Not allowed [9]	Not allowed [10]	Allowed	Not allowed	Not allowed [11]
Is biosimilar substitution allowed (without consulting the prescribing physician)?	Allowed [12]	Not allowed [13]	Not allowed	Not allowed [14]	Allowed	Not allowed	Not allowed
Note:	[1] There is mixed evidence across secondary and primary sources. Secondary evidence suggests that INN prescribing is mandatory in the public sector, while primary evidence suggests that in the public sector prescribers are not obliged to prescribe by INN. [2] In the public sector, the UPA has allowed availability of both originator and generic medicines, therefore it is up to the decision of the treating physician and hospital committee in certain cases. [3] However, there some instances when prescribing by brand name may be considered. [4] In the private sector, substitution is allowed only in case of unavailability. [5] Pharmacists can substitute only if the prescription is written by INN. [6] Dispensing of biosimilars differs between sectors. However, there is no clear biosimilar prescribing policy. [7] Some organisations, such as the Health Insurance Organisation, are using the product trade name; while others, such as the State Fund, use the generic name as per their protocols, and pharmacists dispense the originator or the biosimilar according to their budget. [8] The brand name must be included in addition to the INN when prescribing biosimilars. [9] Prescribing by INN not permitted. Biosimilars are prescribed by physicians using their brand name. [10] Prescribing based on active substance does not apply to biosimilars as these are not considered interchangeable with the reference product or other products of the same class. [11] Biosimilars are prescribed by physicians using their brand name. [12] In the public sector, it is at the discretion of the pharmacist to substitute a biosimilar or not, only if interchangeability of the original biologic and the biosimilar has been approved by the Technical Committee for Pharmaceutical Control. In addition, dispensing of biosimilars differs between sectors. [13] In case both the biologic and biosimilars are available on the formulary, pharmacists can only dispense the prescribed option. Guidelines from KSA state that pharmacists cannot substitute biosimilars without consultation with treating physicians. It should be noted though that, according to the local industry, pharmacists have considerable impact on updating the formular, through the Pharmacy and Therapeutics Committee. This committee is coordinated by physicians, pharmacists and nurses decides, in the majority of cases, only one option (either the biologic or a biosimilar) to be available on the formulary. [14] Interchangeability and automatic substitution of biosimilars and reference products is not permitted. The decision to substitute an original biologic with a biosimilar product should be based on science and clinical data.						
Abbreviations:	DEN: Denmark; EGY: Egypt; INN: International non-proprietary name; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; UK: United Kingdom; UPA: Unified Purchase Authority.						
Source:	Generic prescribing: [24], [33] (EGY); [160] (KSA); [105] (DEN); [52], [105] (NED); [161] (MYS); [18], [105], [162] (SPA); [119], [163], [164] (UK). Generic substitution: [33] (EGY); [165]–[168] (KSA); [105] (DEN); [105], [124], [157] (NED); [131], [161] (MYS); [105], [162] (SPA); [119], [144] (UK). Biosimilar prescribing: [33] (EGY); [39] (KSA); [121] (DEN); [122] (NED); [161] (MYS); [121] (SPA); [106], [156], [169] (UK). Biosimilar substitution: [33], [38] (EGY); [35], [33] (KSA); [121] (DEN); [122] (NED); [37] (MYS); [121] (SPA); [106] (UK).						

4.3.3. Financial incentives for healthcare professionals

Table 8 presents findings on incentives for healthcare professionals used to influence prescribing and dispensing behaviour.

Prescribing. No evidence was found on financial incentives for physicians in Egypt. There are no financial incentives targeting prescribers in KSA in the public sector [27]. A formulary was recently implemented in the private sector to control prescribing [27]. On the contrary, most of the comparator countries use several financial incentives targeting physicians. For example, financial incentives for physicians are common in the UK - specifically in England - in the form of prescribing budgets (See **Box 2** for more information).

Dispensing. Financial incentives for pharmacists are limited to higher margins for generics as well as financial deals such as discounts and bonuses for generics[22], in Egypt [33]. Financial deals and discounts for generics are also seen in chain pharmacies in KSA [33]. Financial incentives for dispensing are used in the Netherlands, Malaysia, and the UK, mainly in the form of clawbacks and profit margins. For example, in Malaysia, generic substitution results in higher profit margins for community pharmacies [170]. The maximum profit margin obtained with generics is higher than 100%, whereas for branded medicines it is between 81% and 100%. A survey of community pharmacies in Malaysia found that high profit margins were the main reason pharmacists substituted for generic medicines [171]. Discounts offered by manufacturers to pharmacies are regulated in Spain and limited to 10% for both originator and generic medicines leaving no incentive for pharmacists to dispense generics [69].

Pharmacy remuneration strategies can influence dispensing behaviour. There are no payment strategies likely to promote generic dispensing in the public sector in KSA, as pharmacists receive fixed salaries set by the government [27]. On the contrary, according to local experts, pharmacists prefer to dispense originators as they generally obtain a higher revenue [27]. However, primary evidence from local industry states that the profit margin for generics is higher in some cases due to financial deals offered by generic manufacturers [33]. Moreover, some private chain pharmacies request financial deals such as discounts to be offered from companies in order to purchase and dispense their medicines [33]. A similar effect is seen from regressive mark-ups used in Malaysia, a strategy which is likely to disincentivise pharmacists to dispense expensive medicines [172]. In Egypt the rates of profit for pharmacists are established by law and depend on

[22] *Applies to both imported and locally manufactured generics* [33].

the distributor selling price or the public selling price; Decree 499 incentivises pharmacists to dispense locally manufactured products by allowing higher markups compared to imported products [33].

In the UK, pharmacists get a fixed fee - currently 90p per item - for every item they dispense [173]. Since pharmacists are rewarded based on their level of service, their dispensing decisions are not influenced by medicines prices and, as a result, pharmacists may be stimulated to dispense generic medicines [126]. In the Netherlands, pharmacies are reimbursed only if they dispense an insurer's 'preferred' medicine, as specified in their preference policy [124].

Box 2 Financial incentives for physicians and pharmacists in the United Kingdom

Physicians

Prescribing Incentive Schemes (PIS) are currently used by the Clinical Commissioning Groups in England as an incentive and reward mechanism for general practitioners (GPs) who are automatically registered in the scheme [173]. GP practices are required to use 'ScriptSwitch', a decision support software, which helps to achieve cost savings in prescribing and informs prescribers about quality issues. The scheme comprises of the following elements: (i) prescribing within budget allocation, (ii) quality, (iii) antibacterial prescribing, and (iv) cost saving audits. A payment for any of the above elements cannot be made to the GP practice unless the target of the first element has been achieved [174].

The Quality and Outcomes Framework (QOF) scheme is a voluntary annual reward and incentive programme implemented in the United Kingdom (UK) since 2004 for GP practices, detailing practice achievement results [175]. GPs are rewarded based on the proportion of patients who achieve certain quality indicators. GP practices score points for the aforementioned areas, and therefore, actively try to deliver high quality care. The final payment is adjusted based on the workload of the GP practice, local demographic characteristics, and the prevalence of chronic diseases in the local area [175].

Pharmacists

The medicine margin system in the UK incentivises pharmacists to dispense generic medicines and further provides an incentive for community pharmacies to procure efficiently [176]. The medicine margin is the difference between the purchase price paid by the pharmacist and what they have been reimbursed by the National Health Service (NHS) for dispensing the product against an NHS prescription [176]. Pharmacists are reimbursed at fixed price indicated by the Drug Tariff [177]. However, discounting from wholesalers and manufacturers is allowed and, therefore, pharmacists buy generic medicines at a discounted price [177]. Dispensing margins for generic medicines are higher than margins on branded medicines [176].

4.3.4. Non-financial incentives for healthcare professionals

Box 3 'Medicine Profile' database in Denmark

The Danish Medicines Agency (DKMA) has introduced the 'Medicine Profile', a database accessed by physicians and patients to check individual medicine use and to compare the price of the prescribed product with that of equivalent products [178]. There is a central database where all purchases of prescription medicines are recorded [179] and a medicine profile for each individual patient maintained in a web-based application [179]. The profile shows all the medicines prescribed for the patient over the previous two-year period, as well as the prescribing physician, the dispensing pharmacy and the manner of reimbursement [179].

Only few non-financial incentives for healthcare professionals are used in Egypt, including distribution of initiation kits and training and education activities by the National Training Institute targeting both physicians and pharmacists. In KSA some non-financial incentives are in place targeting only physicians, such as electronic prescribing and awareness campaigns on social media.

Non-financial prescribing incentives (controls) for physicians are implemented in all comparator countries. For instance, physicians in the UK are empowered with a decision support system which automatically reminds them to prescribe a generic medicine when available [180]. Physicians in Denmark have access to a database which allows them to compare a medicine's price with that of equivalent products (See **Box 3** for more information). Denmark also has medicine quotas in place for physicians to increase uptake, with a focus on prescribing biosimilars [181].

4.3.5. Pharmaceutical industry activities

Another strategy that influences prescribing is pharmaceutical detailing. In all study countries, pharmaceutical representatives are allowed to visit healthcare professionals to promote pharmaceuticals [182]–[188].

The distribution of product samples is allowed in all study countries except the Netherlands [33], [182], [184]–[188]. In the UK, the relevant legislation provides that samples should be supplied only following a written request, signed and dated by the recipient; only a limited number of samples of each medicinal product may be supplied annually to a single recipient [188].

In KSA, advertising and product bonuses offered by pharmaceutical companies are reported as key factors influencing generic substitution by Saudi community pharmacists [189].

Table 8: Financial and non-financial incentives for healthcare professionals for encouragement of generic and biosimilar uptake and use

	EGY	KSA	DEN	MYS	NED	SPA	UK
Financial prescribing incentives for physicians	No evidence	No	Mandatory quotas (the focus is on prescribing biosimilars)	No evidence	No evidence	Yes, in some autonomous communities [1]	- Prescribing Incentive Schemes - QOF
Non-financial prescribing incentives for physicians	- Distribution of initiation kits (e.g., free product samples) - National Training institute for educating healthcare professionals	- Application ("We Care for you") that provides the available generics for each originator - Awareness campaign on social media about generics - Electronic prescribing system - Naming strategies policy for biosimilars in MNGHA formulary	- Electronic prescribing - Monitoring of prescribing behaviour through a system called 'Ordipax' - 'Medicine Profile' database - Monthly newsletter published by the DKMA for physicians with advice on cost-effective prescribing	- Formulary management and prior authorisation	- Electronic prescription system using INN - Prescribing behaviour monitored by the NZa - 'Biosimilars toolbox' designed to educate and inform hospital physicians on the use of biosimilars and to provide guidance on biosimilar prescribing	- Yes, in some autonomous communities [1] - Electronic prescribing using INN	- Electronic prescribing using INN - IT system which automatically reminds physicians to prescribe a generic medicine when available - Prescribing monitoring - Prescribing guidelines - Information materials/training targeted at physicians
Financial dispensing incentives for pharmacists	- Higher margins for locally manufactured products - Commercial deals and discounts for generics	Commercial deals and discounts for generics [2]	No evidence	Higher profit margin is obtained with generic medicines	List-price minus claw back of up to 6.82%	Claw-back: pharmacists must make payments based on a proportion of sales of reimbursable medicines. The legally allowed discount to pharmacies is limited at 10% for both originator and generic manufacturers.	Medicine margin system in place: dispensing margins on generic medicines are higher that margins on branded medicines
Non-financial dispensing incentives for pharmacists	· Distribution of initiation kits (e.g., free products samples) · National Training institute for educating healthcare professionals	No evidence	No evidence	No evidence	No	No evidence	No evidence
Note:	[1] Some Autonomous Communities like Andalucía, Catalonia, Madrid, and others, have already implemented various policies targeting physicians to prescribe generic medicines such as guidelines, drug information bulletins, financial incentives, prescribing by international non-proprietary name (INN), and so on. For instance, INN prescribing, supported by electronic prescribing systems, has been stimulated in Andalucía since 2001. [2] There are no official government incentives in place for pharmacists in KSA to dispense generics. However, some chain pharmacies give bonuses to pharmacists for dispensing the most profitable medicines (that is, the medicines with high profit margin which is usually driven by commercial deals and discounts away from the official margin).						
Abbreviations:	DEN: Denmark; DKMA: The Danish Medicines Agency; EGY: Egypt; INN: International non-proprietary name; IT: Information technology; KSA: Kingdom of Saudi Arabia; MNGHA: Ministry of National Guard Health Affairs; MYS: Malaysia; NZa: the Dutch Healthcare Authority; NED: Netherlands; QOF: Quality and Outcomes Framework; SPA: Spain; UK: United Kingdom.						
Source:	Financial prescribing incentives: [27] (KSA); [63], [178], [181] (DEN); [63], [102] (SPA); [190]–[192] (UK). Non-financial prescribing incentives: [33] (EGY); [39], [193], [27] (KSA); [63], [178] (DEN); [52], [158] (NED); [140], [194] (MYS); [63], [102], [163] (SPA); [63], [105], [122], [180] (UK). Financial dispensing incentives: [33] (EGY); [33] (KSA); [124] (NED); [170] (MYS); [102] (SPA); [176], [195] (UK). Non-financial dispensing incentives: [33] (EGY); [124] (NED).						

Patient-level policies and behaviours

Co-payment arrangements can influence patient medicine choice. Patients do not face co-payments in the public sector in KSA [24]. However, according to primary evidence, co-payments are reviewed by the government and are expected to be introduced for the insurance policy [33]. More specifically, depending on the individual's monthly income, the beneficiary of the insurance policy may be required to pay a proportion of the cost if they choose to use the originator than the generic medication [33]. In Egypt co-payment policies are in place: in the Egyptian public sector, patients are subject to a co-payment to get the originator or a generic alternative to the product covered by the public tender [27], [33].

Patient co-payments are in place in Denmark, the Netherlands, Spain, and the UK. However, in both Spain and the UK (England), the co-payment is not specific to generics: in Spain patients pay a proportion of the medicine cost with no differential co-payment for generics and originator medicines [163], while in the UK (England), there is a flat fee per prescription at £9.15 [196] [163]. In the Netherlands there is differential co-payment for generics and originator medicines, and patients pay the difference between the reimbursement price and the national list price [163]. Finally, patients in Denmark who want to get a medicine other than the one reimbursed and dispensed by the pharmacist have to cover the difference in price between the currently cheapest option available and the medicine they choose [51].

Box 4 Generic Medicines Awareness Program in Malaysia

A national awareness programme involving road shows about generic medicines, organised by the Ministry of Health, looks to promote generic medicines, educate the general public about the benefits of generic medicines, as well as reassure the public that generics are of high quality and efficacy [132].

As patients are the end-users of medicines, accurate knowledge and positive perceptions towards generics and biosimilars are likely to increase the acceptance and facilitate the use of these products [126]. In KSA, efforts to build trust in generic medicines and promote their use by patients are made by the SFDA, several insurance companies and local manufacturers [27]. These efforts usually take the form of campaigns on social media. However, in Egypt there are no such efforts [27]. Evidence from local experts highlight that there is a negative perception of generics prevalent among the Egyptian public [197]. Efforts to raise patient awareness on generic and biosimilar medicines take place in all comparator countries: in Denmark [198] and the Netherlands [199], pharmacies are responsible for informing patients about cheaper options available, while in Spain pharmacists also inform and educate patients about generics.

Awareness campaigns take different forms: the Danish Medicines Agency (DKMA) has a special focus on raising awareness about generics and biosimilars by information material and Q&As available on the DKMA website [200], [201]. Similar efforts are seen in Spain and the UK: information leaflets for patients about generics and biosimilars are available on the Spanish Agency for Medicines and Health Products website [202], while the UK government uses information leaflets as well as patient organisations (e.g. the Patients Association) to inform patients about generic and biosimilar medicines [192], [203]–[205]. In Malaysia, a national awareness programme promoted generic medicines through road shows [132] (See **Box 4** for more information). Stakeholder involvement is also seen: NHS England has introduced a subgroup responsible for developing education and communication materials on biosimilars for patients [122].

4.4. Simulation exercise: estimating potential savings

4.4.1. Methodology

IQVIA sales and volumes data[23] between 2016 and 2020 were collected and analysed for six genericised and mature classes of products, namely angiotensin converting enzyme (ACE)1 inhibitors, proton pump inhibitors (PPIs), antibiotics, selective serotonin reuptake inhibitors (SSRIs), angiotensin receptor blockers (ARBs), and statins, together with cancer drugs. The analyses consisted in estimating the magnitude of potential savings the two study countries, Egypt and KSA, could have obtained should they manage to achieve low generic prices and high market shares in line with the lowest prices and the highest market shares prevailing in a number of comparator countries. The comparator countries included in the analysis were Germany[24], the Netherlands, Spain, and the UK, all of which emphasise strong generic utilisation and procurement. The sales and volumes data obtained related to the outpatient market. Very mature product classes were selected for analysis to avoid the potential impact of different patent expiry dates between study and comparator countries and to account for the fact that generic penetration would have reached optimal levels after several years of patent expiry.

Of the above product classes, we selected the products with the highest market shares in their product class for analysis and with complete data, notably: lisinopril (ACE1 inhibitors); omeprazole and pantoprazole (PPIs); valsartan and candesartan cilexetil

[23] *IQVIA sales data reflect primarily list prices but may include tender or discounted prices where these are publicly available.*
[24] *The Netherlands, Spain, and the United Kingdom (UK) are used as comparator countries throughout this study. No data was available for Denmark, used as a comparator country in earlier sections of this report. Germany was used as an alternative market considering this.*

(ARBs); amoxicillin and clavulanic acid (antibiotics); atorvastatin and rosuvastatin (statins); escitalopram and citalopram (SSRIs). The cancer drugs considered were trastuzumab, docetaxel, doxorubicin and imatinib. However, due to missing data, only docetaxel and imatinib could be analysed without major assumptions and imputations. Data for the Netherlands were missing for all cancer drugs.

At first, average prices per standard unit[25] (SU) were estimated by dividing the sales data (available in United States Dollar (USD) across all countries for ease of comparison) by the volumes (in SU) for each product. Prices in Egypt included a 5% value-added tax (VAT), which has been removed from the analysis to avoid overestimating drug prices. KSA data refers to the retail market only. Prices, volumes, and volume market shares for both generic and originator products were estimated. Originator products were identified by their brand name and the (expired) patent held by the originator manufacturer. **Figure 3** shows lisinopril (ACE1 inhibitor) prices (A) and volumes (B) for generic and originator products in Egypt in 2016 and 2020, respectively. Similar figures for all products and countries analysed can be found in Appendix 5.

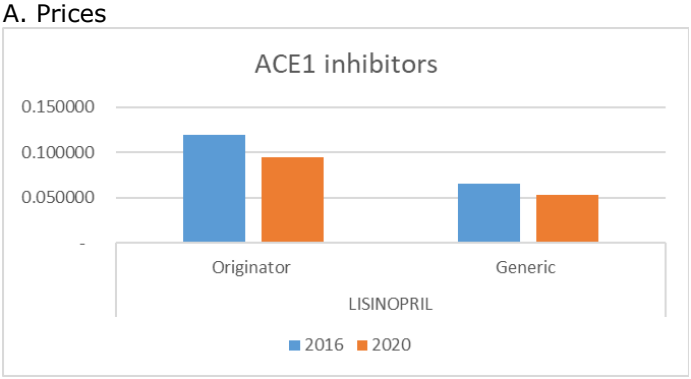
Having calculated average prices per SU and generic vs originator product market shares across all countries, we identified the lowest prices and the highest market shares for each product in the comparator countries. We simulated the effect these prices and market shares would have on sales in each of the products selected in Egypt and KSA (*optimal purchasing*). If the resulting figure was lower than actual sales reported, this would mean that the study countries could be saving on genericised drugs compared with current levels of expenditure. **Figure 4** to **Figure 8** illustrate prices and market shares, as well as potential savings foregone, in the two study countries.

The results for cancer drugs are discussed separately due to differences in prices and market shares dynamics versus the other product categories (see *Cancer drugs* section below).

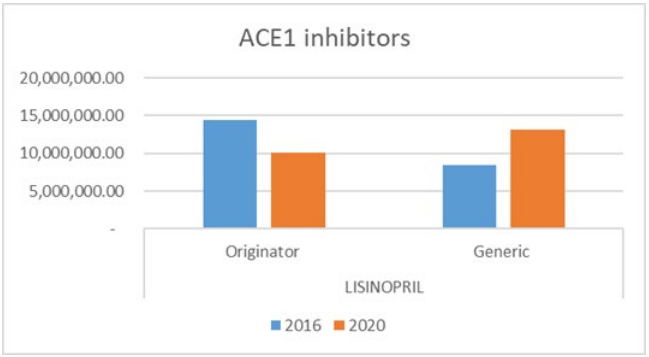
[25] *Standard units are a measure of volume defined by IQVIA and represent a dose of a particular formulation of treatment.*

Figure 3: Originator vs generic prices and volumes (SU sold) of ACE1 inhibitors in Egypt, 2016-2020; values in USD and volumes in SUs.

A. Prices



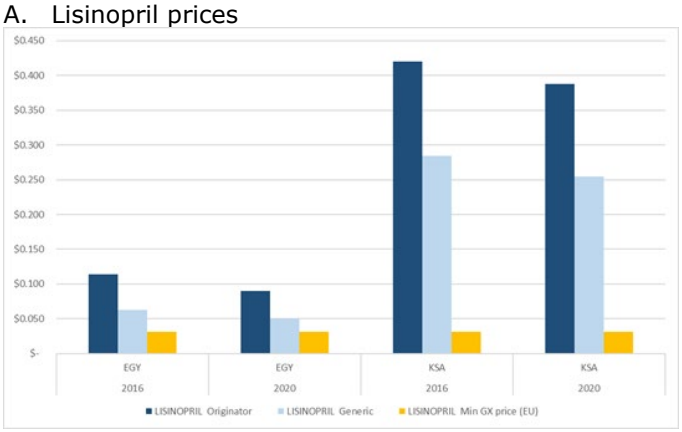
B. Volumes



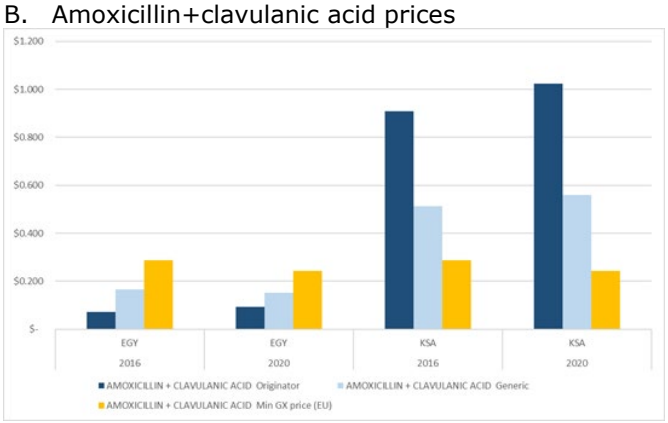
Abbreviations: Angiotensin converting enzyme (ACE), standard unit (SU)

Figure 4: Lisinopril and amoxicillin+clavulanic acid prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020

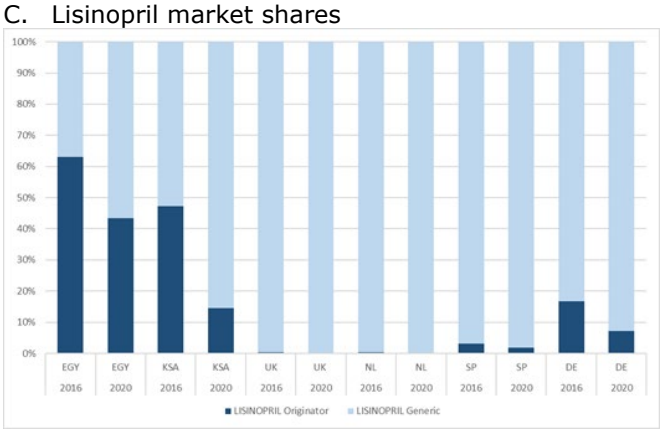
A. Lisinopril prices



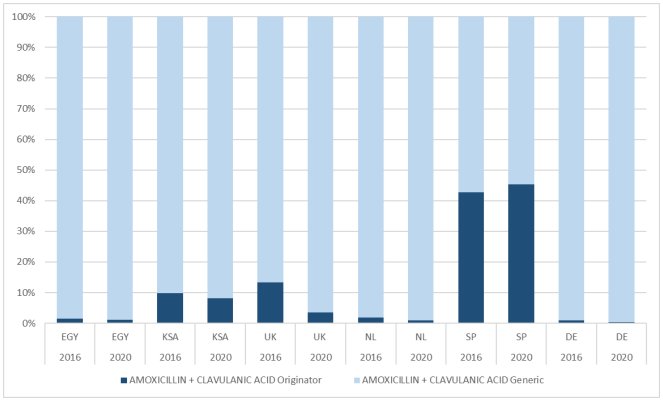
B. Amoxicillin+clavulanic acid prices



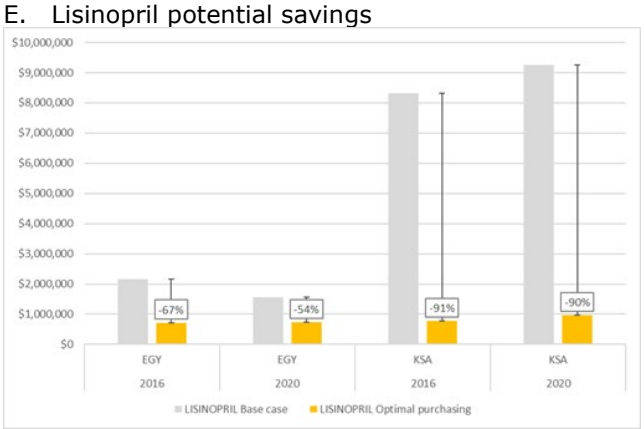
C. Lisinopril market shares



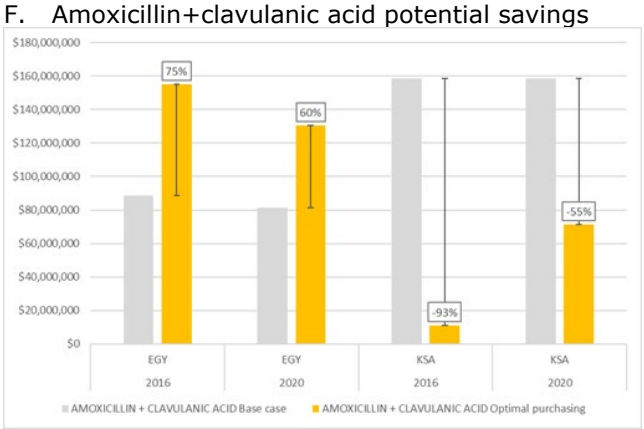
D. Amoxicillin+clavulanic acid market shares



E. Lisinopril potential savings



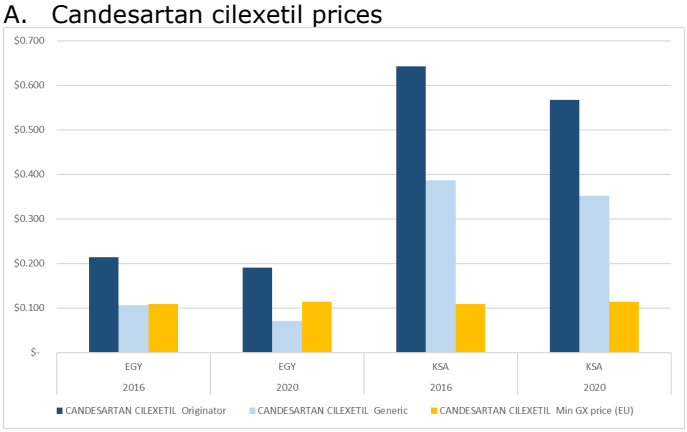
F. Amoxicillin+clavulanic acid potential savings



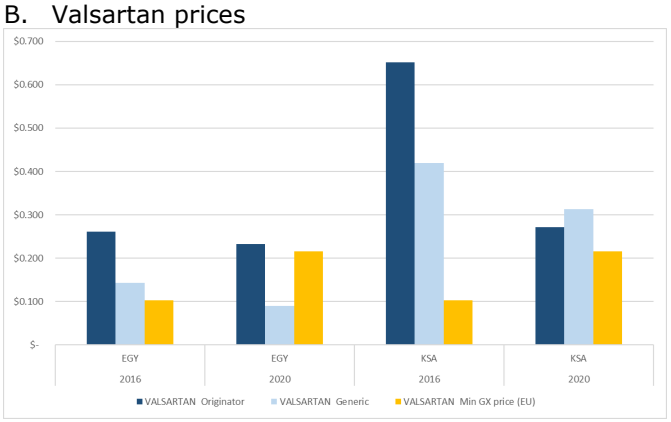
Abbreviations: Germany (DE), Netherlands (NL), Spain (SP), United Kingdom (UK)

Figure 5: Candesartan cilexetil and valsartan prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020

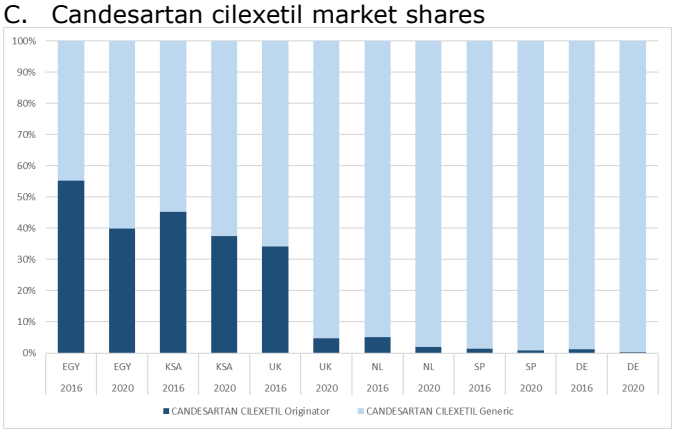
A. Candesartan cilexetil prices



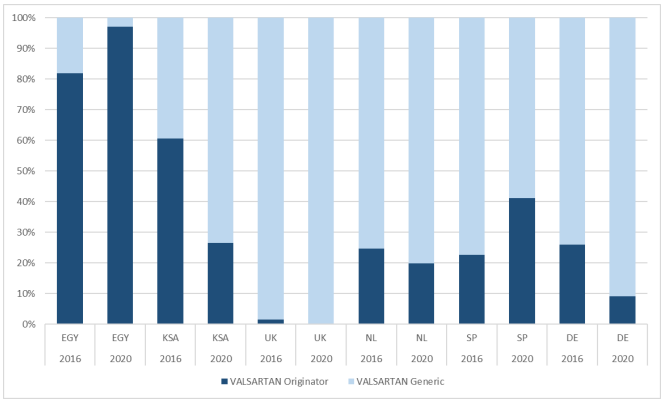
B. Valsartan prices



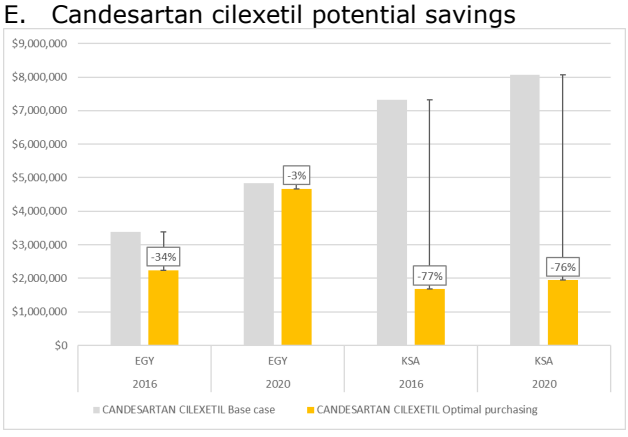
C. Candesartan cilexetil market shares



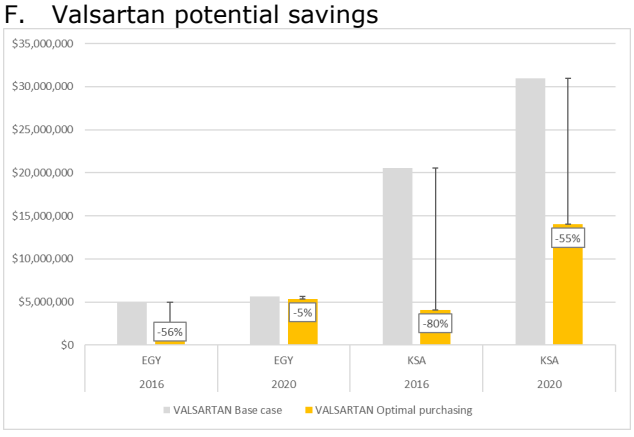
D. Valsartan market shares



E. Candesartan cilexetil potential savings



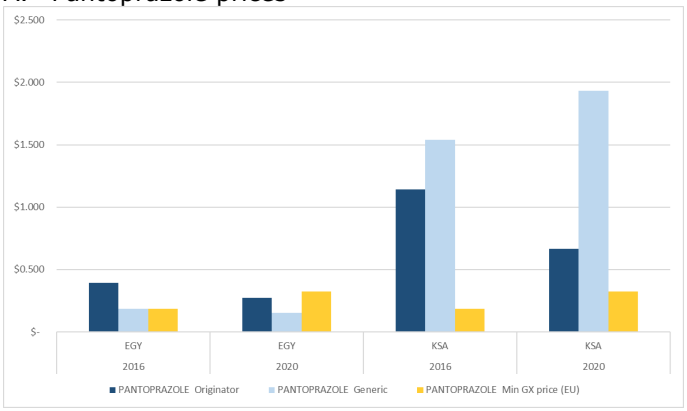
F. Valsartan potential savings



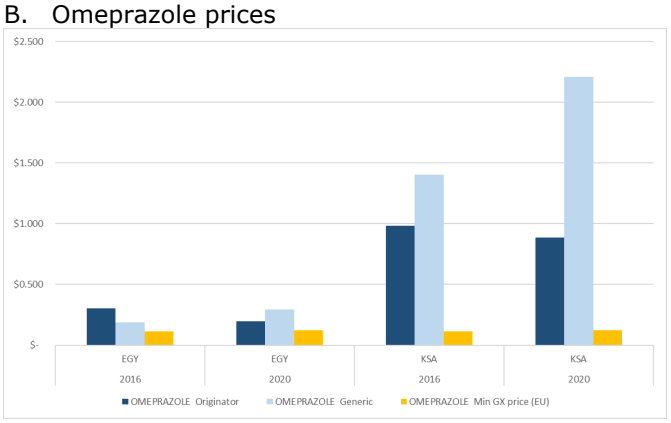
Abbreviations: Germany (DE), Netherlands (NL), Spain (SP), United Kingdom (UK)

Figure 6: Pantoprazole and omeprazole prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020

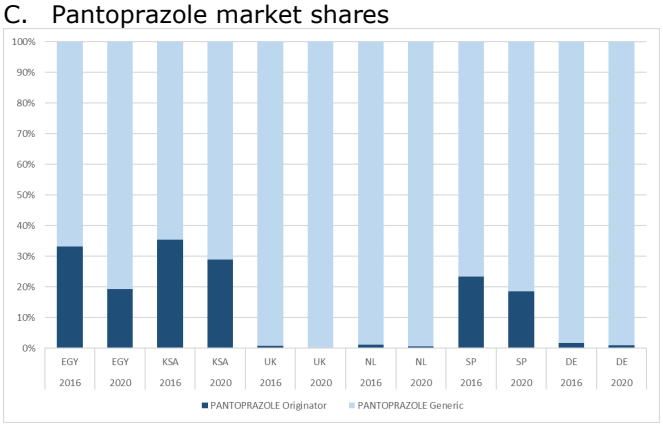
A. Pantoprazole prices



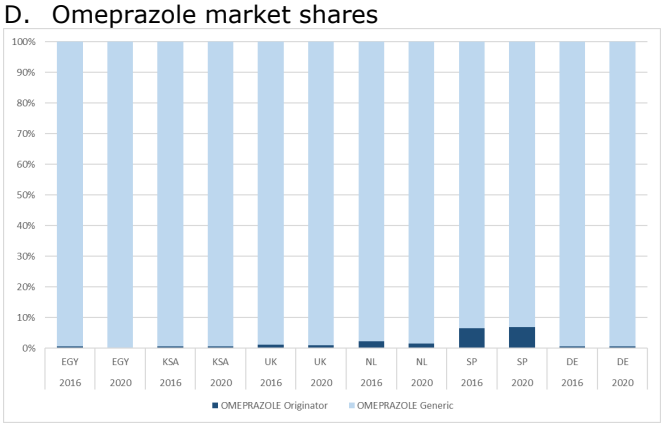
B. Omeprazole prices



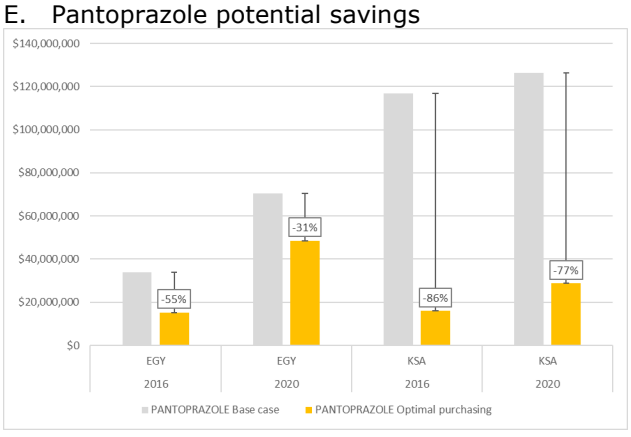
C. Pantoprazole market shares



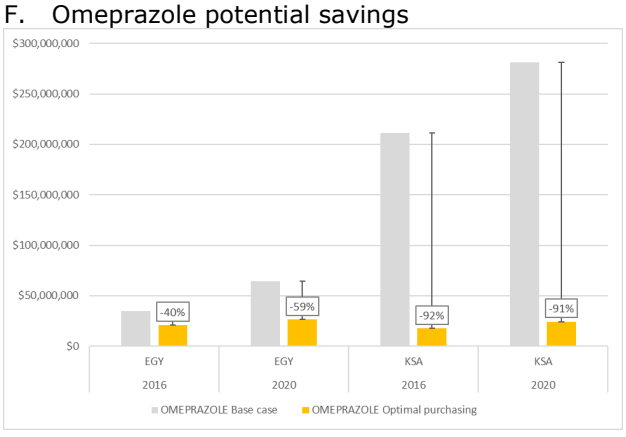
D. Omeprazole market shares



E. Pantoprazole potential savings



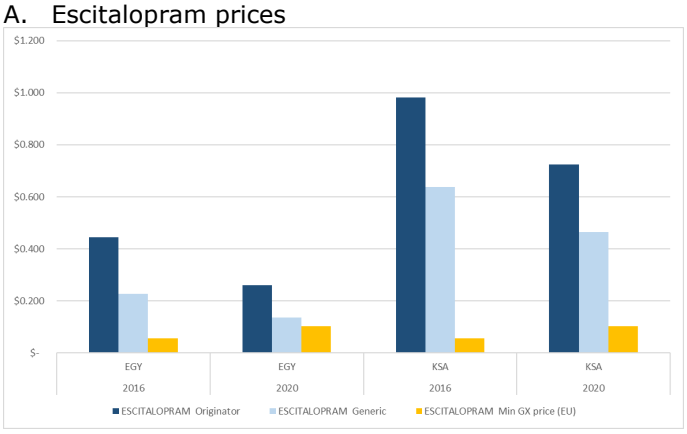
F. Omeprazole potential savings



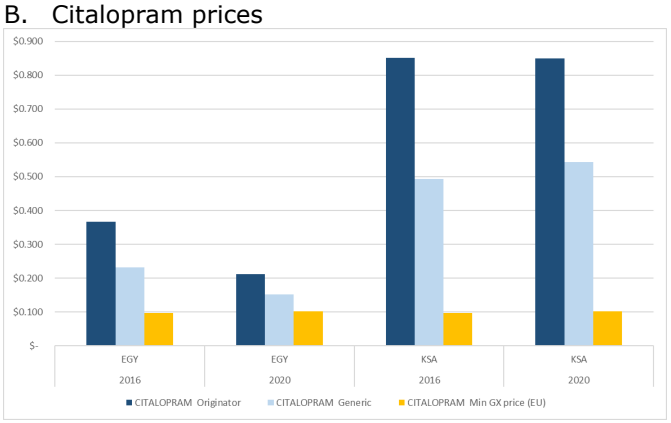
Abbreviations: Germany (DE), Netherlands (NL), Spain (SP), United Kingdom (UK)

Figure 7: Escitalopram and citalopram prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020

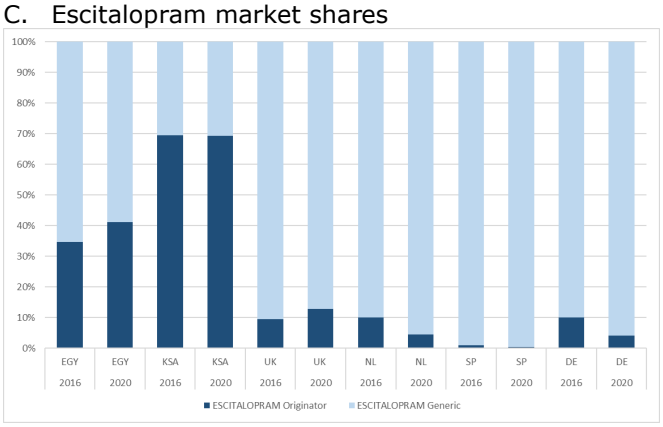
A. Escitalopram prices



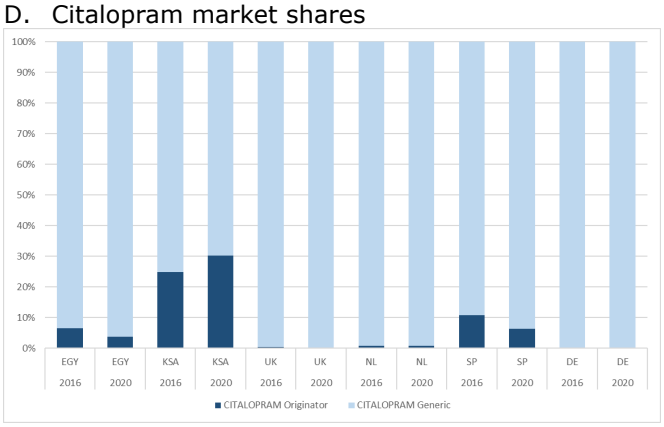
B. Citalopram prices



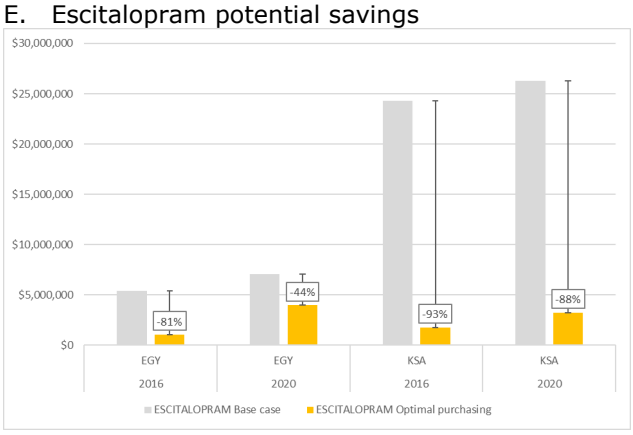
C. Escitalopram market shares



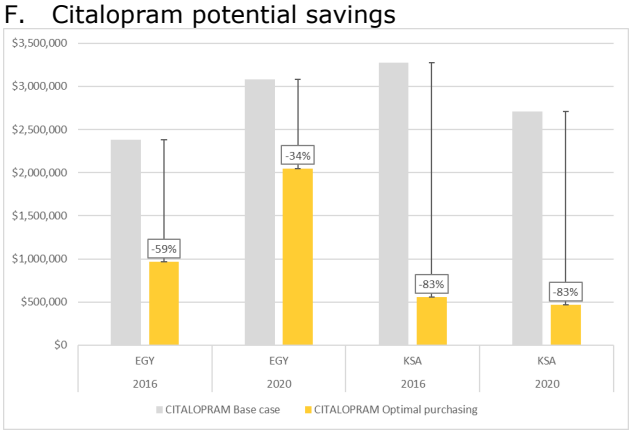
D. Citalopram market shares



E. Escitalopram potential savings



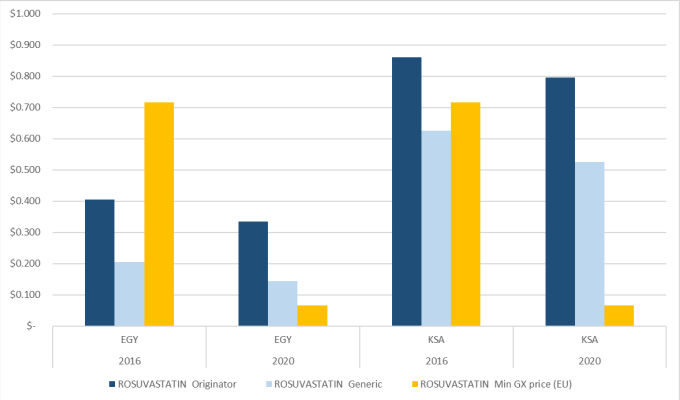
F. Citalopram potential savings



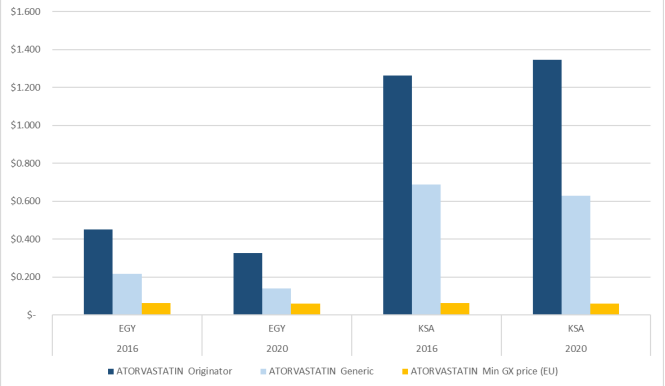
Abbreviations: Germany (DE), Netherlands (NL), Spain (SP), United Kingdom (UK)

Figure 8: Rosuvastatin and atorvastatin prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, NL, SP, DE) in 2016-2020

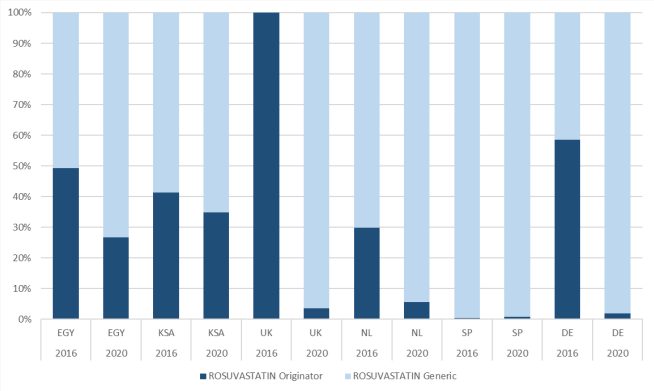
A. Rosuvastatin prices



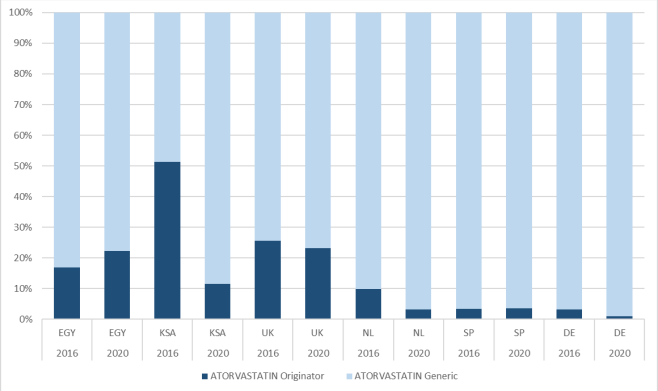
B. Atorvastatin prices



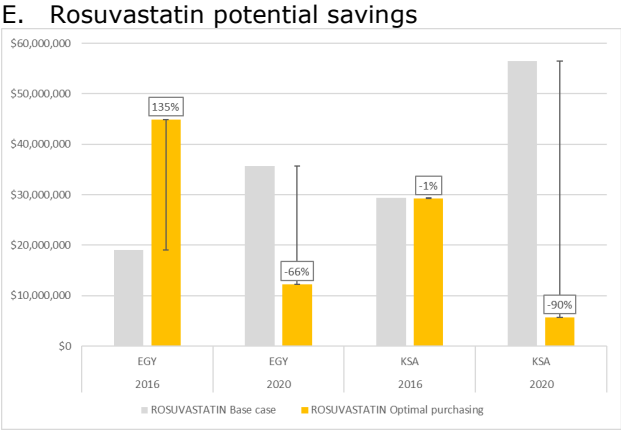
C. Rosuvastatin market shares



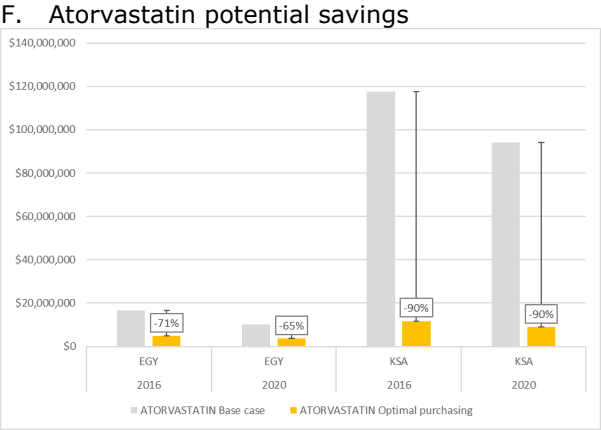
D. Atorvastatin market shares



E. Rosuvastatin potential savings



F. Atorvastatin potential savings



Abbreviations: Germany (DE), Netherlands (NL), Spain (SP), United Kingdom (UK)
Note: the rosuvastatin patent was still in force in 2016 in the UK, as it expired in December 2017

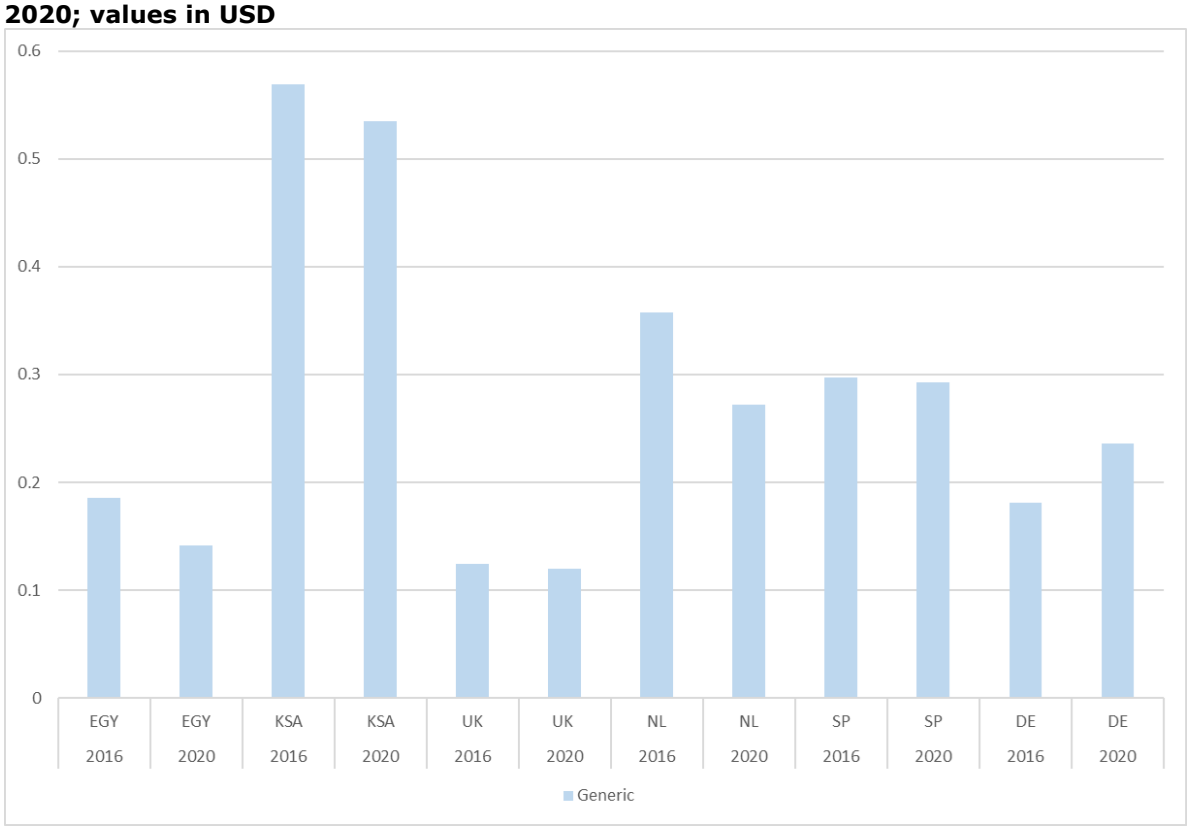
4.4.2. Results

Prices and volume market shares for both originator and generic products (excluding cancer drugs) were compared across the study and comparator countries. To reduce biases due to outliers, median prices and market shares were calculated rather than averages.

Prices

When compared to the comparator countries, Egypt had amongst the lowest originator and generic prices, suggesting that the country is relatively successful in securing prices close to the comparator country prices. However, the picture is different in KSA, whose median generic prices are the highest in the sample (**Figure 9**). At product level, KSA generic prices were lower than the average of the comparator countries only in a handful or products, namely amoxicillin + clavulanic acid (generics, 2020) and rosuvastatin (generics, 2016).

Figure 9: Median generic prices per SU in study and comparator countries in 2016 and 2020; values in USD

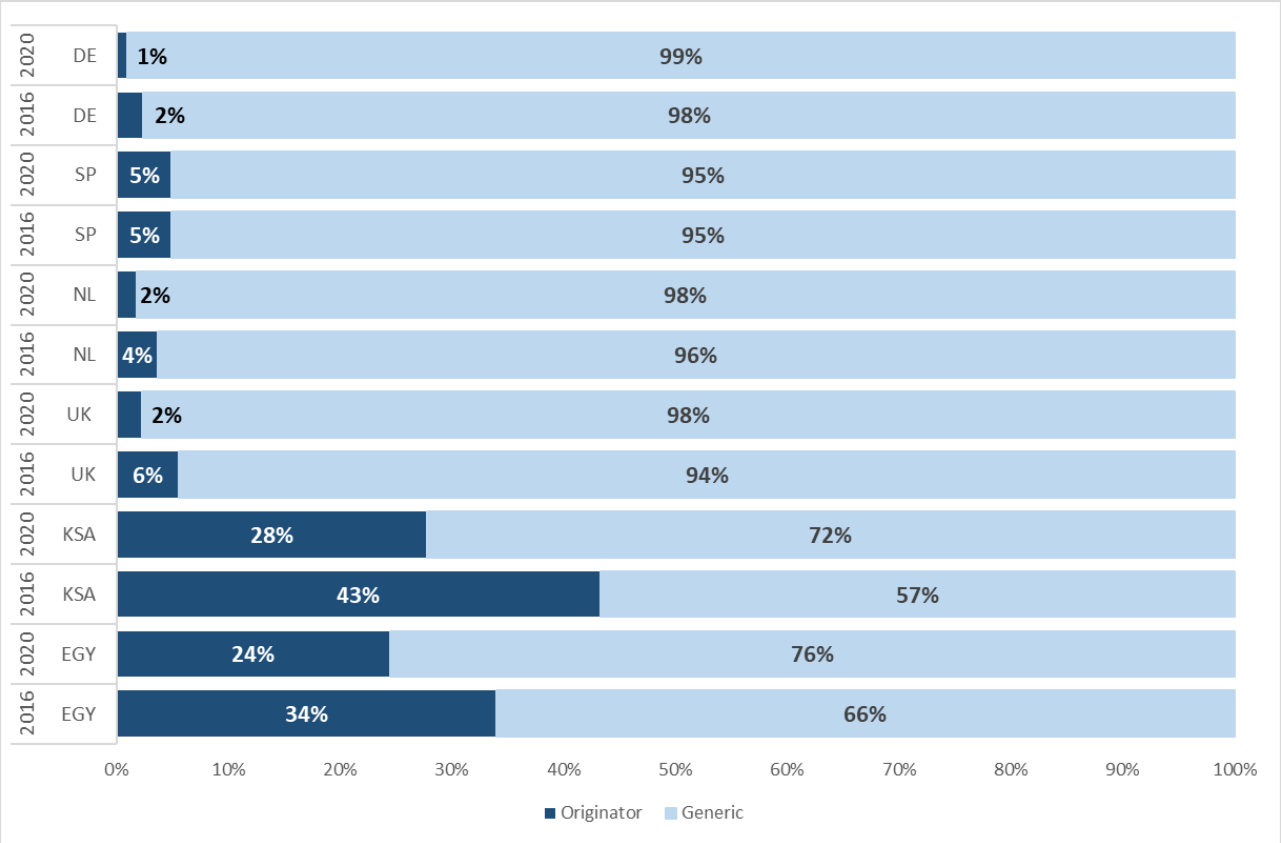


Volume market shares

Egypt and KSA had comparable generic market penetration (72-76% in 2020), with both countries improving their overall generic market shares from 2016 to 2020 (see **Figure 10** below). The product with highest generic penetration in both Egypt and KSA was amoxicillin + clavulanic acid, with a generic market share higher than 90% in both years.

On average, originator market shares were significantly higher in the study versus the comparator countries. Comparator countries had an originator market penetration as low as 1-6% of the entire market in 2016 and 2020. Despite generic market shares increasing in all countries from 2016 to 2020, the difference between the study and comparator countries remains considerable. On average, generic penetration was 34 and 24 percentage points lower in the study versus the comparator countries, in 2016 and 2020 respectively.

Figure 10: Median originator and generic volumes market shares in the study and comparator countries in 2016 and 2020



Optimal purchasing

Overall spending in Egypt could have been reduced from $211 to $156 million in 2016, generating a potential saving of $55 million, if the lowest generic prices and highest generic volume market share observed in the comparator countries for all products in the sample (excluding cancer drugs) could have been achieved. Potential savings in 2020 could have been as high as $95 million. With the highest savings achieved by omeprazole and pantoprazole alone, accounting for more than 60% of all savings in 2020. As evidenced by **Figure 11(A)**, savings from pantoprazole are driven by both lower generic prices and higher generic market shares achieved in the comparator countries. Conversely, generic market shares are close to 100% for omeprazole in Egypt but the lower generic price,

combined with high volumes, allow a substantial reduction in expenditure for this product. On the other hand, no savings would be generated for amoxicillin + clavulanic acid (in both 2016 and 2020) and rosuvastatin (2016 only), as Egypt had among the highest generic market share in the first and average prices lower than the comparator country averages in the latter.

Overall spending in KSA could have been reduced from $697 to $95 million in 2016, generating a potential saving of $602 million. Potential savings in 2020 could have amounted to $634 million. Similar to Egypt, the highest savings would have been achieved by omeprazole and pantoprazole alone, accounting for more than 55% of all savings in 2020. As evidenced by **Figure 11(B)**, savings from pantoprazole are driven by both lower generic prices and higher generic market shares achieved in the comparator countries. Conversely, generic market shares are close to 100% for omeprazole in KSA but the lower generic price, combined with high volumes, allow a substantial reduction in expenditure for this product. Generic pantoprazole and omeprazole prices in KSA seem to be consistently higher than the originator price. Savings from rosuvastatin were minor in 2016 ($194,724) because the rosuvastatin patent was still in force in some European countries until 2017, hence increasing both prices and originator market shares. In 2020, rosuvastatin was estimated to generate more than $50 million savings.

Overall, optimal purchasing would yield a reduction in expenditure on the drugs in the sample of 26% and 34% in Egypt and of 86% and 80% in KSA, in 2016 and 2020 respectively. Over time, Egyptian generic prices dropped by about 23% while generic market shares increased by 10 percentage points. While this should have led to a reduction in the extent of savings from optimal purchasing (as the gap with the comparator countries should have narrowed), this was not the case, as overall savings increased by 8 percentage points between 2016 and 2020. A possible explanation for this is that while spending on most drugs remained stable over time in Egypt, expenditure on omeprazole and pantoprazole increased by a factor of 2. As omeprazole and pantoprazole have respectively higher prices and lower generic market share in Egypt versus the comparator countries, this translates into an overall increase in potential savings.

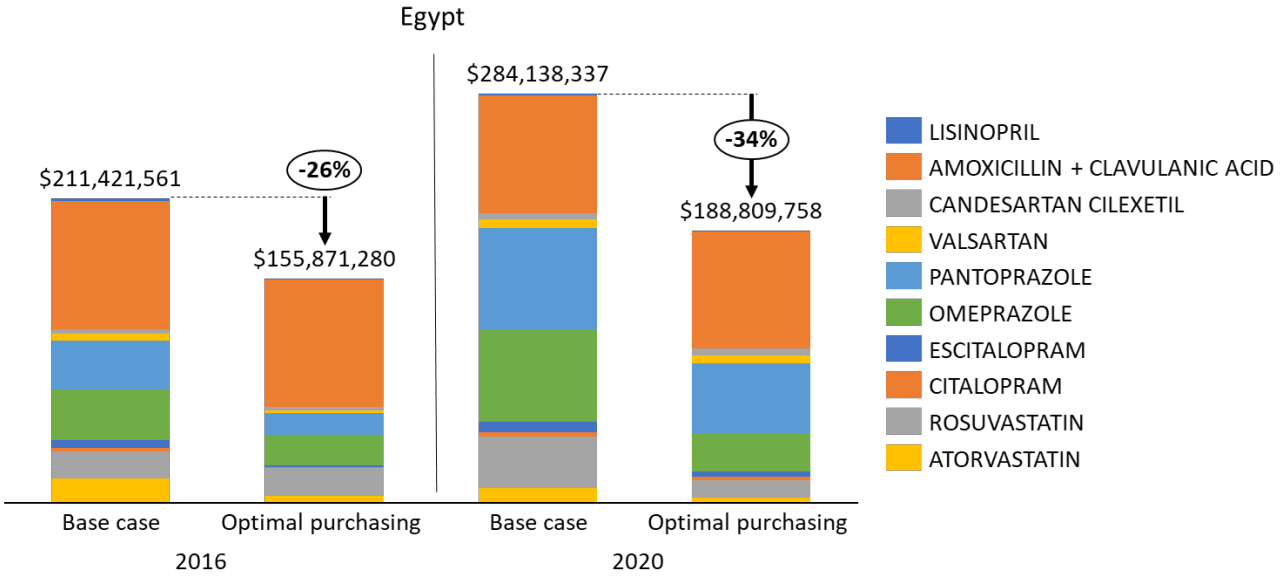
On the other hand, KSA saw a decrease of 6 percentage points in expected savings from 2016 to 2020. This can be attributed to a reduction in both originator and generic prices (-14% and -6%) as well as an increase in generic market shares (+27%), which suggests KSA was able to negotiate better prices and increase the share of generic drugs, leading to a reduction in the gap with the comparator countries.

Most savings are expected to come from the reduction in generic prices alone (*price effect*), which would generate a reduction in spending in 2020 of 23% in Egypt and 67% in KSA

(see **Figure 12**). Conversely, the increase in generic market shares alone (*market shares effect*) would reduce spending in 2020 by 10% in Egypt and 14% in KSA (see **Figure 13**).

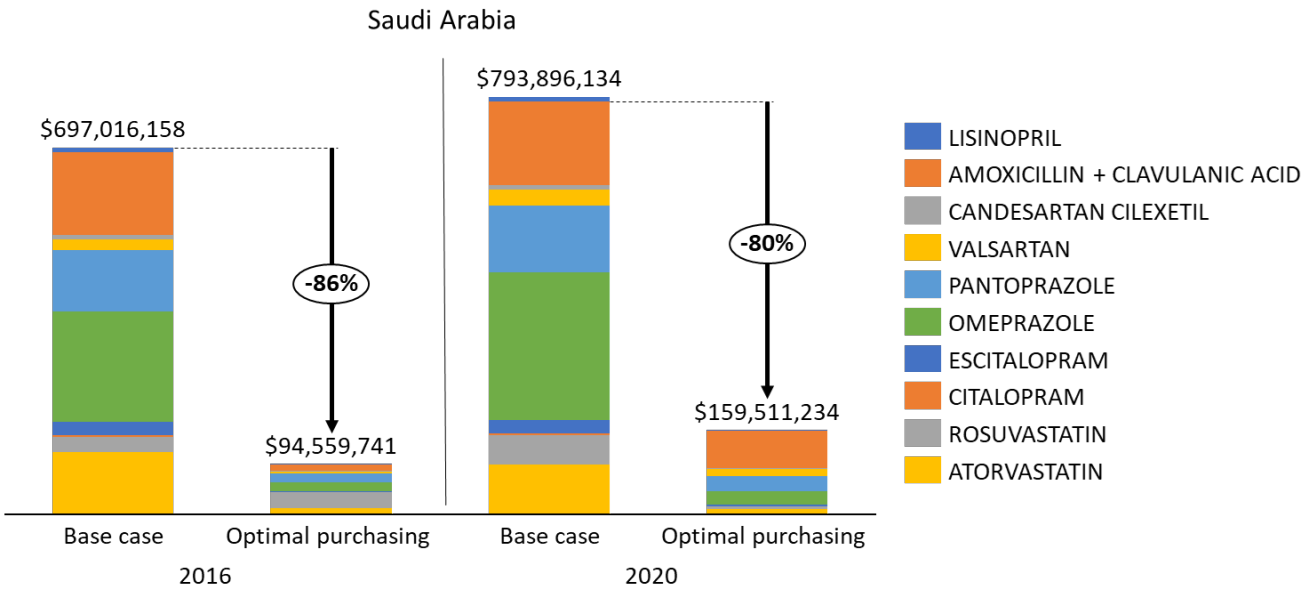
Figure 11: Base case spending vs potential savings from optimal purchasing in Egypt and KSA in 2016-2020; values in USD

A.



Note: spending for amoxicillin+clavulanic acid and rosuvastatin (2016 only) were kept as the base case as their generic prices/generic market shares were lower/higher in Egypt compared to the comparator countries.

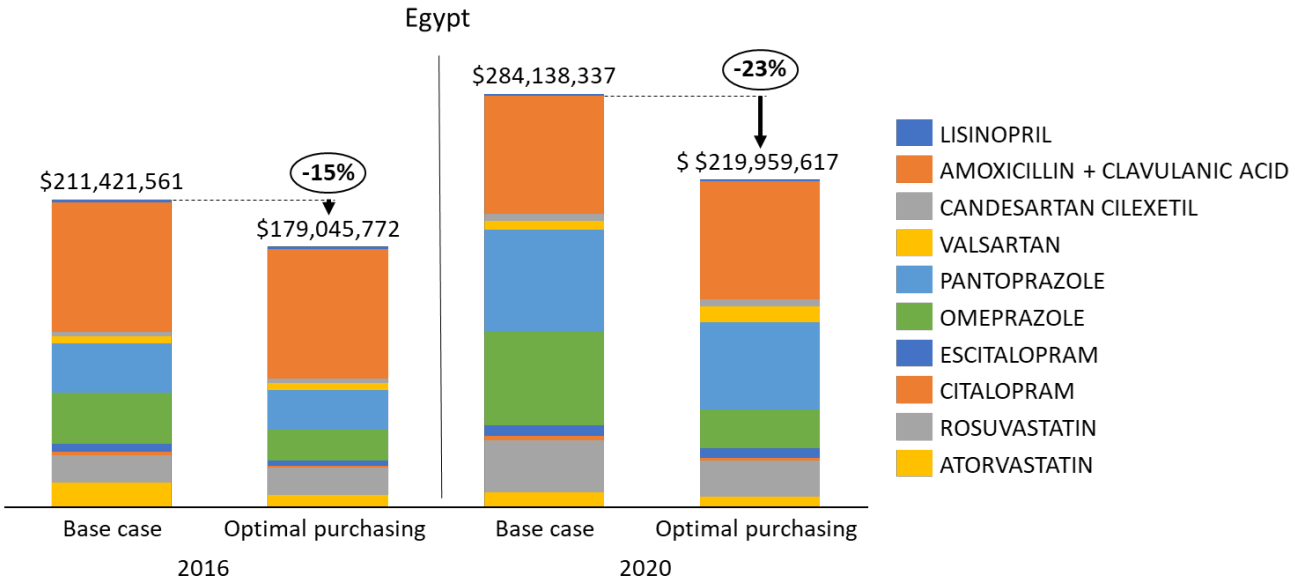
B.



Abbreviations: Egypt (EGY), Saudi Arabia (KSA)

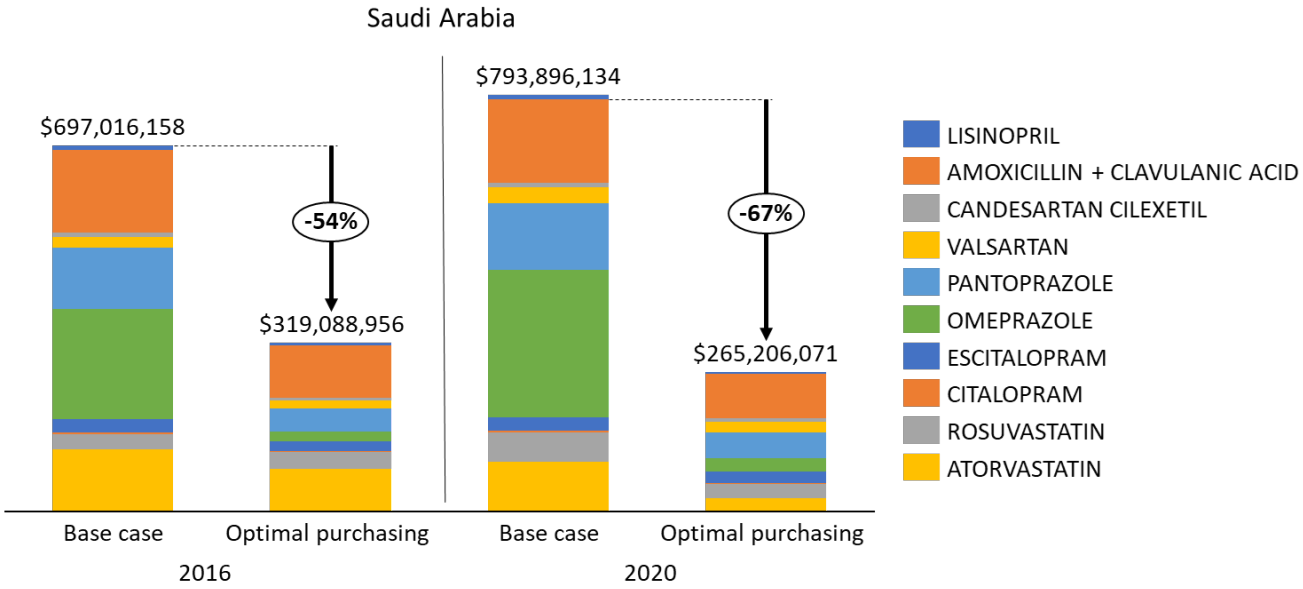
Figure 12: Base case spending vs potential savings from reduction in generic prices in Egypt and KSA in 2016-2020; values in USD

A.



Note: spending for amoxicillin+clavulanic acid, candesartan cilexetil, valsartan (2020 only) and rosuvastatin (2016 only) were kept as the base case as their generic prices/generic market shares were lower/higher in Egypt compared to the comparator countries.

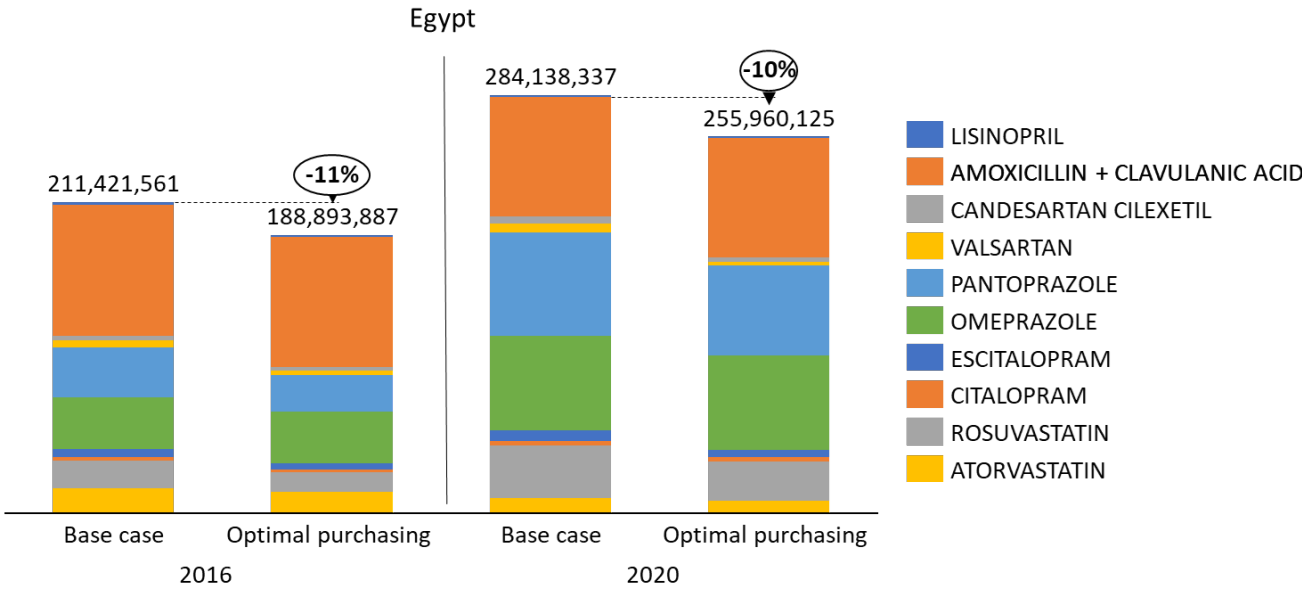
B.



Note: spending for rosuvastatin (2016 only) was kept as the base case as its generic prices/generic market shares were lower/higher in Saudi Arabia compared to the comparator countries.
Abbreviations: Egypt (EGY), Saudi Arabia (KSA)

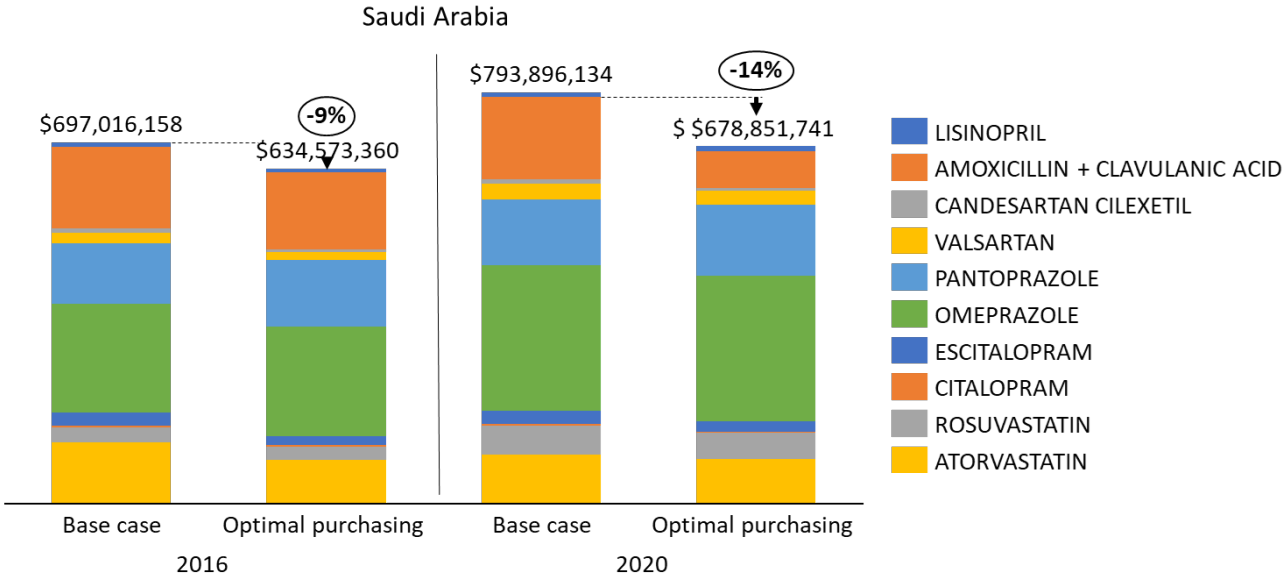
Figure 13: Base case spending vs potential savings from increase in generic market shares in Egypt and KSA in 2016-2020; values in USD

A.



Note: spending for amoxicillin+clavulanic acid and omeprazole were kept as the base case as their generic prices/generic market shares were lower/higher in Egypt compared to the comparator countries.

B.



Note: spending for pantoprazole and omeprazole were kept as the base case as their generic prices/generic market shares were lower/higher in Saudi Arabia compared to the comparator countries.
Abbreviations: Egypt (EGY), Saudi Arabia (KSA)

Cancer drugs

Docetaxel is a chemotherapy drug administered via intravenous injections (IV). As such, IQVIA SU may be less reliable and seemed to have produced a number of price outliers (e.g., price per SU as high as $22,000). Therefore, the analysis for this product was restricted to optimal purchasing via higher generic market shares only. The lowest imatinib generic price and market share were observed in Egypt. Therefore, the optimal purchasing analysis was limited to KSA and assumed German generic market shares and Spanish generic prices, as they were respectively the lowest price and highest market share observed in the comparator countries. Results of the analysis for cancer products are illustrated in **Figure 14** below.

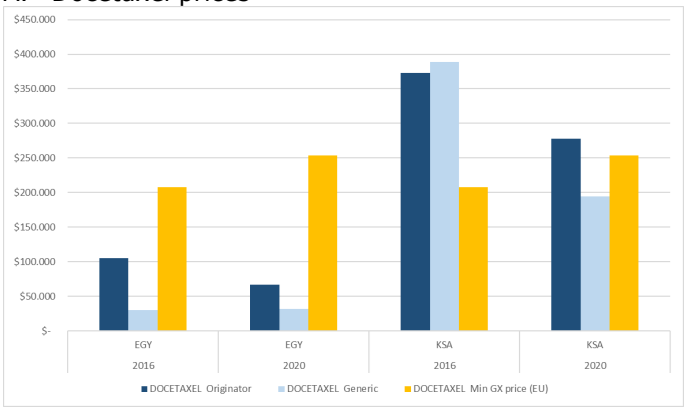
Generic docetaxel prices were seven times higher in the comparator countries compared to Egypt, while they were almost 50% lower than KSA generic prices. As mentioned above, data on prices are unreliable due to measuring issues with IV products. The price for Imatinib dropped almost 95% in the comparator countries due to patent expiry in Europe in December 2016, while it remained roughly stable in both Egypt and KSA; this may be due to different patent expires in the comparator countries vs. Egypt or KSA. The lowest imatinib generic price in 2016 was $41 per SU in the comparator countries versus $2 and $8 in Egypt and KSA, respectively. This difference dropped in 2020, with imatinib costing $2 per SU in comparator countries versus $1.5 and $8 in Egypt and KSA, respectively.

Savings from the increase in docetaxel generic market shares in 2020 were higher in Egypt (45%) than in KSA (1%). On the other hand, should KSA have been able to achieve imatinib generic market shares as high as Egypt together with the lowest generic price observed in the comparator countries the country could have achieved savings as high as 50% in 2020.

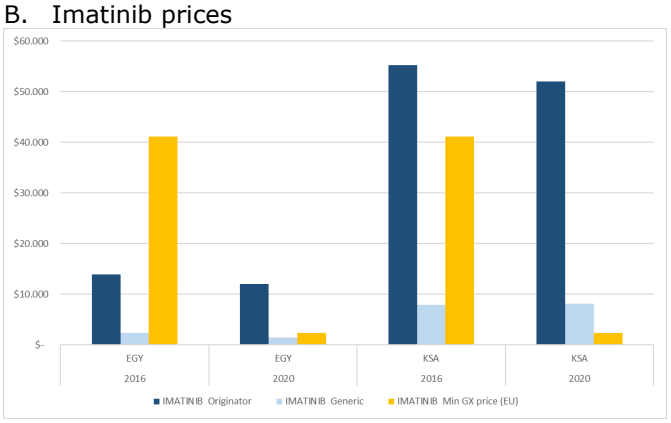
Detailed originator vs generic prices and volumes for cancer drugs by country and year can be found in Appendix 5.

Figure 14: Docetaxel and imatinib prices, market shares and potential savings in Egypt and KSA vs comparator countries (UK, SP, DE) in 2016-2020

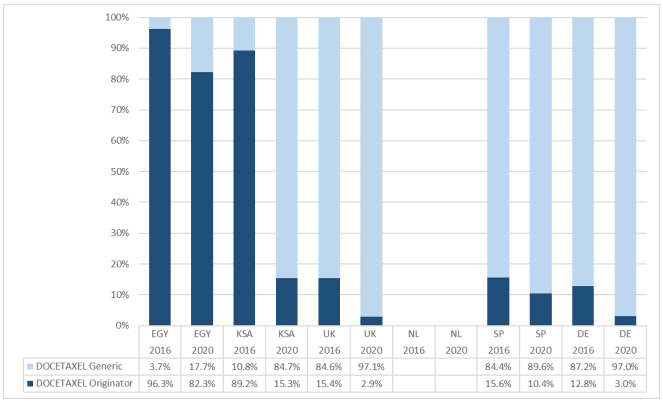
A. Docetaxel prices



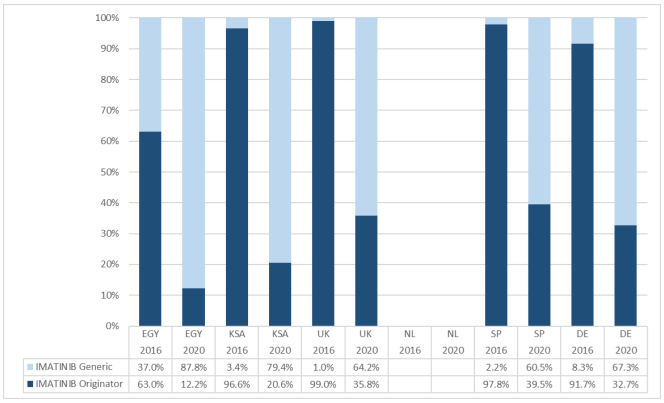
B. Imatinib prices



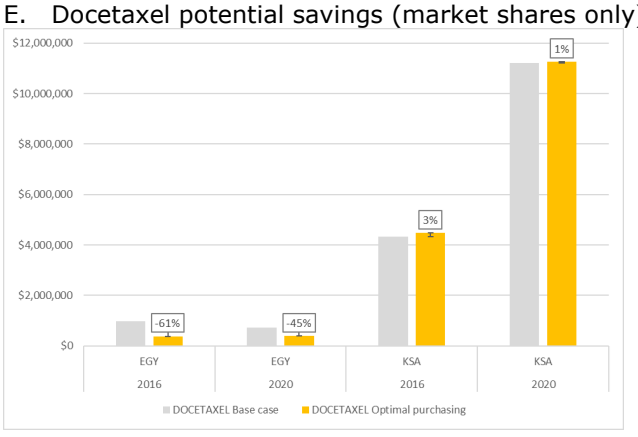
C. Docetaxel market shares



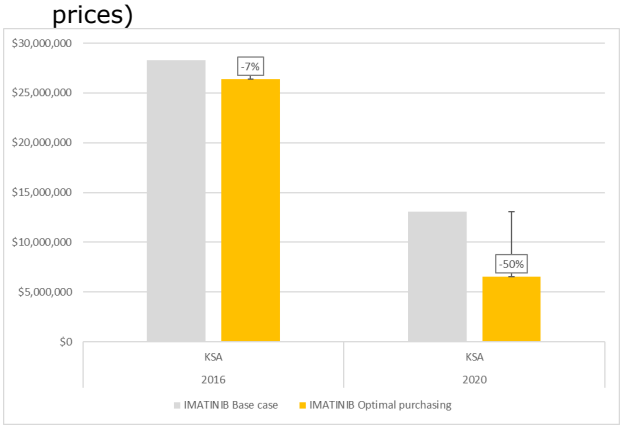
D. Imatinib market shares



E. Docetaxel potential savings (market shares only)



F. Imatinib potential savings (EGY market shares, SP prices)



Abbreviations: Germany (DE), Netherlands (NL), Spain (SP), United Kingdom (UK)

4.4.3. Sensitivity analysis

A sensitivity analysis was conducted to account for the fact that for a proportion of total sales, procurement prices in the two study countries may be confidential and any estimation of these could be biased. This means that prices estimated in the study countries could be in fact lower than those estimated from IQVIA sales data.

We calculated the expenditure on drugs included in the analysis if the price effect in the study countries was not related to the lowest price in the comparator countries but to 40% higher than that, in order to capture the extent of potential discounting through procurement in the study countries (**Figure 15**). This would draw a more conservative picture under the assumption that the list to net price gap is likely to be wider in Egypt and KSA compared to the comparator countries, where list and net prices of off-patent drugs are usually close.

Compared to the base case (**Figure 11**), this scenario led to more conservative but still significant savings. In Egypt, the drop in expenditure went from 34% in the base case to 20% in 2020. In KSA the scenario assuming a 40% higher minimum generic price in comparator countries yielded to a reduction in expenditure of 72% versus 80% in the base case, in 2020.

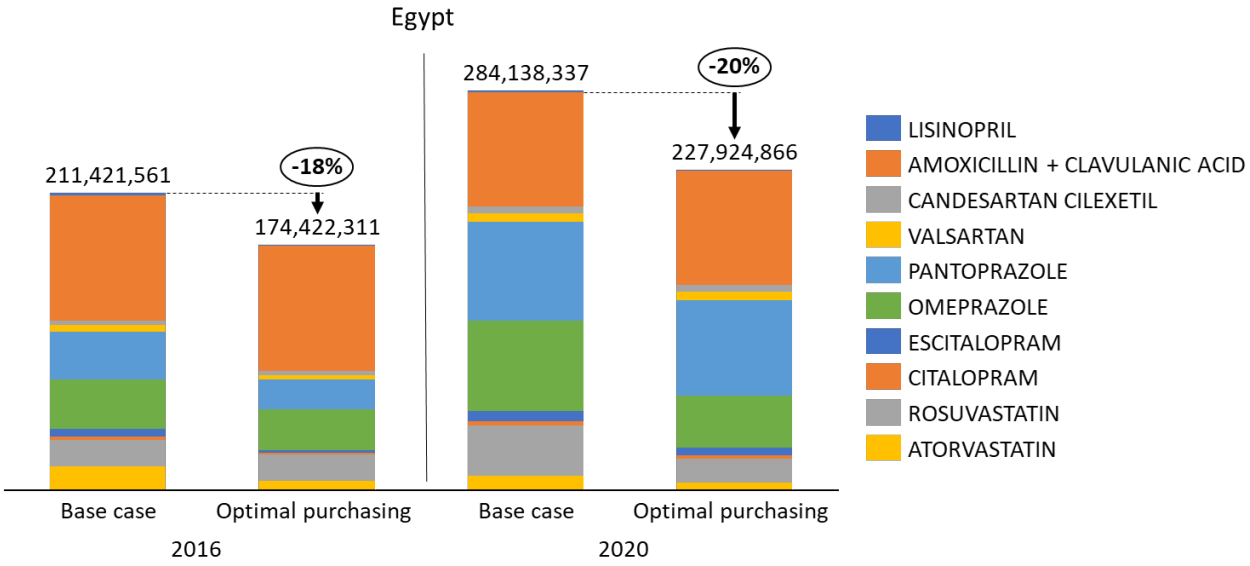
4.4.4. Limitations

This analysis is not without limitations. First, it was based on IQVIA yearly sales data which may be subject to reporting errors and other biases. For example, IQVIA data fail to capture all retail channels by which a product might become available in a country (e.g., pharmacies, hospitals, manufacturers etc.). Second, while IQVIA standard units should ensure comparability across products, this is not always the case especially when solutions for infusions vs tablets are considered. Third, net prices from Egypt and KSA are not available as IQVIA data includes only list prices. Despite this, we believe that the observed differences still hold value in demonstrating differences between countries as we have used list prices for all countries included in the simulation but recognise the healthcare systems may negotiate or obtain other net prices through other means. IQVIA data may also not capture the full extent of outpatient procurement. However, this could also affect prices in the comparator countries; we have strived to mitigate this effect through the sensitivity analysis in the previous section. Finally, as mentioned in the first paragraph, a manufacturer was considered as originator if it held the patent for the first branded product. Therefore, if more than one branded product by an originator manufacturer exists on the market, only the first patented branded product is considered as originator; this could be

attributed to co-licensing arrangements which are not always known and might have potentially biased the results if branded products are systematically more expensive than generic products and are grouped as 'generics'.

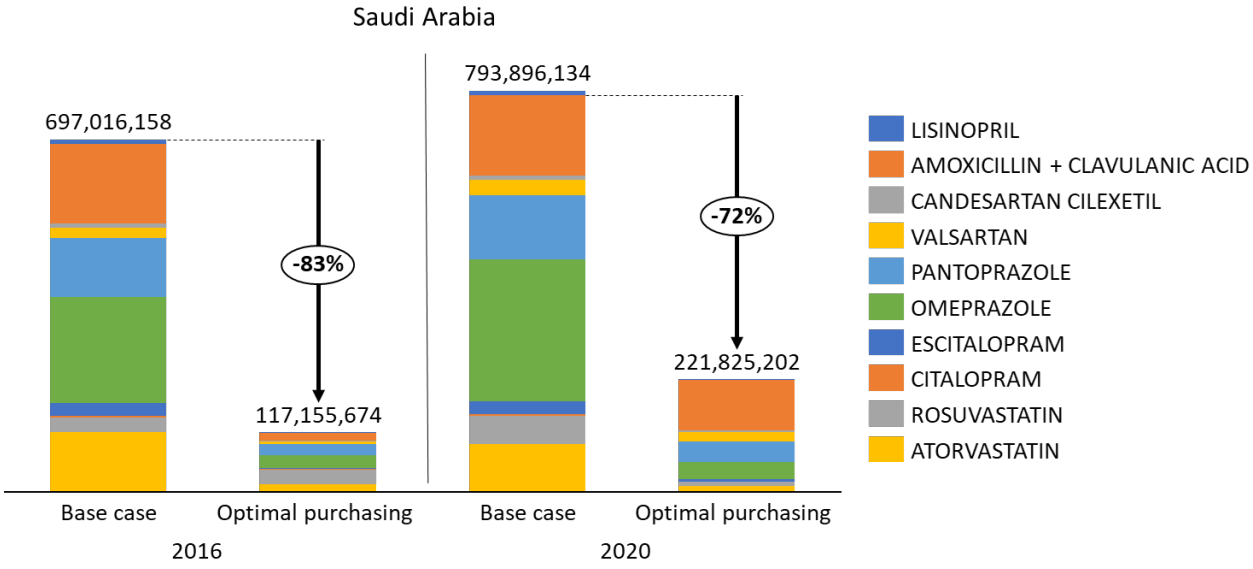
Figure 15: Base case spending vs potential savings from optimal purchasing in Egypt and KSA in 2016-2020 (generic market shares + 40% higher minimum generic price in comparator countries); values in USD.

A.



Note: spending for amoxicillin+clavulanic acid, candesartan cilexeti (2020 only), valsartan (2020 only) and rosuvastatin (2016 only) were kept as the base case as their generic prices/generic market shares were lower/higher in Egypt compared to the comparator countries.

B.



Note: spending for rosuvastatin (2016 only) was kept as the base case as its generic prices/generic market shares was lower/higher in Egypt comapred to the comparator countries.
Abbreviations: Egypt (EGY), Saudi Arabia (KSA)

4.5. Best practices promoting use and uptake of innovative medicines

This section outlines best practice examples of targeted efforts to promote and encourage the use of innovative medicines, reward research and development and discuss policies targeting the re-direction of healthcare savings to new products creating headroom of innovation. The policies and interventions are presented in the following structure: efforts embedded in pricing and reimbursement policies, efforts which ensure earmarking of funds and, efforts which allocate those earmarked funds.

Box 5 presents an overview of the strategies for improved and dedicated spending on innovative products employed in other settings, discussed in more detail in the sections which follow.

Box 5 Example strategies aimed at earmarking savings and allocating funds to innovative products

1. Earmarked funds for innovative medicines or for disease areas which have high financial impact.
2. Establish effective policies which allow innovative medicines to come to market quickly and reduce access issues.
3. Design policies which balance health policy objectives with motivation and incentivisation of the pharmaceutical industry.
4. Earmarking expenditure on innovative products to ensure efficient spending and allocation of resources.
5. Implement conditional reimbursement for innovative products where uncertainty remains about cost-effectiveness.
6. Use of MEAs and/or PASs to mitigate uncertainty for expensive products.
7. Reward innovation through upward price revisions based on HTA outcomes where the product in question showcases cost-effectiveness relative to appropriate comparators.
8. Award innovative medicines a premium on top of their set price.
9. Obtain additional savings from price reductions on in-patent products.
10. Use of horizon scanning activities to prepare for upcoming innovative products.

4.5.1. Earmarking funds for innovative medicines

Australia, Italy, the Netherlands, and the UK have adopted approaches to earmarking funds for new innovative medicines.

The Italian Ministry of Health introduced a €1 billion fund for innovative medicines in 2017, of which €500 million is dedicated to oncology indications and €500 million is dedicated to non-oncology treatments [206], [207]. The fund aims to (i) promote access to innovative

medicines, and (ii) enable faster patient access at regional level [208]. Products eligible for these funds must be innovative according to the Italian Medicines Agency (AIFA)'s innovativeness assessment criteria, which include unmet therapeutic need, added therapeutic benefit, and quality of evidence [206]. Depending on the results of the application of the criteria, medicines with 'full' innovation status can apply to one of the aforementioned two funds, while medicines with 'conditional innovativeness' are added to all regional formularies with no re-assessment needed at that level [209]. Treatments may benefit from the fund for innovative medicines for a maximum of 36 months, after which regions bear the cost [210]. The AIFA criteria have been found to be a "flexible and transparent model" to assess therapeutic innovation [211]. A 2020 review of medicines allocated innovative status by AIFA found only a small minority of therapies receive innovative status, thought due to either stringent application of the criteria or limited numbers of companies applying for the designation [207].

The Cancer Drugs Fund (CDF) in the UK is a special funding mechanism which aims to include earlier patient access to new treatments, an accelerated National Institute for Health and Care Excellence (NICE) process, fast and transparent decision-making around new drug availability, NICE appraisal for all new cancer drugs and indications, financial certainty, data collection, and improved relations for responsible pricing between NHS England and the pharmaceutical industry [212]. While originally aiming to enhance access to treatments for rare cancers, a large proportion of the funds were allocated to more common cancers in a period between 2013 and 2015 [213]. Starting in 2016, the CDF allows for managed entry of oncology drugs that show clinical promise but have uncertainty regarding cost-effectiveness [212]. The initial annual budget when the Fund was introduced in 2016 was £340m and includes drug costs, CDF managed access agreements, approved off label indications, and administrative costs [212]. The CDF overspent in earlier years, resulting in the introduction of stricter budgeting rules in 2016: a proportional rebate is applied to companies which receive funding from the CDF in cases of overspending, and a dedicated NHS England and NICE group will manage the overall budget [213]. Management and financial responsibility for the 2016, 'new' CDF was given to NHS England in participation with other government bodies [213]. NHS England recently announced that an additional £340m is going to be available to support the new Innovative Medicines Fund [214]. This initiative is an extension of the CDF and is expected to support the NHS to expedite patient access to potentially life-saving new medicines which still have uncertainty around their clinical and cost-effectiveness [214]. The Innovative Medicines Fund will operate in a similar way to the CDF: NICE can redirect drugs to managed access funding through the Fund, as opposed to a decision for routine funding [214].

In 2019, a new policy was implemented by the National Health Care Institute (Zorginstituut Nederland) in the Netherlands to improve access to orphan medicines or medicines which received a conditional or exceptional marketing authorisation but were not been reimbursed due to lack of sufficient clinical effectiveness evidence [215] (see Section 3.5.2.2). A specific budget of €24.2 million was available for this policy in 2019, which was increased to €25.5 million in 2020 and €26.8 million in 2021 [215]. To be eligible for this, medicines must be EMA-approved as an orphan medicine and address an unmet medical need per the EMA definition, and the application must be submitted by the manufacturer in connection with clinical, research, and/or patient organisations. The submission must be for research which will allow for effectiveness to be determined within the proposed time period [216].

The 'Potentially Promising Care' programme has been implemented by the National Healthcare Institute and the Netherlands Organisation for Health Research and Development (ZonMw) since 2019, aiming to accelerate patient access to innovative, promising medicines [217], [218]. This subsidy scheme dedicates a maximum of €69 million every year for funding of potentially promising advance therapy medicinal products and specialist medical care - among other categories of health interventions - for which research needs to be conducted to generate data on effectiveness and cost-effectiveness [217]–[220]. A subsidy is given for up to six years [217] to fund the treatment of patients enrolled in the studies and research activities, with the latter being limited to 20% of the total budget [221]–[223]. The fund only reimburses actual costs incurred as a means to limit costs [223]. At the end of the research project, the National Healthcare Institute evaluates the technology and decides on whether it will be included in the basic insurance package [217].

A further best practice example is seen in Australia, where funding for innovative medicines is supported through price reductions for in-patent medicines. In 2017, the Australian government signed a five-year strategic agreement with Medicines Australia, the innovative pharmaceutical industry association, aiming to support ongoing access to the latest innovative medicines, provide savings to the health system, and offer stability to the innovative medicines industry [23]. The agreement estimated a $1.8 billion Australian dollars (AUD) in savings[26] which will be reinvested into the supply of medicines including breakthrough therapies [23]. It also incorporates process improvements to the Pharmaceutical Benefits Scheme (PBS) to speed up access to new medicines [23]. Savings

[26] *Savings obtained as follows: After being on the market for 5, 10, and 15 years there will be respective price reductions of 5%, 10%, and a further 5%* [257]. *Upon entry of generic competition, the originator's price will be reduced 25%* [257].

from the cost reductions will be reinvested into the supply of medicines, particularly breakthrough technologies, through the PBS. In the agreement, the Australian government and Medicines Australia commit to cooperative efforts to improve timelines, transparency, and efficiency in the PBS listing process [224]. This includes revising cost recovery arrangements to better reflect the real costs of activities associated with the PBS process [224].

4.5.2. Allocating funds to innovative medicines

Horizon scanning

Market access of new and innovative technologies can be achieved in a timely fashion through horizon scanning activities. A national horizon scanning system has been established in Denmark by Amgros to get an overview of medicines likely to enter the Danish market in the next two to three years [225]. This enables the organisation to be prepared for future price negotiations with manufacturers and organise tendering processes early [225]. In Spain, horizon-scanning occurs at the national level where the Spanish Inter-ministerial Medicinal Products Pricing Committee (CIPM) and the Ministry of Health make decisions around pricing and reimbursement [27]. The future availability of drugs influences their negotiations. Horizon-scanning activities are also taking place in the Netherlands in order to enable the government and purchasers/commissionaires of services to get informed about the development and market introduction of new medicines as early as possible, and to identify products which are likely to become subject to centralised financial arrangements [226].

The International Horizon Scanning Initiative (IHSI) was introduced in 2019 and is currently a collaboration of nine European countries, including the Netherlands and Denmark [227]. It involves a common database through which the participating countries share a wide set of information about new and emerging medicines [227]. The IHSI will enable the respective governments to identify, prioritise and make informed decisions on pricing and reimbursement of innovative medicines, and will inform negotiations with pharmaceutical companies [227]. This initiative also aims to facilitate the managed entry introduction of new medicines [227]. As a result of this initiative, the respective governments will potentially be better prepared for the introduction of innovative medicines in order to achieve controlled diffusion of and early access to these medicines through better budget planning [227].

Starting in 2019 and replacing the PPRS, the VPAS introduced NICE appraisals at a faster speed and with increased uptake support [228]. The VPAS sets out a range of measures

for England to support innovation and better patient outcomes through improved access to "the most transformative and cost effective" medicines alongside a UK-wide affordability plan [229]. The goal is to promote innovation and access to cost-effective medicines in a way that is centred around patient health and is financially sustainable for the NHS [229]. The VPAS involves clinical, financial and service planning for all products coming through different stages of the production pipeline [229]. This horizontal scanning approach allows for more effective planning, support, and appropriate medicine uptake.

National regulatory, pricing and reimbursement policies

Best practice examples of pricing and reimbursement policies intending to promote uptake of innovative products were observed in Denmark, Japan, France, and the UK.

Marketing authorisation. France has implemented the temporary authorisation for use (Autorisation Temporaire d'Utilisation, ATU) programme since 1994, aiming to provide early access to pre-authorised treatments for patients with severe or rare diseases for which there are no authorised therapeutic options available [230]. The ATU system covers all therapy areas and manufacturers are committed to follow-up on patients and collect clinical data [230]. Under recent reforms of the system, all requests are made to the French Health Technology Assessment (HTA) body, while evidence requirements include demonstration of innovation [230]. However, it is not clear yet how innovation will be defined and quantified. The recent French Social Security Finance Bill 2021 (PLFSS 2021) introduced two routes to ATU approval: (i) early access authorisation and (ii) compassionate use [231]. Under early access authorisation, a manufacturer must commit to apply for a MA or for registration to a reimbursement list within a specific timeline [231]. Free price setting is applied in combination with a series of rebates paid by the manufacturer [231]. Under compassionate use authorisation, medicines can be prescribed for indications other than those already approved under MA. In addition, medicines, which do not have been approved for reimbursement, are priced freely but are subject to a rebate mechanisms system [231]. Rebates are applied to medicines under both early access authorisation and compassionate use authorisation. For both authorisation routes, there is an annual rebate on a progressive scale based on the sales amount billed for the medicine under ATU indication [232]. For early access authorisation only, there is an additional rebate applied retroactively equal to the difference between the sales amount billed under the ATU indication (less the first rebate) and the amount that would have been billed under the net reference price [232].

In 2019, a new policy was implemented by the National Health Care Institute (Zorginstituut Nederland) in the Netherlands to improve access to medicines developed for serious and/or rare diseases which have been designated as orphan medicines or have

been given a conditional or exceptional marketing authorisation, but have not been reimbursed due to lack of sufficient clinical effectiveness evidence [215]. Such products may be granted conditional inclusion in the basic package, provided that the company is going to conduct further research to generate evidence on the effectiveness and appropriate use of these medicines [215]. Patients eligible for treatment with these products must participate in the research carried out in order to be eligible for coverage [215]. Price negotiations take place between the Ministry and the marketing authorisation holder to agree on a discounted price for the duration of the conditional inclusion in the basic package [215]. The National Health Care Institute assesses the medicine's effectiveness outcomes and, based on its advice, the Minister for Health, Welfare and Sport makes a final decision on inclusion in the basic package [215].

Pricing & reimbursement. The 'Premium System for the Promotion of Innovative Drug Discovery and Resolution of Off-Label Use', also known as Price Maintenance Premium (PMP), is an incentive programme introduced in 2010 in Japan [233]. There are various reward types for new medicines, under which innovative medicines are rewarded by a premium applied to the medicine's price [234]. The innovativeness premium rate varies between 70% and 120% [233]. A premium of 10% is applied for novel medicines when they are first approved in Japan [233]. This policy aims to promote investment by pharmaceutical companies into research and development of new, innovative medicines and encourage them to launch their products in the Japanese market [234]. In addition, it is expected to help solve the problem of off-label use of medicines by encouraging clinical development [234]. Until the drug pricing system reform in 2018, PMP protected products from biennial price revisions throughout their exclusivity period [235], providing a powerful reward for innovation. Following the reform, the scope of the PMP has been narrowed to first-in-class medicines and the two next-in-class medicines marketed within three years of the listing of the first-in-class medicine [236], while medicines are subject to annual price revisions [237].

An additional relevant policy has been implemented in Japan at the point of HTA. HTA has been formally introduced in the Japanese system since 2019, for the purpose of adjusting prices of medicines with significant budget impact according to their cost-effectiveness [238], [239]. To ensure that innovation will continue to be promoted and rewarded within this system, if a product is shown to be cost-effective relative to the comparator, upward pricing revision is considered [239]. For certain indications, the upward repricing thresholds have been set at 7.5, 11.25, and 15 million JPY per quality-adjusted life year (QALY) gained [239].

To support the timely uptake and diffusion of new medicines, Japan ensures that the reimbursement process starts immediately after marketing authorisation for a new medicine is granted, and is usually completed within maximum of 90 days, with an average of 60 days [238]. The time from marketing authorisation to reimbursement of new medicines in Japan is among the shortest worldwide [239]. The reimbursement prices of new and innovative medicines listed in the Drug Price Standard[27] are fixed by the Japanese government using a cost-calculation method and are not negotiated with the pharmaceutical companies [238], [239].

In the United Kingdom, the VPAS took effect in January 2019, replacing the 2014-2018 Pharmaceutical Price Regulation Scheme (PPRS). In the new scheme, all new medicines will be appraised by the NICE at a faster speed and with increased support for the uptake of commissioned medicines [228]. In addition, new active substances and pharmaceuticals with an extension of indication within 36 months after MA of the first indication can be priced freely at launch if NICE issues a positive recommendation [228]. In the VPAS affordability plan, there is an allowed net sales growth rate of 2%. A proportion of sales made in excess of this rate must be paid back into the scheme [228]. The payment rate for companies in 2019 was 9.6% with subsequent payments determined by actual sales growth [228]. There is a three-year exemption period for all new active substances and significant exemptions for smaller companies in order to promote innovation [228]. However, if sales of a new active substance are expected to exceed £20 million in any calendar year of the first five calendar years after launch, the manufacturer should inform the Department of Health regarding the list price set and the anticipated level of sales yearly for all the first five years [228]. Earlier schemes set a variable rate which provided for slightly increased total profits for innovative in-patent medicines [240], [241]. The 2014 PPRS also ended initiatives for NHS commissioners to secure rebates, to be paid by manufacturers, for medicines with a positive NICE technology appraisal [241].

Another interesting example seen in the UK is the guidance for end-of-life criteria considered by NICE when appraising treatments for coverage by the NHS [242]. This guidance allows treatments which may extend the lives of patients with short life expectancy to be recommended for use within the NHS even though their incremental cost-effectiveness ratio exceeds the standard cost-effectiveness threshold range (discussed in Section 3.5.1), justifying up to a maximum of £50,000 per QALY [243].

The Danish system has reimbursement provisions which promote the use of new medicines. Pharmaceutical companies are free to determine the prices of their medicines [244].

[27] *Includes all medicines which are available and reimbursed through the National Health Insurance* [318].

Innovative medicines whose price is reasonable with regard to their therapeutic value are usually approved for general reimbursement by the DKMA [245]. However, for medicines which are not available through general reimbursement, the DKMA may grant coverage for certain individual patients following an application made by the treating physician [246]. This special mechanism is known as 'single reimbursement' [246]. Moreover, the Danish reimbursement system authorises some medicines to be conditionally reimbursed, meaning that they are reimbursed only when prescribed to particular patient subgroups or for the treatment of specific diseases [247]. This mechanism has been introduced with the aim to control the use of very expensive medicines as well as medicines which have significant budget impact [248].

Managed entry agreements. Managed entry agreement schemes can be used to promote access on highly innovative products while help decision-makers and purchasers/commissionaires of services to manage the high degree of uncertainty associated with clinical evidence or budget impact. To facilitate coverage and access to new medicines, Denmark often relies on financial managed entry agreements in order to deal with uncertainty at the time of assessment for coverage decisions [238]. Moreover, the Malaysian Ministry of Health has implemented the Patient Access Scheme (PAS), aimed at improving patient access to certain new, innovative medicines which are expected to have significant budget impact [249]. As part of the scheme, innovative pricing agreements are made with the pharmaceutical companies to improve the cost-effectiveness of new medicines [249]. The scheme can be classified in two categories: financial-based (e.g. discounts or rebates, price-volume agreements, utilisation caps) and performance-based (i.e. the rebate or product supply is based on patient outcomes after treatment) [249]. Pharmaceutical companies which are interested to participate in the scheme follow specific guidelines for submission of their application to the Ministry of Health [249]. PASs are also used in the UK to bring new technologies to market that would otherwise not be approved. The standard cost-effectiveness threshold in the UK is £20,000 to £30,000 per QALY [229]. Where NICE's assessment of value is higher than this threshold, the parties undertake commercial arrangements (simple confidential discounts or complex published PASs) to obtain a cost-effective price [229]. PASs have been available through NICE since 2002 and more recently through the CDF [212]. PASs operate under two mechanisms: straightforward price discount schemes and manual managed discount schemes [212]. There is a very high level of uptake of these schemes, with a total cost avoidance of approximately £44 million in 2013/2014, rising to just under £196 million in 2019/20 [212].

At the local level, Spanish actors prefer simple financial agreements with confidential negotiated discounts [27]. Where there is competition, the preferred agreement is a price/volume agreement [27]. There are several performance-based agreements at the national level which utilise patient databases. In these national level agreements, the outcome criteria are usually confidential, indicating little transparency surrounding outcome-based financial agreements [27].

Financial managed entry agreements are currently used in the Netherlands for medicines placed in the 'lock chamber'[28] [250]. The office of financial arrangements (Bureau Financiële Arrangementen) was established in 2015 by the Ministry of Health, Welfare and Sport and it negotiates with manufacturers in order to agree on a price that is reasonable in relation to the value added by the medicine [250]. When agreement is reached, the Minister makes the final decision on inclusion in the basic package [250].

Shared values and commitment to real world evidence (RWE)

A common sentiment throughout various initiatives reviewed in the above sections is a commitment to public-private cooperation and data collection. This commitment can be included at national policy level. For example, the Australian Strategic Agreement outlines a shared set of values agreed upon by the Australian government and Medicines Australia: stewardship of the health system and a shared responsibility for its ongoing sustainability, partnership in the delivery of the National Medicines Policy, stability and certainty for the investment in innovative medicines, transparency and efficiency of processes for listing medicines, and integrity of Australia's health system including patient safety and high-value clinical care [224]. Very recently, the Japanese Pharmaceuticals and Medical Devices Agency stated its plan to support real world data utilisation throughout the product life cycle to enhance early patient access [251]. Additionally, the UK VPAS explicitly recognises the importance of cooperation between the public and private sectors [229]. Lastly, as reflected through the life science growth plan launched by the Danish government in 2017, Denmark is also highly-supportive of public-private cooperation [252].

Several countries have also embedded RWE initiatives in specific programmes. The new French ATU allows manufacturers to collect and use RWE for dossier submission [230]. PAS in Spain, the UK[29], the Netherlands, and Malaysia have policies that require data

[28] *This mechanism is used to allow the government to seek solutions for new, expensive medicines not included in the standard health insurance package, and shows that the rejection of a high price does not translate to a medicine being_permanently unavailable to patients who can benefit from it* [319]*. In general, new hospital medicines are automatically entered in the medicines reimbursement system (GVS) if they are considered "established medical science and medical practice". However, since 2018, new, high-priced inpatient medicines which cost more than €50,000 per patient annually or an overall amount of more than €40,000,000 annually* [139], [319]*, are placed on a negative list, known as 'lock chamber' or 'sluis'.*

[29] *PAS in the UK is available via the CDF.*

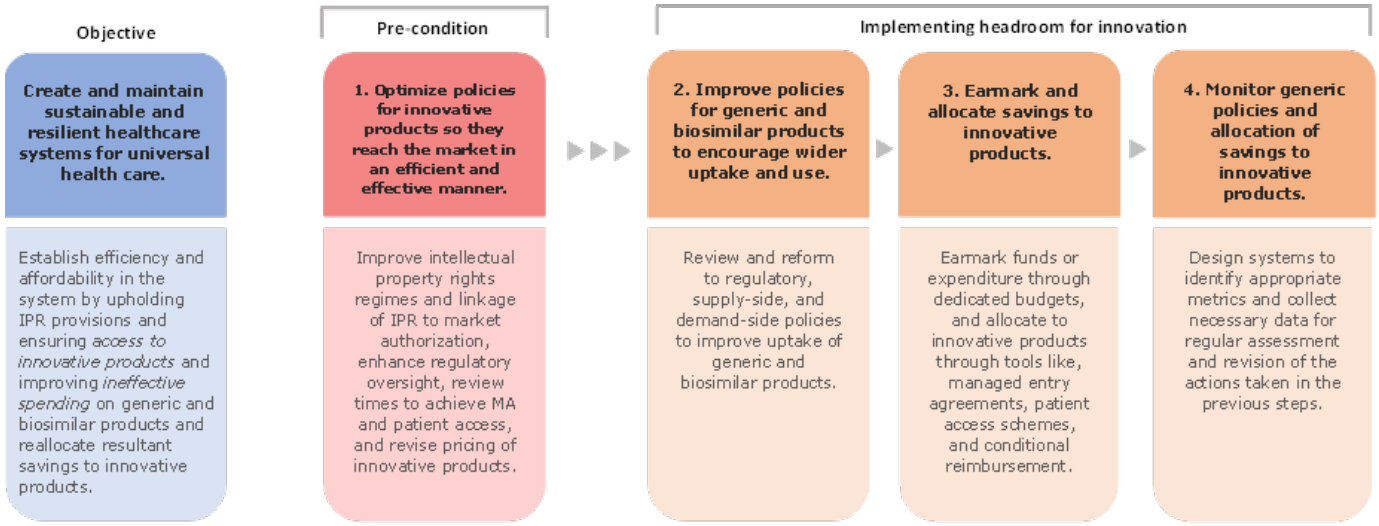
collection, often in the form of patient registries, to track uptake and effectiveness of innovative medicines. The Dutch require manufacturers to conduct further research to generate evidence on the effectiveness and appropriate use of the medicines granted conditional inclusion in the basic package.

Commitments to evidence-based decision-making can also take the form of embedding tools to do so into the wider system. To increase uptake of products of exceptional value and significant health gain the NHS England will provide tailored support, taking into account whether the medicines address high unmet needs or health inequalities [229]. To track and access uptake, the VPAS outlines the use of measurement tools including the Innovation Scorecard which involves a comprehensive approach to tracking uptake to identify variation in prescribing and measuring the impact on health outcomes [229]. This plan involves crucial engagement with NICE for fast and regular appraisals of all new active substances and additional therapeutic indications regarding clinical and cost effectiveness.

5. Discussion & recommendations

This section outlines next steps and recommendations for Egypt and KSA to create headroom for innovation in their budgets through improved policies for generic, off-patent and innovative products. **Figure 16** provides an overview of the four steps required to achieve this.

Figure 16: Four concrete steps in working towards headroom for innovation in Egypt and KSA



Step 1 is a pre-condition to consider in the context of both Egypt and KSA. Both countries should ensure access to novel and potentially innovative products is established and maintained before being able to allocate any savings to these products. These efforts should aim at ensuring innovative products reach their markets efficiently, effectively, and in a timely fashion; it is important to establish these components, particularly IPR, before moving on to next steps.

Once access to innovative products, including appropriate enforcement of IPR, is established, Step 2 optimises national spending on new and potentially innovative originator products by promoting price competition in the generic/off-patent market, which ideally, would lead to savings in the healthcare budget. This step focuses on lessons learned for policies for generic and biosimilar products from a comparative exercise of regulatory, supply-side, and demand-side policies between Egypt and KSA (study countries), and Denmark, Malaysia, the Netherlands, Spain, and the United Kingdom (comparator countries). This section is bolstered by results from a simulation exercise estimating the magnitude of potential savings for Egypt and KSA, should they manage to

achieve low generic prices and high market shares in line with comparator countries[30]. The focus of this step is to outline where efforts in these two countries should be focused to improve policies for generic and biosimilar medicines.

Only after solidifying the provisions for both these categories of medicines, can the mid- to longer-term focus for these countries be to earmark and allocate savings resulting from improved generic and biosimilar policies (Step 2) to funding innovative products (Step 3) and how to monitor whether changes to policies are effective and a redirection of savings is achieved (Step 4). Countries should prepare for these steps in parallel with other steps by designing and implementing appropriate policies which earmark savings, allow for their allocation to the funding of innovative products, and monitor the success of these efforts.

Note, the latter three steps may not necessarily need to occur in an entirely linear fashion and **Figure 16** only serves as a simplified overview of the components of action to create and redirect headroom for innovation. Section 5 provides roadmaps for Egypt and KSA which outline priorities in the short-, mid-, and long-term.

5.1. Step 1: Optimise access to innovative medicines

The number of NMEs coming to market in Egypt and KSA has been increasing over the past years. Prior to rerouting savings secured from improved generic policies, it is essential to consider whether innovative products are able to reach the market in an unobstructed fashion. There is an underlying need for countries to implement strong protection mechanisms for innovative healthcare technologies to encourage and reward innovation in the healthcare system which contributes to better healthcare system sustainability. Without solid access to the market for innovative products, any budgetary headroom created to support these products will not be able to be allocated efficiently.

Steps towards this are seen in KSA, where efforts are being made to create a more efficient and sustainable healthcare system more efficient and sustainable as part of the Saudi Arabian Vision 2030 plan. As part of this plan, a Health Sector Transformation program was launched in 2022 to promote value-based healthcare and ensure transparency and financial sustainability while offering universal healthcare coverage to the Saudi population [253].

Despite such efforts, there is still scope to optimise access to innovative medicines in both countries. Three issues for Egypt and KSA are discussed in this section - (a) strengthening IP provisions, (b) regulatory issues, such as improving time-to-market and time-to-patient

[30] *The comparator countries for the simulation exercise were Germany, the Netherlands, Spain, and the UK.*

access and (c) adjusting pricing regimes – which need to be established prior to any changes to generic policies.

5.1.1. Intellectual property rights

Establishing robust IP regulations, such as patent protection, regulatory data protection, and compulsory licensing provisions, is key to ensuring novel products are awarded suitable protection for their innovative nature. Such efforts also reward manufacturers for often very high research and development costs and the risk associated with innovative medicines and may subsequently increase a manufacturer's willingness and desire to market a product in a given setting with appropriate speed. Without appropriate enforcement of these protection periods, innovation is not encouraged nor rewarded.

Evidence suggests there may be misalignment in the IP regimes in the MENA region. To benefit fully from IPR and Bolar provisions, robust patent enforcement should be in place, including transparency on products protected by patents and when a patent is in place and when it will expire. While both countries have regulations for 20-year patents in place, neither Egypt nor KSA allows for the extension of the patent term beyond the original 20-year period, and have shorter, and potentially weaker, periods of data exclusivity than the comparator countries. Additionally, both KSA and Egypt host compulsory licensing provisions which reach beyond TRIPS provisions, further impacting patent protection in both these countries.

In Egypt, no specific regulatory data periods are set. IP rights can be ignored and create an unclear distinction between originators and generics, as there is no link between the patent-issuing office and the EDA and patents are usually only upheld in courts [33]. KSA does have regulatory data protection periods, though these are shorter than in the comparator countries. There is evidence in KSA of locally manufactured generic medicines which infringe on active patents or RDP terms. There can be further implications for the system due to a weak IP regime: the simulation results indicate that, for occasional cases in KSA, the generic is more expensive than the corresponding originator, which could be seen as a consequence of poor patent protection and highlights a further need to establish and uphold robust IPR provisions.

Best practices in balancing industry and health system interests are seen in other countries: the American Hatch-Waxman Act protects innovative products while also providing a framework for generic products to come to market under an Abbreviated New Drug Application (ANDA), providing an example of a structure in which both originator and generic products are protected and encouraged. A similar example is seen in the European

Union, where supplementary protection certificates (SPCs) serve as an extension to a patent right for a maximum of five years. SPCs aim to offset lost patent protection time which occurs due to lengthy compulsory testing and clinical trials required prior to regulatory marketing approval [254].

Recommendations on intellectual property rights

	Egypt
1	Efforts should continue to establish a robust IPR framework, specifically focusing on (a) having mechanisms that lead to the adequate enforcement of IPR provisions, complying with standards set by international agreements, (b) adherence to the TRIPs agreement, particularly around provisions relating to compulsory licensing, (c) the introduction of adequate regulatory data protection (data exclusivity provision); and (d) the establishment of a possibility for patent term extension. Efforts should also consider reviewing whether current procedures for grants and trademarks are efficient, and whether any amendments can be made.
2	Establish and implement a system which provides transparent information on patent expiry. Among others, this will improve the use of Bolar provisions especially once patent terms are sufficiently enforced in Egypt. This will also provide an incentive for generic entry to occur immediately after loss of exclusivity.
3	Strengthen national court systems to resolve any disputes arising around IPR and related issues. Issues to consider include enforceability of court decisions, the possibility of re-examining patent validity, and the availability of timely measures for recourse. Depending on country context, specialised IPR courts may be appropriate.

	KSA
1	Efforts should continue to establish a robust IPR framework, specifically focusing on (a) having mechanisms that lead to the adequate enforcement of IPR provisions, complying with standards set by international agreements, (b) adherence to the TRIPs agreement, particularly around provisions relating to compulsory licensing, (c) the introduction of adequate regulatory data protection (data exclusivity provision); and (d) the establishment of a possibility for patent term extension. Efforts should also consider reviewing whether current procedures for grants and trademarks are efficient, and whether any amendments can be made.
2	Establish and implement a system which provides transparent information on patent expiry. Among others, this will improve the use of Bolar provisions. This will also provide an incentive for generic entry to occur immediately after loss of exclusivity.
3	Strengthen national court systems to resolve any disputes arising around IPR and related issues. Issues to consider include enforceability of court decisions, the possibility of re-examining patent validity, and the availability of timely measures for recourse. Depending on country context, specialised IPR courts may be appropriate.

5.1.2. Regulatory issues for innovative products

Regulatory issues, such as time to marketing authorisation and to access to innovative products are key. Both Egypt and KSA are experiencing increases in the number of novel

and potentially innovative products being registered and authorised. When comparing timelines for approval of NMEs in Egypt and KSA to other countries, both countries have long registration timelines in practice: Egypt sets out a 180-day timeline but is reported to take up to two years for some regulatory pathways, and KSA sets out a 290-day timeline which can reportedly take 16 to 20 months. These effects are also seen more widely on patient access; Egypt and KSA both experience much longer times between dossier submission and local authority approval (average time to patient access) when compared to Denmark, the Netherlands, Spain, and the UK. The time between when a product is registered by the FDA and/or EMA and when it is registered in Egypt or KSA is significant but, in Egypt, this is improving under the abridged pathway due to the elimination of the condition that medicines must be marketed for one year in the reference country [33]. These delays could be resulting, at least in part, from systems in Egypt and KSA which allow for the completion of registration of originator products only once prices have been set through ERP.

Recommendations on regulatory issues for innovative products

	Egypt
4	Shorten the timelines for market entry of innovative products.
5	Improve oversight capabilities of national regulatory agencies. Adherence to timelines is a function of the volume of applications and the number of assessors to review those applications. Egypt should seek adequate staffing levels for MA processes, with suitably trained assessors.
6	Egypt could seek to introduce an early market access scheme to close the access gap between EMA/FDA approval and Egyptian licensing and reimbursement decisions. Financial resources to this end should be identified and allocated to allow for such a programme to be implemented.
7	Delink pricing from MA beyond the abridged track 820, allowing for MA to be completed in a timelier fashion.

	KSA
4	Shorten the timelines for market entry of innovative products.
5	Improve oversight capabilities of national regulatory agencies. Adherence to timelines is a function of the volume of applications and the number of assessors to review those applications. KSA should seek adequate staffing levels for MA processes, with suitably trained assessors.
6	Delink pricing from MA, allowing for MA to be completed in a timelier fashion.

?

How could market entry timelines for innovative products be shortened?

Reduce the time between submission and MA, strengthen abridged processes (verification reviews), introduce accelerated access pathways for specific products (e.g., orphan drugs, or products with high

unmet need or products with limited evidence but with high potential). These efforts could be accompanied by monitoring systems and/or legislative intervention.

5.1.3. Pricing and reimbursement

Egypt and KSA may also need to revisit pricing arrangements for innovative products to realise headroom for innovation: this will require putting forward reform proposals for certain components of ERP in Egypt and KSA which currently render ERP a cost minimisation tool (e.g., basket countries, price selection, use of exchange rates). Weak design features of ERP systems, across either the design, implementation, or administration, can result in overcomplication and bureaucracy which leads to time delays and inappropriate prices for the setting.

Recommendations on pricing and reimbursement of innovative products

	Egypt
8	Reform and recalibrate the ERP system for innovative products in line with best practice principles.
9	Ensure reimbursement decisions for new molecules are compliant with value-based assessment by competent authorities taking into consideration clinical, budgetary, and contextual criteria related to the disease (e.g., severity, unmet need), but also system-level considerations (e.g., historical spending levels, share in the annual budget, epidemiology, among others).
10	Innovative products, which may carry a disproportionate budget impact, need to be referred to a negotiation process and an MEA (where applicable).

	KSA
7	Reform and recalibrate the ERP system for innovative products in line with best practice principles.
8	Ensure reimbursement decisions for new molecules are compliant with value-based assessment by competent authorities taking into consideration clinical, budgetary, and contextual criteria related to the disease (e.g., severity, unmet need), but also system-level considerations (e.g., historical spending levels, share in the annual budget, epidemiology, among others).
9	Innovative products, which may carry a disproportionate budget impact, need to be referred to a negotiation process and an MEA (where applicable).

Which best practice principles should be considered when recalibrating ERP systems?

(a) the revision of the ERP basket to avoid an unduly large basket focusing on reviewing countries which may not be appropriate comparators.
(b) the price calculation should be based on the mean or median price based on ex-factory prices.
(c) price revisions post-launch should be kept to a minimum.

(d) focus on in-patent products only (once patents are sufficient enforced) as off-patent medicines are subject to greater competition.
(e) innovative products referred to reimbursement negotiations should be excluded from subsequent price revisions.
(f) price setting should be completed swiftly (e.g., within a month) following MA.

5.2. Step 2: Improve policies for generic and biosimilar products in Egypt and KSA

A simulation exercise, performed to show potential savings from improved policies for generics and biosimilars, found Egypt had amongst the lowest originator and generic prices in relation to the comparator countries utilised for the modelling, while median generic prices in KSA were the highest. Egyptian prices suggested the country is relatively successful in securing low prices. The exercise also showed that originator market shares are much higher in both Egypt and KSA than in the comparator countries, indicating generic penetration remains lower in these two countries. If the study countries optimised both prices and volume market shares for the products covered by the simulation (excluding cancer drugs) in line with the comparator countries, this could lead to significant potential savings in Egypt and KSA.

Any results from the simulation and use in the discussion should be considered with the limitation that the data used reflect mostly list prices and do not necessarily capture the effect of discounts from tendering processes. Although, of course, any impact on this effect will be the same for the data for Egypt and KSA, and for the comparator countries.

Sections 3.2 to 3.4 of this study provided a comparative assessment between Egypt and KSA and a selection of comparator countries. Considering the findings of the simulation exercise and the potential for either price or volume modulation to have an impact on expenditure and the generation of savings, the findings in these sections are discussed here, with key learnings and recommendations extracted for Egypt and KSA. The overall aim of this section is to provide an indication of the differences between Egypt and KSA and the comparator countries, and what kind of action may be useful to consider in achieving more efficient spending, after access to innovation is established successfully.

5.2.1. Regulatory issues

Regulatory policies in Egypt and KSA have key features expected from such policies, including frameworks for assessing GMP and conducting pharmacovigilance and policies for bioequivalence testing. Both countries also have processes for abridged approvals for products approved and marketed by the FDA and the EMA: in Egypt this process is used for both originator and generic medicines with a submitted CTD, while in KSA it is applied

to solve unmet clinical need and for all innovative products. Both countries also have Bolar provisions in place, though timelines for generic entry in both Egypt and KSA remain long in comparison to other countries. Despite somewhat limited evidence, the marketing authorisation process for generics seems to take a long time in both countries, often exceeding official set timelines. Additionally, the time taken differs significantly between local and foreign manufacturers in KSA.

Recommendations on regulatory issues for generics and biosimilars

	Egypt
11	Continue to utilise abridged approval pathways for generics and collect evidence on the performance of these pathways to improve their performance.
12	The length of time taken for the market authorisation of generics should be reviewed to assess whether this can be shortened, in line with international best practice.
13	Continue to enforce and uphold the quality of generic and biosimilar products outlined in existing GMP and quality assurance regulations.

	KSA
10	The length of time taken for the market authorisation of generics should be reviewed to assess whether this can be shortened, in line with international best practice.
11	Continue to enforce and uphold the quality of generic and biosimilar products outlined in existing GMP and quality assurance regulations.
12	KSA could develop abridged approval pathways for generics or seek to expand the process in use for locally manufactured to all generics.

?

How could timelines for marketing authorisation of generics or biosimilars be shortened?

Examples include:

- Reducing the time between submission and MA, setting out official timelines and monitoring whether these are kept to. If not, seek to find the source of the delay to address it.
- Encouraging manufacturers to take advantage of Bolar provisions, allowing them to develop the relevant information needed to submit for regulatory approval of generics and biosimilars while the relevant originator or biologic is still under patent.
- Using abridged approval pathways for generics to reduce times for MA reviews.

5.2.2. Supply-side issues

Generic pricing. Egypt and KSA rely on price capping with managed competition and ERP for the pricing of generics, also seen in Spain. Other countries rely on free pricing (Malaysia, the United Kingdom), a combination of price capping and free pricing (Denmark) or rely on similar rules used for the pricing of originator medicines (ERP using the average of four countries in the Netherlands). Countries with free pricing, or relatively free pricing, have much more significant price competition between generic competitors compared to countries with strictly regulated markets. This is explained by the fact that there are more competitors in those markets because manufacturers can set prices after originator patent expiry, resulting in potentially higher margins for generics.

KSA imposes a price reduction for originator medicines upon entry of a generic or biosimilar equivalent, a practice also seen in Denmark and Spain. Whether such a reduction should be imposed, as opposed to encouraging competition, depends on the setting: oftentimes, a system relying on competition is an aspirational option particularly if a command-and-control approach is in use.

Additionally, KSA, and until recently, Egypt implemented preferential pricing policies favouring locally manufactured products. Protectionist policies may be suitable for supporting local industries in their infancy but should ideally be relaxed and gradually removed once infant industries mature to increase efficiency.

The simulation exercise found Egyptian prices for generic pharmaceuticals seem to be similar to the comparator countries, whereas KSA generic prices seem to be higher. This observation may indicate the KSA generic pricing policy of price capping with managed competition and ERP works less effectively than the very similar system in place in Egypt.

Biosimilar pricing. Pricing for biosimilars in Egypt and KSA is based on a price capping mechanism in both countries. Denmark, Malaysia, and the United Kingdom rely on free pricing, though with indirect controls, such as bulk purchasing (Malaysia) or the VPAS (UK), or in conjunction with other mechanisms, such as price capping (Denmark). The Netherlands relies on tendering to determine reimbursement.

Generic reimbursement. Egypt relies predominantly on tendering and occasional formulary management and therapeutic IRP efforts, while KSA relies mainly on tendering and formulary management with occasional IRP efforts. Most of the comparator countries rely on IRP and tendering for the reimbursement and procurement of generic and biosimilar medicines. The KSA system retains preferential practices for local manufacturers in its reimbursement policies, which have external effects which could be seen as counter-productive alongside their original aim of supporting local industry. Similar practices

existed in Egypt prior to the system-wide restructure, and it remains to be seen whether these changes have an impact on preferential practices for local manufacturers.

Biosimilar reimbursement. Egypt, KSA, and the comparator countries all rely on tendering for the reimbursement of biosimilars.

Procurement. Both Egypt and KSA are moving towards centralised procurement practices, with the introduction of the UPA in Egypt and the long-established presence of NUPCO in KSA, in line with practices seen in other countries.

Recommendations on supply-side issues for generics and biosimilars

	Egypt
14	Consider introducing a price reduction for patent-expired originator medicines upon entry of a generic or biosimilar equivalent once an appropriate patent system is in place; this could have an immediate knock-on effect on the list prices of generics.
15	Monitor and/or review policies and practices of the newly created UPA to ensure new, non-preferential practices are implemented and adhered to.
16	Consider a nationwide tendering system for biosimilar products to encourage price competition among products on the market.

	KSA
13	Ensure that phenomena whereby generic list prices are higher than those of originator products are eliminated.
14	Consider revisions to the price capping system for biosimilars which encourage more aggressive price reductions. Currently, prices are set 70% below the biologic for the first entrant, with prices set 60% below the biologic for all subsequent entrants. Reducing price by a larger percentage will lead to a greater incentive to use the biosimilar.
15	Reduce and gradually eliminate the use of preferential pricing and reimbursement practices for local industry to open the market to more competition.

5.2.3. Demand-side issues

Demand-side action for pharmaceutical policy remains limited within the region, but it is important the MENA countries focus on ensuring uptake of available generic medicines is as high as possible [1]. The simulation exercise conducted provides insights into the potential to achieve savings through modulating volume and uptake in cases where further price reductions may not be possible[31]. In these cases, savings related to volume remain substantial, further highlighting the need for Egypt and KSA to review and prioritise

[31] *The base case for prices was modelled on the prices achieved in the comparator countries used for the simulation. The sensitivity analysis considered price levels of 40% higher for Egypt and KSA, which still allowed for significant savings in both settings.*

changes to demand-side pressures for generic and biosimilars. This becomes even more essential in light of the heavy reliance on originator medicines and the general culture of brand loyalty in these countries.

Generic prescribing. Generic prescribing is mandatory in both the public and private sector in KSA, but the enforceability of these policies is limited as relevant tools are unavailable or in development. In Egypt, prescription choice remains with the prescribing physician. All comparator countries uphold their generic prescribing policies through IT systems which offer the possibility of monitoring prescribing adherence; KSA has an IT system in place, though it is unclear to what degree it is able to monitor healthcare professionals' adherence, while Egypt has only very recently started the implementation of an IT system for generic prescribing.

Generic substitution. Generic substitution is allowed in KSA and in Egypt, though in the latter this is restricted to cases in the private sector where the prescribed product is not available. In the public sector, Egyptian pharmacists must dispense the product reimbursed under the tender. Generic substitution is allowed in the Netherlands, Malaysia, and the UK, and is mandatory in Denmark and Spain.

Biosimilar prescribing and substitution. In all countries biosimilars are being prescribed by physicians using their brand name, except for Egypt where differences are observed across different institutional settings. INN prescribing for biosimilars is only allowed in the Netherlands and Egypt, while biosimilar substitution for biologics is only allowed in the Netherlands.

Financial and non-financial incentives or rewards. No evidence was found on financial incentives or rewards for physicians in Egypt and KSA. Financial incentives for pharmacists in Egypt are limited to higher margins for generics as well as financial deals such as discounts and bonuses for generics, while financial deals and discounts for generics are seen in chain pharmacies in KSA. A few non-financial incentives are used in Egypt for both physicians and pharmacists (e.g., distribution of initiation kits, training, and education activities), and some non-financial incentives are in place for physicians in KSA (electronic prescribing and awareness campaigns).

There is significant scope to reflect on the use of such incentives in Egypt and KSA as, on the contrary, most of the comparator countries use several financial and non-financial incentives for healthcare professionals. Several examples of financial incentives for physicians arise from the UK: the PIS, an incentive and reward mechanism for physicians which assists with cost-effective and quality prescribing, and the QOF, a voluntary annual reward and incentive program which looks at practice achievements. The UK also

incentivises the dispensing of generic medicines through a margin system. Financial incentives for pharmacists are also used in the Netherlands, Malaysia, and the UK, through strategies such as regressive mark-ups (Malaysia), fixed fees regardless of the type of product dispensed (UK), or reimbursement based on a 'preferred' list (the Dutch preference policy).

Non-financial incentives are seen in all comparator countries. Some solutions look to providing a simplified way in which physicians can check for generic alternatives: for example, the UK has a decision support system which provides reminders of when generic alternatives are available, and Denmark has designed a database to allow physicians to compare prices across equivalent products. Other incentives can include medicine quotas for physicians, used in Denmark to promote the prescribing of biosimilar medicines. Other non-financial incentives can include generic volume targets by contracted physicians, with penalties or warnings if generic volume targets are not reached, prior authorisation mechanisms, more aggressive formulary management, including closed formularies, and "negative" guidelines, which provide structure on what not to prescribe in certain diagnoses.

Patient co-payments. Patients do not face co-payments in the public sector in KSA, though co-payments are expected to be introduced for insurance policies. Patient co-payments are in place in Denmark, Egypt, the Netherlands, Spain, and the UK. All countries engage in efforts to raise awareness on generic and biosimilars, bar Egypt where no evidence was found.

Recommendations on demand-side issues for generics and biosimilars

	Egypt
17	Encourage greater use of generic prescribing. Efforts could consider options like the education of new doctors or the reform of practices that do not support it.
18	Encourage greater use of generic substitution based on current dispensing practices and subject to coverage and procurement policies being improved.
19	Coordinate and create a set of common rules for demand-side policies across all payer segments.
20	Consider options to encourage and incentivise generic prescribing and/or substitution by healthcare professionals, for example, changes in education/training, awareness raising campaigns for generic and biosimilar medicines, electronic prescribing, and prescribing support systems, among others.
21	Current financial incentives or rewards for pharmacists should be reviewed for impact and revised based on a holistic approach, which accounts for the limitations with which dispensing functions.
22	Explore whether the local context is conducive to the introduction of some form of financial incentive or reward for physicians to encourage quality of care improvements and behavioural change in prescribing (see examples from comparator countries in Box 2). Such incentives or rewards should be part of an overall health system reform strategy and driven by institutional stakeholders.
23	Identify non-financial incentives or controls in prescribing which suit the country context, e.g., prior authorisation, negative clinical guidelines, closed formularies, among others) and adapt to local health system specificities.
24	Complete the implementation of and continue to use the IT system to monitor adherence to generic prescribing behaviour by physicians and support the use and performance of financial or non-financial incentives when these are implemented.
25	Link e-prescribing with clinical guidance (a) mandating INN prescribing and the use of generics to improve prescribing of generic products and (b) the positioning of new and innovative products in the appropriate disease stage.

	KSA
16	Ensure existing IT systems are able to (a) monitor generic prescribing behaviour in real time and (b) support the use and enable the assessment of any financial and non-financial incentives/rewards to health care professionals.
17	Encourage greater use of generic prescribing. Efforts could consider options like the education of new doctors or the reform of practices that do not support it.
18	Strengthen biosimilar prescribing policies. Initial efforts may need to focus on establishing evidence of interchangeability among the biologic originator and all biosimilars in an indication.
19	Encourage greater use of generic substitution, subject to coverage and procurement practices being improved.

20	KSA could introduce differential co-payments to steer patients towards generic options, such that patent-expired originator brands attract higher co-pays compared with equivalent generic options.
21	Explore whether the local context is conducive to the introduction of some form of financial incentive or reward for physicians to encourage quality of care improvements and behavioural change in prescribing (see examples from comparator countries in Box 2). Such incentives or rewards should be part of an overall health system reform strategy and driven by institutional stakeholders.
22	Identify non-financial incentives or controls in prescribing which suit their country context, e.g., prior authorisation, negative clinical guidelines, closed formularies, among others) and adapt to local health system specificities.
23	Link e-prescribing with clinical guidance (a) mandating INN prescribing and the use of generics to improve prescribing of generic products and (b) the positioning of new and innovative products in the appropriate disease stage.

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How could you introduce generic prescribing or generic substitution behaviours?

Consider starting with identifying key genericised markets which contribute a large portion of costs, such as statins, and applying these policies to those products first to reduce spending. Generic prescribing and/or generic substitution policies will provide larger financial returns if they make such behaviours mandatory, as opposed to optional, but policies can vary from allowing such practices to take place, to encouraging them, to making them mandatory. Countries will have to decide what is most appropriate in their setting and for their objectives.

5.3. Step 3: Earmark and allocate savings to innovative products

Once a country derives savings from improving generic policies and optimizing access and presence of innovative products, savings can be used to fund innovative products. The design and implementation of such policies should, however, occur in parallel to Steps 1 and 2 to ensure the landscape is set and primed to allocate savings to innovative products once savings can be reaped.

5.3.1. Earmarking funds for innovation

Earmarking relates to specific revenues or funds being set aside for the purpose of using these resources for designated expenditure, a tool used in many countries to ring-fence funding, create cost-awareness, and increase accountability [255]. Approaches to earmarking funds towards new innovative medicines can take the form of a specific fund for innovative medicines (i.e. an earmarked revenue base [255]), which can be tailored to a specific disease area or specific group of medicines (usually disease areas which are often linked to high expenses, e.g. orphan drugs).

What features are important when designing and implementing processes to earmark funds?

- Clear definition of the scope of the fund.
- Incorporate ways to ensure the suitable allocation of funds and limited overspending.
- Use the opportunity to link to other needs, such as data collection.
- Develop funds to recognise country organisation and context, as well as national needs and prioritisation.

Funds should clearly demarcate the scope of their reach. The use of specialised funds for specific disease areas will need to rely on a country-specific prioritisation based on the national burden of disease spread. If such information does not exist readily, it may need to be generated. Most of these funds are accompanied by specific criteria for inclusion or exclusion should be set and the types of expenditure or instances of use it covers. For example, the Italian Ministry of Health fund for innovative medicines finds products eligible through the Italian Medicines Agency's innovativeness assessment criteria. NICE will make one of three recommendations for cancer drugs: recommended for routine commissioning, not recommended for routine commissioning, or recommended for use in the CDF [256].

Egypt and KSA can look beyond disease-specific funds as, while they may alleviate some access problems, they also contribute to system fragmentation. There are examples of funds which have a wider reach, such as the innovative medicines fund in Italy and the Innovative Medicines Fund in the UK. With this, it does become essential to define clear inclusion criteria and use parameters to avoid overspending and collapse of the fund.

Funds should be accompanied by efforts to ensure suitable allocation of funds and limited overspending. In Australia, savings from price reductions for innovative medicines are earmarked for reinvestment to secure access to newer medicines through a strategic agreement between the Australian government and Medicines Australia. This includes a detailed agreement on what the savings can be used for and the setting of an oversight committee to review the costs of PBS annual expenditure and the effectiveness and sustainability of the reserved savings [257]. The UK CDF also limits overspending through a proportional rebate applied to manufacturers receiving funding from the CDF [256].

Earmarked funds can also use the opportunity to link to other needs, such as data collection. The Netherlands has demarcated a special budget to support access for serious and/or rare diseases which have been designated as orphan medicines. Such products may be granted conditional inclusion in the basic package, with price negotiations taking place to agree on a discounted price for the duration of the conditional inclusion in the basic package. The company must also conduct further research to generate evidence on the effectiveness and appropriate use of these medicines and patients eligible for

treatment with these products must participate in the research carried out in order to be eligible for coverage.

The exact nature of how funds are earmarked and upheld depend on country organisation and context, as well as national needs and prioritisation. Guides, like the WHO Earmarking for Health checklist [258], can provide a framework for setting up earmarked funds. Often, these efforts should identify the revenue source and link it to expenditure, with design and adoption focusing on collection, flow, allocation, and use of funds [255]. Any earmarked funds should have built-in accountability measures. Some funds, such as the CDF in England, are managed by a partnership of organisations and/or overseen by an independent committee. Additionally, the debate around earmarking, could provide relevant advice for policies and tools being designed to link savings from improved generic and biosimilar spending to innovative medicines. Notably, more general earmarking is criticised for creating budget rigidity and fragmentation in the healthcare system [255], [259], lessons which could be relevant for Egypt and KSA.

Political will and commitment must exist for financial resources to be set aside and used as intended. Earmarking is a political choice to prioritise a given issue [255], and therefore must be set in a desire to uphold this choice. Establishing such a commitment may require an alignment on objectives between different health and/or finance institutions in Egypt and KSA. The political viability of earmarking savings from improved generic and biosimilar policies may be higher than usual earmarking revenue sources (such as taxation), though this will be influence by local contexts and national behaviours and drivers, such as strong brand loyalty.

5.3.2. Allocating funds to innovation

What kind of tools can be used to ensure earmarked funds are allocated to innovative products?

- Pricing and reimbursement tools, such as:
  - Upward price revisions based on positive HTA outcomes where the product in question showcases cost-effectiveness relative to appropriate comparators.
  - Premium price for innovators on top of their set price.
  - Conditional reimbursement mechanisms for high uncertainty products
- Managed entry agreements and/or patient access schemes.
- Horizon scanning activities.
- Real-world data collection.

**See also Box 5 (Section 3.5)*

Horizon scanning. Countries such as the Netherlands and Spain rely on horizon scanning activities to plan for potential products to come to market, and to allow the system to prepare and accommodate such products and ensure access to them is as quick and easy as possible. There are regional initiatives, such as IHSI, where countries collaborate on horizon scanning and other activities. Greater preparedness in terms of horizon scanning could be a useful tool for Egypt and KSA in order to ensure funding and other related activities to be as well adapted and prepared as possible, a key effort to ensure funds are allocated efficiently.

Marketing authorisation. Some countries have funds linked to marketing authorisation decisions: the Dutch system allocates funds to products with conditional MA, providing manufacturers with additional time to create further clinical effectiveness evidence. Both KSA and Egypt have long timelines associated with marketing authorisation; focusing on this step may provide an opportunity to share the burden of developing evidence for innovative products in light of uncertainty, allowing access to these products more quickly. However, whether funds allocated to innovative medicines through such a process is a suitable solution will depend on the country context.

Pricing & reimbursement. Numerous other countries rely on cleverly designed pricing and reimbursement policies to promote the uptake of novel products. An initial focus point in this area, however, is to ensure that these processes are as streamlined as possible, ensuring products come to market in a timely manner. Evidence from both Egypt and KSA suggests this is an area that can benefit from more stringent adherence and finetuned regulation, as they lag in the speed of completion of these processes when compared to other countries. Similar reflection is taken on board in other settings too: provisions were added to the 2019 UK VPAS, which replaced the 2014 PPRS, to ensure NICE appraisals would be completed faster and to support improved uptake of medicines. Japan ensures the reimbursement process starts immediately after marketing authorisation, resulting in some of the shortest times taken between these two processes in the world.

Beyond streamlining the time taken for these processes, Egypt and KSA can look to several other solutions. Pricing and reimbursement policies can be designed in a manner which balances aims of both health and industry policy: in Denmark, manufacturers benefit from free pricing, but reimbursement is only granted for products which offer a reasonable price for the therapeutic value provided. As part of an 'affordability mechanism', the UK VPAS applies a maximum allowed net sales growth percentage and sales in excess of this rate must be paid back under the scheme, creating a cap on NHS spending on branded medicines and providing a balance between company growth and reasonable prices.

Countries such as Japan build in incentive structures for potentially innovative products. The Japanese incentive scheme which allows for a premium price for innovation, rewards R&D and encourages product launches in the country. These kinds of policy design features can enhance the appeal of a given setting and the likelihood of manufacturers looking to launch in that setting, especially where there is an incentive or perceived 'reward' and ensure access to potentially innovative medicines is established at the earliest possible time. A similar solution was seen in the UK PPRS, which sets a cap on the amount of profit manufacturers can make. Numerous previous iterations of the scheme set a variable rate for innovation in in-patient medicines, essentially increasing the amount of profit a manufacturer could make under the scheme if they had NHS sales of innovative, in-patent products above a certain level [240], [241].

Policies can also incorporate solutions for medicines which are so expensive that the budget impact would be significant: for example, tools such as the Danish mechanism which allows for conditional reimbursement for specific patient groups or diseases, or the Dutch conditional reimbursement policy under which manufacturers must generate additional evidence and the product is provided at a discounted price for the duration of the conditional inclusion in the reimbursed package. The Dutch policy is also accompanied by a specific budget to cover the costs of conditional inclusion.

Managed entry agreements. Commercial agreements such as MEAs are a tool which allow policymakers to share the burden of remaining uncertainty around products. An example of such use is seen in the UK where MEAs are implemented for products which exceed the NICE cost-effectiveness threshold or in Denmark, which uses agreements to mitigate uncertainty in clinical evidence. Agreements can take various forms: under the Malaysian Patient Access Scheme, financial- and performance-based agreements are set between the Ministry of Health and manufacturers to improve patient access to medicines with significant budget impact, while a similar PAS in the UK arranges price discounts or managed discount schemes. The UK also undertakes commercial arrangements for products where NICE's assessment is above the standard cost-effectiveness threshold. The Spanish healthcare system uses price/volume agreements or, in some cases, performance-based agreements. The Dutch healthcare system places high price medicines in the 'lock chamber', after which price negotiations occur between the Ministry and the manufacturer to establish a financial arrangement. Importantly, newly approved innovative drugs referred to a negotiation process, which will result in a MEA, will need to be excluded from external reference pricing considerations beyond the initial price-setting phase. Acceptance of net price confidentiality is also an important pre-requisite for MEAs to function appropriately.

What considerations should be taken into account for MEAs?

Newly approved innovative drugs referred to a negotiation process for MEAs will need to be excluded from external reference pricing considerations beyond the initial price-setting phase and net price confidentiality should be a pre-requisite for MEAs to function properly.

Data collection and RWE. Many of the comparator countries discussed in this section have an explicit commitment to public-private cooperation and data collection. PAS in Spain, UK, the Netherlands, and Malaysia require data collection to track uptake and effectiveness of innovative medicines while the Japanese Pharmaceuticals and Medical Devices Agency stated its plan to support real world data utilisation throughout the product life cycle to enhance early patient access. Efforts could also consider embedding data collection into the healthcare system to create an evidence base which is useful for empowered decision-making. For example, the UK relies on an Innovation Scorecard to track uptake to identify variation in prescribing and to measure impact on health outcomes.

Section 3.5 presents an overview of the strategies for improved and dedicated spending on innovative products employed in other settings. Embedding such options in Egypt and KSA will be a long-term commitment which requires reflection on what solutions may function in the context of the respective countries. Above all, there needs to be willingness and commitment from key stakeholders to ensuring the connection between savings and innovation is maintained and protected, and to uphold the commitment to earmark funds for innovative medicines. This is especially critical in countries where various components of healthcare or related budgets are held by different budget holders, such as for reimbursement and some specialised funds. To achieve synergy across multiple means to redirect savings, ministries of health or other key players need to take up a leading role in identifying and encouraging effective collaboration across these areas, relying on shared values and aims for the healthcare system. Establishing this commitment will be paramount to identifying which strategies may work in a local setting.

Lessons that can be drawn from this include priority considerations for Egypt and KSA which will assist in creating a favourable environment for the implementation of any reallocation efforts.

Recommendations on tools for earmarking and allocating savings

	Egypt
26	Identify efforts to streamline processes for the pricing and reimbursement of innovative products to ensure products reach patients in a timely manner. Efforts to this effect can take the form of commitments to ensure newly approved drugs enter reimbursement negotiations immediately after they are launched and for these negotiations to be completed within a fixed amount of time.
27	For the use of MEAs: - Newly approved innovative drugs referred to a negotiation process, which will result in an MEA, will need to be excluded from external reference pricing considerations beyond the initial price-setting phase. - Acceptance of net price confidentiality should be an important pre-requisite for MEAs to function appropriately.
28	Consider building up horizon scanning activities to identify future products which will be critical based on disease burden and unmet need. Horizon scanning should consider both innovative drugs in development and already marketed medicines, which are approaching loss of exclusivity, allowing for generic products to come to market. Understanding both these elements will allow for improved budgetary resource planning.
29	Secure the commitment of all relevant institutional stakeholders to earmark and redirect genericisation savings to innovative products.
30	Design and implement policies which earmark and allocate savings from genericisation to innovative products through funds, budgets, or other methods/policies.

	KSA
24	Identify efforts to streamline processes for the pricing and reimbursement of innovative products to ensure products reach patients in a timely manner. Efforts to this effect can take the form of commitments to ensure newly approved drugs enter reimbursement negotiations immediately after they are launched and for these negotiations to be completed within a fixed amount of time.
25	For the use of MEAs: - Newly approved innovative drugs referred to a negotiation process, which will result in an MEA, will need to be excluded from external reference pricing considerations beyond the initial price-setting phase. - Acceptance of net price confidentiality should be an important pre-requisite for MEAs to function appropriately.
26	Consider building up horizon scanning activities to identify future products which will be critical for their populations and disease burdens. Horizon scanning should consider both innovative drugs in development and existing medicines which are coming towards the end of their patent period, allowing for generic products to come to market. Understanding both these elements will allow for improved budgetary resource planning.
27	Secure the commitment of all relevant institutional stakeholders to earmark and redirect genericisation savings to innovative products.
28	Design and implement policies which earmark and allocate savings from genericisation to innovative products through funds, budgets, or other methods/policies.

5.4. Step 4: Monitor allocation of savings to innovative products to ensure a sustainable healthcare system

Any policy changes looking to allocate savings to innovative products should be accompanied by a robust monitoring scheme. This section considers all three of the previous steps discussed and provides insights into the type of measures Egypt and KSA could rely on. Any monitoring efforts requires a commitment from the outset, not only to collect such data, but to collect it with a frequency and regularity which allows for comparison and to use the results for informed policymaking. Assessment metrics for change to generic products (Step 2 in **Figure 16**) should cover various components of the supply and demand: availability, price, and volume. For *availability*, this involves tracking whether specific drugs are available after patent expiry, with the assumption that such provisions have been put in place based on previous recommendations. Considering whether this availability is at a suitable speed is also relevant[32]. For *price*, the price levels of originators and generics after loss of exclusivity are essential to assess whether there is sufficient price competition and whether this translates to affordability for either the local purchaser or patient. For *volume*, both the number of competitors after patent expiry and the volume of the generic market can provide suitable measures.

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What kind of metrics would be suitable for monitoring reform in generic and biosimilar products?

- Drug availability post-patent expiry.
- The speed with which generics/biosimilars launch after expiry of IP protection on innovative products.
- Number of (generic/off-patent) competitors post-patent expiry.
- Price development of originators and generics after loss of exclusivity.
- Evolution of generic volume market share.

Assessing the results for innovative products (Steps 1 and 3 in **Figure 16**) should consider at least six key metrics. Firstly, efforts should look to track observable changes and efforts at reform for policies for innovative products to combat the issues in discussed in Section 4.2. With no change in how originator products reach and engage with the local market, increasing availability of the most novel, beneficial products on their markets, both Egypt and KSA will struggle to ensure the redirection of savings to innovative products. Such efforts also need to consider the wider system; for example, the recent changes to the pharmaceutical system in Egypt, such as with the introduction of the UPA, access to novel products may be vastly improved.

[32] *In Egypt there are currently no delays in generic entry as there are no strong IP regulations or management of patent expiry dates, and generics can enter the market at will.*

What kind of metrics would be suitable for monitoring reform in innovative products?

- Observed changes and reform to policies for innovative products.
- New product uptake.
- Coverage decisions for a new product.
- Time taken between global launches and local launches.
- Time taken for regulatory completion.
- Time taken to achieve reimbursement.

Secondly, rates of new product uptake, measured as the rate of uptake on the market for products with admission to reimbursement, should be collected. Example measures could be figures for sales or market coverage. Monitoring should reflect on such rates at suitable intervals (for example, one-, three-, and five-years post-launch). This data can be essential to identifying bottlenecks otherwise omitted, with the potential to question issues resulting from supply and demand-side factors. For example, whether treatment guidelines updated with sufficient regularity to promote the prescription of key medicines. Thirdly, Egypt and KSA could collect data on coverage decisions for a new product according to the product's indication. Lastly, three key time measures can also assist with assessing the impact of changes on innovative products. For such measures to be fully realised, countries will need to commit to frequent and regular data collection to assess progress over time. Not only this, but these measures will require appropriate benchmarks to be set based on international norms and historical evidence. Countries should look to understand the time taken between global launches and local launches, which may also depend on local circumstances including pricing arrangements, company strategies, the time taken for regulatory completion (from submission to MA) over time, and the time taken to achieve reimbursement with appropriate tools and procedures, including negotiation processes.

Recommendations on monitoring

	Egypt
31	Secure institutional support from relevant bodies to commit to collecting suitable data for monitoring and analysis.

32	Establish a policy monitoring and evaluation function within competent authorities by designing and implementing data collection efforts which ensure collection cycles are at an appropriate frequency and collect the right data for the country context.

	KSA
29	Secure institutional support from relevant bodies to commit to collecting suitable data for monitoring and analysis.
30	Establish a policy monitoring and evaluation function within competent authorities by designing and implementing data collection efforts which ensure collection cycles are at an appropriate frequency and collect the right data for the country context.

6. Roadmaps for Egypt and KSA

This section presents two roadmaps – one for Egypt, one for KSA – which outline the recommendations made for each country and prioritises each recommendation across the short-, mid-, and long-term.

Table 9: Roadmap for key priorities for Egypt

		Pre-requisite	Short-term	Mid-term	Long-term
Step 1: Optimise access to innovative products	*IPR*	- Introduction of regulatory data protection provisions (Recommendation 1) - Establishment of mechanisms which enforce IPR provisions (Rec. 1) - Adherence to TRIPs, particularly for compulsory licensing (Rec. 1) - Establish possibility for patent extension (Rec. 1) - Establish system to provide transparent information on patent expiry (Rec. 2) - Strengthen national court systems to resolve any disputes (Rec 3.)			
	Regulatory	- Seek to shorten market entry timelines for innovative products (Rec. 4) - Improve oversight capabilities of national regulatory agencies and ensure adequate number of suitably trained assessors to review applications (Rec. 5) - Introduce an early market access scheme (Rec. 6) - Seek to delink pricing from marketing authorisation (Rec. 7)			
	Pricing	- Recalibrate the ERP systems used for innovative products (Rec. 8) - Ensure reimbursement decisions are compliant with value-based assessment (Rec. 9) - Refer innovative products to a negotiation process and MEAs (Rec. 10)			
Step 2: Improve policies for generic and	*Regulatory*		- Utilise abridged approval pathways (Rec. 11) - Review the length of time taken for market authorisation of generics (Rec. 12) Enforce quality of generic products (Rec. 13)		

biosimilar products	*Supply-side*		- Introduce price reduction for originator medicines (Rec. 14) Monitor new system for the use of preferential practices (Rec. 15)	- Create nation-wide tendering system for biosimilars (Rec. 16)	
	Demand-side		- Encourage generic prescribing (Rec. 17) Encourage generic substitution (Rec. 18)	- Create a set of common rules for demand-side policies across all payer segments (Rec. 19) - Consider options to incentivise generic prescribing and substitution (Rec. 20) Review current financial incentives for pharmacists (Rec. 21)	- Explore financial and non-financial incentives for physicians (Rec. 22 - 23) - Complete and continue use of IT system (Rec. 24) - Link e-prescribing to clinical guidelines (Rec. 25)
Step 3: Allocate savings to innovative products			- Identify efforts to streamline the time taken for P&R processes (Rec. 26) - Use horizon scanning (Rec. 28) - Secure commitment from relevant institutional stakeholders (Rec. 29) Design policies to earmark savings through funds, budgets, or other means (Rec. 30)	- Consider the use of MEAs and necessary pre-requisites (Rec. 27) - Implement policies which earmark savings through funds, budgets, or other means (Rec. 30) - Design & implement methods for allocating genericisation savings to innovative products (Rec. 30)	
Step 4: Monitor allocation of savings to innovative products		-	- Securing institutional support from relevant bodies for monitoring efforts (Rec. 31) Design data collection policies (Rec. 31)	- Implement data collection efforts as soon as possible (Rec. 31) - Establish a monitoring and evaluation function within competent authorities (Rec. 32)	

Table 10: Roadmap for key priorities for KSA

		Pre-requisite	Short-term	Mid-term	Long-term
Step 1: Optimise access to innovative products	*IPR*	- Introduction of regulatory data protection provisions (Recommendation 1) - Establishment of mechanisms which enforce IPR provisions (Rec. 1) - Adherence to TRIPs, particularly for compulsory licensing (Rec. 1) - Establish possibility for patent extension (Rec. 1) - Establish system to provide transparent information on patent expiry (Rec. 2) - Strengthen national court systems to resolve any disputes (Rec 3.)			
	Regulatory	Seek to shorten market entry timelines for innovative products (Rec. 4) Improve oversight capabilities of national regulatory agencies and ensure adequate number of suitably trained assessors to review applications (Rec. 5) Seek to delink pricing from marketing authorisation (Rec. 6)			
	Pricing	- Recalibrate the ERP systems used for innovative products (Rec. 7) - Ensure reimbursement decisions are compliant with value-based assessment (Rec. 8) - Refer innovative products to a negotiation process and MEAs (Rec. 9)			
Step 2: Improve policies for generic and biosimilar products	*Regulatory*		- Review the length of time taken for market authorisation of generics (Rec. 10) - Enforce quality of generic products (Rec. 11) - Develop abridged approval pathways for generics (Rec. 12)	-	
	Supply-side		- Eliminate phenomena where generic list prices are higher than originator prices (Rec. 13) Consider revisions to price capping for biosimilar products (Rec. 14)	- Reduce the use of preferential pricing and reimbursement practices (Rec. 15)	

	Demand-side		- Ensure existing IT systems monitor generic prescribing behaviour (Rec. 16) - Encourage generic prescribing (Rec. 17) - Strengthen biosimilar prescribing (Rec. 18) - Encourage generic substitution (Rec. 19)	- Introduce differential co-payments (Rec. 20)	- Explore financial and non-financial incentives for physicians (Rec. 21 - 22) - Link e-prescribing to clinical guidelines (Rec. 23)
Step 3: Allocate savings to innovative products			- Identify efforts to streamline the time taken for P&R processes (Rec. 24) - Use horizon scanning (Rec. 25) - Secure commitment from relevant institutional stakeholders (Rec. 26) Design policies which earmark savings through funds, budgets, or other means (Rec. 27)	- Consider the use of MEAs and necessary pre-requisites (Rec. 25) - Implement policies which earmark savings through funds, budgets, or other means (Rec. 28) - Design & implement methods for allocating genericisation savings to innovative products (Rec. 28)	
Step 4: Monitor allocation of savings to innovative products			- Secure institutional support from relevant bodies for monitoring efforts (Rec. 28) Design data collection policies aimed at frequent and relevant data collection cycles (Rec. 28)	- Implement data collection efforts as soon as possible (Rec. 29) - Establish a monitoring and evaluation function within competent authorities (Rec. 30)	

7. Conclusion

Egypt and KSA both experience difficulties in patient access to innovative medicines, particularly in the context of high brand loyalty and low uptake of generic products. This study suggests a fourfold approach to improving financial resource allocation across these two groups of pharmaceuticals. Initial efforts should be made to improve access to innovative medicines, in particular ensuring patent protection is optimal, after which improvements should also be made to pricing policies and reform to improve time to market. After this, efforts could be made across pricing and reimbursement policies to improve generic/off-patent use and uptake. However, there is a bigger dearth of intervention and behavioural nudges in the form of demand-side policies; action in both countries could seek to improve trust in and use of appropriate, high-quality generics for physicians, pharmacists, and the end-user population. Pricing and reimbursement policies could be streamlined to bring more key products to market quicker, but it will be near impossible to create a sustainable change in generic/off-patent uptake without the policy landscape and improved understanding among these stakeholders to engage with generic/off-patent products. Data modelling for key product groups suggests there is room for such efforts to result in significant savings, which can be redirected to more innovative products. Parallel efforts should be made to secure the timely market entry of new and potentially innovative products, looking at appropriate IP regimes, and pricing and reimbursement mechanisms, to ensure any savings obtained from improved generic policies can actually be directed to those novel products.

Egypt and KSA can earmark revenue which results from improved generic and biosimilar policies. Earmarked funds can be redirected in various ways: efforts in this direction can vary in size and shape across pricing and reimbursement policies, MEAs, specialised or dedicated funding, or wider activities like horizon scanning and data collection. Monitoring efforts could seek to provide long-term review of the policies for generics and biosimilars, innovative products, and the way in which savings are redirected to innovative products. The results from monitoring efforts may require one or more of the aforementioned components to be revised.

Above all, these efforts will need to be calibrated to suit the contexts of Egypt and KSA, respectively, with immediate steps taken to address access to innovative products, improve generic/off-patent uptake, and design policies and methods to earmark and reallocate savings to innovative products. Attuning policies for both generic/off-patent and innovative products and looking to other countries for examples on how to establish

efficient spending on innovative products and on system monitoring will allow both these countries to work towards ensuring access to necessary pharmaceutical products.

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Appendix 1. Overview of best practice countries

Healthcare system organisation

Of the five comparator countries, four (Denmark, Malaysia[33], Spain, and the UK) have public universal healthcare systems [149], [260]–[262]. Under the Dutch health care system, all residents are required to purchase basic coverage from approximately 60 private non-profit insurance providers [263] [264].

An overview of population health coverage and services covered in the five study countries is shown in **Table 11**. As of 2019, the health care systems in Denmark, Spain and the UK covered the entire population, whereas in the Netherlands 99.9% of the population was covered for healthcare. No exact figure was found for Malaysia, but coverage is wide as health services in the public sector are accessible to nearly the entire population [265]. The Universal Health Coverage (UHC) service coverage index in these five countries ranged from 73.3 in Malaysia to 87 in the UK in 2017.

As shown in **Table 11**, a proportion of the population in all these countries also purchase voluntary private health insurance which is supplementary or complementary.

Table 11: Health insurance coverage in comparator countries

	DEN	MYS	NED	SPA	UK
Population health coverage (%)	100%	~100% [1]	99.9%	100%	100%
Service coverage index [2] (2017)	81.0	73.3	86.0	83.0	87.0
Population with private/voluntary health insurance (%)	42% (2020)	49.4% (2019)	84% (2020)	20% (2018)	10.4% (2017)
Notes:	[1] No exact percentage was found in the literature for this indicator. However, breadth of coverage is wide as health services in the public sector are accessible to nearly all the population. [2] This index gives an indication of coverage of essential health services and is reported on a scale of zero to 100, which is calculated as the "geometric mean" of several health service coverage indicators. These indicators are organised in the following components of service coverage: (i) Reproductive, maternal, new-born and child health (ii) Infectious diseases (iii) Noncommunicable diseases (iv) Service capacity and access. [266]				
Abbreviations:	DEN: Denmark; EGY: Egypt; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; UK: United Kingdom.				
Sources:	Population health coverage: [267] (DEN); [267] (NED); [265] (MYS); [267] (SPA); [267] (UK). Service coverage index: [266] (DEN); [266] (NED); [268] (MYS); [266] (SPA); [266] (UK). Population with private/voluntary health insurance: [149] (DEN); [263] (NED); [269] (MYS); [261] (SPA); [270] (UK).				

Branded medicines market

[33] *In addition to its universal healthcare system, Malaysia has two main social security funds - the Social Security Organisation (SOCSO) and the Employee Provident Funds (EPF) - providing health coverage for people working in the private sector* [320].

Table 12 provides data on total pharmaceutical sales (USD per capita) and branded medicine expenditure as a proportion of the total pharmaceutical expenditure.

Based on the latest available data for each country, spending on branded medicines was highest in the UK (72% in the period 2016-17), followed by the Netherlands (63.1% in 2019), and Denmark (55.5% in 2017). Total pharmaceutical sales were 526 USD per capita in the UK in 2018, 525 USD per capita in Spain in 2018, 430 USD per capita in the Netherlands in 2019, 427 USD per capita in Malaysia in 2018 and 339 USD per capita in Denmark in 2018.

Table 12: Use of branded medicines in comparator countries

	DEN	MYS	NED	SPA	UK
Total pharmaceutical spending (Total, US dollars/capita)	339 (2018)	427 (2018)	430 (2019)	525 (2018)	526 (2018)
Spending on branded medicines (% of TPE)	55.5%[1] (2017)	No evidence	63.1% (2019)	No evidence	72% (2016/17)
Notes:	[1] % total spending has been calculated based on data extracted from Table 1 of "Total sales of medicine, 2013-2017" report by Sundhedsdatastyrelsen.				
Abbreviations:	DEN: Denmark; EGY: Egypt; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; TPE: Total Pharmaceutical Expenditure; UK: United Kingdom; US: United States.				
Source:	Spending on branded medicines: [20] (DEN); [21] (NED); [22] (UK). Total pharmaceutical spending: [271] (DEN); [271] (NED); [272] (MYS); [271], [267] (SPA); [271] (UK).				

Generic and biosimilar medicines markets

Table 13 provides data on generic medicine expenditure as a proportion of the total pharmaceutical expenditure (TPE), size of generic sales, and value of generic sales. The five comparator countries represent large generic markets when comparing the volume and value of their generic market with other countries[34] [267]. Based on the latest available data for each country, spending on generic medicines was highest in the UK (28% in the period 2016-17), followed by Spain (21.8% in 2014), the Netherlands (21.5% in 2019), and Denmark (16.6% in 2017). Generic medicine sales made up 85.3% of total pharmaceutical sales in the UK, followed by 79.9% in the Netherlands, approximately 70% in Malaysia, 65% in Denmark, and 46.4% in Spain. Across these countries, the value of generic medicine sales ranged from 55% in Malaysia in 2016 to 18.8% in Denmark in 2018.

[34] *For instance, in 2018-2019, the volume of generics in the reimbursed pharmaceutical market among Organisation for Economic Co-operation and Development (OECD) countries for which data is available ranged between 11.8% (Luxembourg) and 82.6% (Germany), whereas the value of generics ranged between 5.8% (Luxembourg) and 50.8% (Austria)* [267].

Table 13: Use of generic medicines in comparator countries

	DEN	MYS	NED	SPA	UK
Generic spending (% of TPE)	16.6%[1] (2017)	No evidence	21.5% (2019)	21.8% (2014)	28% (2016/17)
Size of generic sales	65%[2] (2018)	70%[3] (year unknown)	79.9% (2019)	46.4%[2] (2018)	85.3%[2] (2017)
Value of generic sales	18.8%[2] (2018)	55% (2016)	20%[2] (2018)	22.4%[2] (2018)	36.2%[2] (2017)
Notes:	[1] % total spending has been calculated based on data extracted from Table 1 of "Total sales of medicine, 2013-2017" report by Sundhedsdatastyrelsen. [2] Data reflecting the reimbursed pharmaceutical market. [3] Whilst there is no exact data available on generic sales by volume in Malaysia, it has been reported that generics account for around 70% of market share by volume.				
Abbreviations:	DEN: Denmark; EGY: Egypt; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; TPE: Total Pharmaceutical Expenditure; UK: United Kingdom.				
Source:	Generic spending: [20] (DEN); [21] (NED); [162] (SPA); [22] (UK). Size of generic sales: [267] (DEN); [21] (NED); [140] (MYS); [267] (SPA); [267] (UK). Value of generic sales: [267] (DEN); [267] (NED); [140] (MYS); [267] (SPA); [267] (UK).				

Generic consumption is high in several comparator countries. Generic medicines cover 67% of Denmark's consumption of prescription drugs [273], while in Malaysia, it has been estimated recently that 74.8% of medicines in the public sector are generics, which is four times higher than the average availability of originator drugs (19.4%) [274]. The use of generic medicines in the Netherlands is also high, stimulated by the generic substitution and preference-based policies[35] [157]. These figures may vary for private sectors: the average availability of generic medicines in Malaysia has been estimated at 49.1%, which is slightly lower compared to the average availability of originator drugs (52.2%). Relative to other countries in Europe, Spain's performance is average in generic market share [162]. Finally, uptake of generic medicines in England could be characterised as high considering that 83.7% of all drugs were prescribed generically, and 77.6% of items were prescribed and dispensed generically in the community, in 2017 [275]. It has been reported that unbranded generic medicines generally dominate the UK market [276].

Contrary to generic medicines, evidence on biosimilar medicines is limited. There is no evidence available on spending, uptake and use for this category of medicines in Denmark. There is also a lack of utilisation data for biosimilars in Malaysia [32]. In Dutch in-patient settings, market penetration of biosimilar medicines has remained low as large discounts are offered by manufacturers of originator biologic medicines [159] . In Spain, biosimilar medicines accounted for less than five percent of the total biologicals market in 2009 [277], with uptake of biosimilar medicines in the country characterised as moderate [121]. Uptake of biosimilar medicines in the UK is low compared to other European countries,

[35] *Tendering that covers extensive parts of the outpatient market, conducted by some health insurers and relying on the most economically advantageous tender price, with emphasis on the lowest price supplemented by commitments to supply the market.*

despite their introduction in the UK since 2006 and the support of their appropriate use by NHS England [278]. Significant differences in the uptake of biosimilar medicines have been observed among different pharmacological classes [279].

The size of the generic industry ranges across the comparator countries, from seven members registered with the national generic industry association in the Netherlands to 74 local manufacturers in Malaysia (**Table 14**). With regards to the local production of biosimilar medicines, the number of manufacturers ranges from two in Malaysia to 13[36] in Denmark (**Table 14**). Beyond supplying the national market with medicinal products, several of the members of national generic and biosimilar industry associations in the comparator countries work and supply products on a multi-national scale. Out of the 13 members of the Danish Generic Medicines Industry Association, seven members are operating not only in Denmark, but the whole Nordic market and the other six members work at a global scale [280]. In comparison, six out of seven members registered with the Dutch Generic and Biosimilars Association work on a multinational scale while the other member focuses only on the local market. However, it is part of the Stada manufacturing group which operates at a global scale [281]. Similarly, the majority of the members of the Spanish Association of Generic Medicines and the British Generic Manufacturers Association operate globally [282],[283].

Table 14: Local production of generic and biosimilar medicines in comparator countries[1]

	DEN	MYS	NED	SPA	UK
Number of local manufacturers/members of the generic industry association	13 [2]	74	7 [3]	21 [4]	34 [5]
Number of local manufacturers/members of the biosimilar industry association	13 [2]	2 [6]	7 [3]	No evidence	9 [7]
Note:	[1] Information on this table should be interpreted with caution. For most of the countries, it depicts the number of members of the generic/biosimilar industry association in the relevant country and does not necessarily capture the precise number of local generic and biosimilar manufacturers. [2] Reported as members of the Danish Generic Medicines Industry Association Website. Number includes both generic and biosimilar manufacturers. [3] Number of members in the Dutch Generic and Biosimilars Association, which represents about 90% of the generic pharmaceutical industry in the Netherlands. [4] Reported as members in the Spanish Association of Generic Medicines, which has a sector representation of 90%. [5] Number of registered members as reported in the British Generic Manufacturers Association website. [6] The biosimilars produced are limited to insulin products and erythropoietin. [7] Number of registered members as reported in the British Biosimilars Association website.				
Abbreviations:	DEN: Denmark; EGY: Egypt; KSA: Kingdom of Saudi Arabia; MYS: Malaysia; NED: Netherlands; SPA: Spain; UK: United Kingdom.				
Source:	Number of generic manufacturers: [280] (DEN); [281] (NED); [131] (MYS); [282] (SPA); [283] (UK). Number of biosimilar manufacturers: [280] (DEN); [281] (NED); [32] (MYS); [278] (UK).				

[36] *The number represents members of the Danish Generic Medicines Industry Association listed on the association's website. The number includes both generic and biosimilar manufacturers.*

Appendix 2. Policy and practice in Egypt

I. Market overview

Healthcare system organisation

The Sustainable Development Strategy "Egypt Vision 2030" launched in 2015 aims to make changes to the financing of the healthcare system [284]. Health programs under this reform include the creation of new authorities[37] in the pharmaceutical sector: the Egyptian Drug Authority (EDA) as a new regulatory body, the Unified Purchase Authority (UPA) as a centralised purchase agency, and the Universal Health Insurance Authority (UHIA), which aims to provide universal healthcare coverage to all Egyptians by 2032 [33].

In the public sector, the Health Insurance Organisation (HIO, under the Ministry of Health and Population) covers the public sector workforce in Egypt, accounting for coverage of around 55-60% of the population [109], [285], [286]. Estimations are that around 43% of the population are not covered by any health insurance [287].

The private sector in Egypt is represented by OOP spending which accounts for the largest source of financing health care in Egypt [288]. In 2018, OOP spending accounted for 62% of current health expenditure and has remained at these high levels since 2000 [2]. OOP spending is based on the list prices of pharmaceuticals which are set by the EDA, while in the public sector prices of pharmaceuticals are substantially lower as they are set based on procurement and tendering [27]. However, due to heavy reliance on originator medicines and the general culture of brand loyalty, patients usually choose to pay OOP for originators rather than generics which are more likely to be included in the tender list [27].

Medicine market

In 2016, the value of pharmaceutical spending in Egypt was US$3,538 billion accounting for 25.9% of total medical expenditure [289]. Generic medicines had a share of 33.2% of the total pharmaceutical spend in 2017, with the value of generic sales at $0,712 billion in 2017 and projected to be $0,967 billion in 2020 [289]. Older evidence from 2011 reported that the market share of branded generics was 3% [26]. The value of biosimilar sales in 2020 in Egypt was $148.6 million [33]. No recent data was found on pharmaceutical spending on originator products.

Local manufacturing

[37] *Prior to these changes, the Ministry of Health and Population (MoH) was solely responsible for health regulation in Egypt, but under the new reform it is no longer responsible for drug regulation and purchasing* [290].

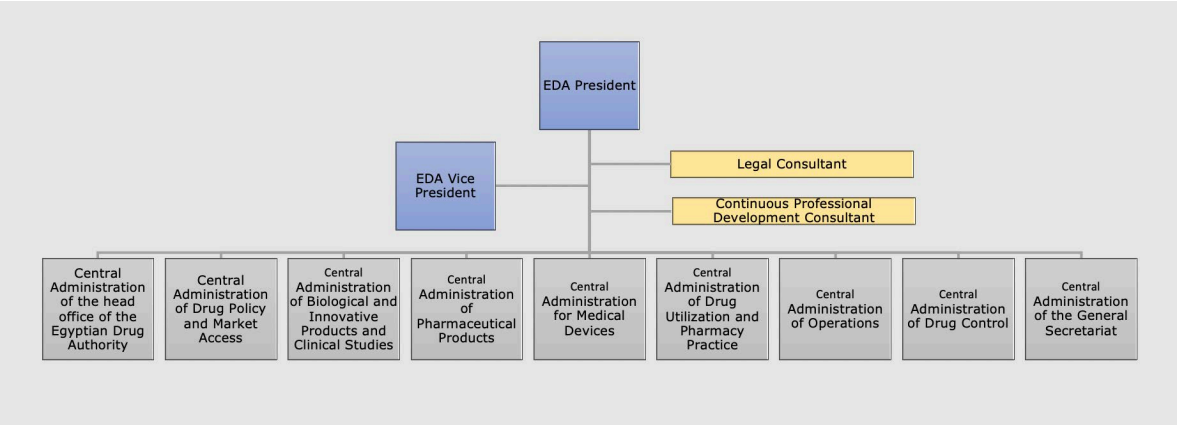
The national pharmaceutical industry in Egypt covers 92-94% of the market share by volume and 82% by value [110]. There are 119 licensed pharmaceutical manufacturers, however there are no manufacturing capabilities for research and development of new active substances and national manufacturers mainly produce generics [289]. [24]. Nine of these manufacturers are multinational companies with local production bases [111]. Most active pharmaceutical ingredients are imported [27]. In 2017, the Prime Minister issued a decree which granted the Egyptian military's National Agency for Military Production a license to take part in the founding of the Egyptian National Company for Pharmaceuticals in order to address medicine shortages [111].

II. Regulation

Regulatory authority

The EDA is the pharmaceutical regulatory body in Egypt, responsible for all drug-related matters including the registration, pricing, analysis and availability of pharmaceutical products [33], [290]. The EDA combines nine central administrations under its operation, presented in **Figure 17** below. The UPA is the public authority responsible for unified procurement, medical supply, and medical technology management (further discussed in Section 3.3.1.3). In addition, the UPA and the UHIA have been given the right to perform HTA by law [27]. Currently there is no coordination between HTA activities of various agencies though there is an ongoing effort to unify HTA processes [27].

Figure 17: The Egyptian Drug Authority (EDA)



Source: [33].
Abbreviations: EDA: Egyptian Drug Authority.

Regulation/policies for generic and biosimilar products

Egypt has an abridged approval process for products approved and marketed by the FDA in the US and the EMA, used for NMEs, generics, and biological medicines [33], [41], [81]. If already approved and marketed by both agencies, official registration timelines are one month, while the 'abridged process' for products that are approved and marketed by either

the FDA or the EMA has official registration timelines of two months [41], [82]. Additionally, under a different approval pathway, generic medicine submissions in the CTD format can be registered in 180 days in Egypt [33], a shorter timeframe than for new chemical entities.

Under the recent Decree 645, the EDA accepts registration requests above the official number allowed in a box[38] of similar pharmaceuticals in certain cases[39] [291], allowing more generic products to be registered. Primary evidence states that generic registration occurs in 12 to 18 months under this pathway [33]. An Emergency Use Authorisation mechanism has also been implemented due to the Covid-19 pandemic [292], which so far has allowed registration of two products, one of which is generic, in one to four weeks [33].

Biosimilar approvals rely only on bioequivalence testing and sometimes pharmacovigilance risk mitigation plans for new forms and concentrations [33].

Bolar provisions

Bolar provisions, which allow generic manufacturers to develop and register products while the originator is still under patent, are in place in Egypt [60]. However, the practical use of these provisions in Egypt remains unclear since generics can be registered and launched during patent protection of originators due to lack of a well-established link of intellectual property rights and patent protection [33].

Good manufacturing practices and quality assurance

Decree 539/2007 adopts the WHO GMP standards as a reference for Egyptian GMP; all Egyptian manufacturing firms are required to abide to these standards [290]. The standards are set out in the Egyptian Ministry of Health and Population (MoH)'s Guide to Good Manufacturing Practice for Medicinal Products. Within one month of a company applying for a license to manufacture pharmaceutical products, a special committee formed by the MoH visits the site to ensure compliance with technical and health requirements [290].

Quality control is conducted by the Central Administration of Drug Control through laboratory tests of pharmaceuticals against standards of 'identity, strength, quality and purity' [33]. Pharmacovigilance is the duty of Central Administration of Drug Utilisation and Pharmacy Practice [33]. Manufacturer must submit a pharmacovigilance plan

[38] *The 'box system' was introduced to regulate registration and defines the maximum number of pharmaceuticals with similar active ingredients and product specifications* [321]*. It is composed of one branded and 11 generic products in most cases* [321].
[39] *Shortage drug lists which do not have alternatives or product lists which are determined by EDA according to the market need; Rare production lines; Products produced for local marketing and exportation purposes; Products being submitted for the past 10 years by licensed manufacturing plants; Products submitted by manufacturing plants under construction.*

according to the Egyptian Pharmaceutical Vigilance Centre guidelines [38]. Inspections were planned to begin in 2020 but have been delayed due to the 2019 coronavirus (COVID-19) pandemic, though a few companies had pharmacovigilance inspections in late 2019 [33].

IP rights and data exclusivity

The main national law regulating patents in Egypt is Law No. 82 of 2002 relating to the Protection of IP Rights and its Executive Regulations [65]. Under this law a patent is valid for 20 years with no possibility of extension beyond this period. Patentability of additional medicine indications beyond the first indication is not possible under Egyptian patent law [65], [68]. There is no specific guidance on data and marketing protection periods in Egypt [65].

Primary evidence states the IP registration process in Egypt is a lengthy process which can take five to seven years, that there is no specific guidance on data and marketing protection periods, and that generic and biosimilar medicines can be registered before originators in the Egyptian market [33]. Overall, data exclusivity in Egypt is considered to be weak by the local industry [33].

Time to entry

All medicines. Long MA approval timelines of two to three years were experienced before the establishment of the EDA. Under the new arrangements, Registration Decree 820 allows the EDA to conduct abridged approvals for US FDA and/or EMA approved drugs and for drugs in the CTD format[40] [81]. Under these new guidelines, the EDA expects to be able to approve EMA/FDA approved drugs in only one to two months and in six months for medicines in CTD format [81].

Biosimilars. The timeline for biosimilar market access is eight to ten months in Egypt [24].

Originators. The official timeline for registration of NMEs is 105 working days in Egypt, though the observed time is reported to take up to one to two years for small molecules [33] and two to three years for biologics and vaccines [81], [33].

III. Supply-side policies

Pricing

Originators. In Egypt, the vast majority of originator medicines are priced based on the lowest price of a reference basket of thirty-six countries [27]. Value-based pricing is used rarely when manufacturers appeal on the prices set by the pricing committee based on

[40] *The common technical document (CTD) provides a common format for technical documentation required for the registration of medicines across Europe, North America, and Japan.*

ERP. In this case, EDA uses value-based pricing to set up the prices of these medicines [27].

Generics. A price capping system with managed competition based on sequential entry is utilised for pricing generics in Egypt. The Egyptian system clusters the first five generics which enter the market, to be priced at 35% below the originator price[41], after which all subsequent entrants are priced 40% below the originator price [109]–[112], [293]. High-tech[42] generic medicines are priced 30% to 35% below the lowest retail price in the reference basket, depending on whether they are imported from a reference country (30%) or a country outside the reference basket (35%) [33].

Biosimilars. Biosimilars are priced based on price capping [27], [33]. Usually, the first biosimilar entrant is priced at 70% of the biologic while subsequent market entries are priced at 60% of the biologic's price [33]. Graded biosimilars[43] are priced 30% lower than the originator and non-graded biosimilars or non-reference country biosimilars are 35% lower than the originator [33]. According to local industry, biosimilar prices are closely linked to the price of the originator and as such cannot be priced equal to or above the price of the originator [33]. Equally, biosimilars may receive price cuts whenever the originator does [33]. Only, in exceptional cases such as medicine shortages, a biosimilar may be priced differently [33].

Preferential practices for local manufacturers in pricing. According to Pricing Decree 499/2012, there are no preferential pricing practices for local manufacturers between imported and locally manufactured generics. However, imported medicines are exempt from VAT [108]. Previously there had been generic pricing policies to encourage local production and provide more beneficial pricing arrangements to local over imported generics, such as pricing based on availability of similar generics [108]. However, based on the current evidence, there is no indication whether in the new regulation this practice will continue.

Reimbursement

Reimbursement policies under the newly reformed system are not yet fully established and implemented [33]. To date, the UPA has been honouring existing tenders and has had an additional two settled tenders and two ongoing tenders, all four of which have different processes and requirements [33]. The first finalised tender was a price-driven monopoly

[41] *In Egypt, originator medicines are priced based on the lowest price of a reference basket of thirty-six countries.*
[42] *High-tech generics are those which are considered to require rare production lines and are distinguished by a list published quarterly by the High Committee of Inspection upon Pharmaceutical Manufacturing.*
[43] *Graded biosimilars are those already approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).*

award for a cancer treatment and the second was for multiple sclerosis products which had multiple winners based on a committee decision [33]. The UPA has generated a list of all available generics, biosimilars, and originator medicines with a Tender Drug List to be announced[44] [33].

Preferential practices for local manufacturers in reimbursement. Prior to the recent system restructure, public procurement in the region gave preferential treatment, including price advantages, to locally manufactured products [294]. According to primary evidence, locally manufactured products were more likely to win a tender even if the price submitted was up to 15% higher than the lowest submitted price by a foreign manufacturer [33]. Support provided to local manufacturers has included predominantly preferential reimbursement practices rather than pricing practices favouring local over foreign or multinational manufacturers [108]. However, based on the current evidence, it is unclear whether preferential policies for local manufacturers will remain under the new UPA practices.

Procurement

The UPA is the sole authority able to carry out purchase transactions of pharmaceutical products and medical equipment on behalf of all governmental and public entities in Egypt [33]. The purpose of the UPA is to buy in bulk, have a higher negotiating power, and obtain high discounts [295]. The UPA mandate involves managing medical technologies, establishing a comprehensive database for medical technologies in all public health institutions, and the ability to establish joint stock companies for procurement purposes as well as managing medical technologies and databases if necessary [33]. However, the specific role and strategy of UPA for the management of medical technologies has not been yet established.

Before the health system reform, separate public and private procurement processes co-existed. Upon creation of the UPA individual institutions such as hospitals and groups of pharmacies are no longer permitted to procure medicines on their own but can voluntarily decide to purchase their own medicinal products through the UPA [33], [295].

IV. Demand-side policies

Generic prescribing

Generic prescribing is encouraged by the Egyptian government as cost containment is a health system priority [108]. According to secondary evidence, using the molecule name for prescribing is mandatory [294]. In the public sector, the UHIA issues a formulary where

[44] *The Tender Drug List was not yet available at the time of publication.*

products are listed by INN and are available through the UPA procurement system [27]. However, according to evidence from local experts, prescribers in the public sector do not always prescribe by molecule name [27], [33]. The UPA ensures availability of both originator and generic medicines in the public sector, therefore what is being prescribed depends on the decision of the treating physician and the hospital committee in certain cases [33]. Primary evidence states that the lower price of generics is a factor that encourages physicians to prescribe them; especially non-branded generics are more likely to be used to support cost-saving as their price is lower than of branded generics [27]. Moreover, physicians tend to prescribe generics in order to reduce the financial burden to patients [27]. Patients can shift from the generic to the originator by paying the price difference out-of-pocket [33]. According to primary evidence, the UHIA works closely with physicians on prescribing by molecule name but this system is still being established [27]. The UHIA in Egypt has only recently launched an IT system for electronic prescribing which is currently at its first phase of implementation [27].

In the private sector, about 70% of prescriptions are branded [33]. Based on primary evidence, the market for biosimilars in the private sector is very limited as a result of pharmaceutical marketing and the perception of Egyptian patients that biologic products are better than biosimilars [27]. Biosimilars are usually prescribed in cases when the biologic is not available or the patient has limited ability to pay for it [27].

Generic and biosimilar substitution

There are no strict guidelines to regulate generic substitution in Egypt [296]. In the Egyptian retail market, prescribing decisions are made by physicians but can be substituted by pharmacists only when the prescribed product is unavailable [33]. In the public system, pharmacists must dispense the product covered by the public tender which might include both generics and originators [33]. Pharmacists may substitute a generic if they get approval from the physician and the patient [27]. Patient affordability and the higher profit margin obtained from generics are factors the positively influence generic dispensing by pharmacists [27].

In inpatient settings the only available option is the medicine covered by the tender, which is usually the generic or biosimilar as it is cheaper [27]. Pharmacists are generally not permitted to switch patients from biologics to biosimilars; the biosimilar can only be prescribed by the physician [38]. According to primary evidence though, interchangeability between biologic medicines is a debatable issue in Egypt. However, if the Technical Committee for Pharmaceutical Control approves interchangeability between a biologic and a biosimilar, pharmacists in the public sector can switch [33]. In addition, as per the local industry, dispensing of biosimilars differs between sectors [33]. Under the health

insurance organisation, the biologic is prescribed using the branded name and pharmacists should only dispense the biologic. While in the State fund, products are prescribed by INN, and it is at the pharmacist's discretion on whether to dispense the biologic or the biosimilar depending on their allocated budget [33].

Incentives for healthcare professionals

There are few prescribing incentives in the Egyptian system. Initiation kits, such as free medical samples, can be distributed to healthcare professionals [33].

Pharmacy and wholesaler renumeration strategies

Profit rates for pharmacists and distributors are determined using the rates in **Table 14**.

Table 15: Profit rates for pharmacists and distributors in Egypt

Essential Medicines List	A) Distributor profit: 7.86% of the factory selling price. B) Pharmacist profit: 25% of the distributor selling price.
Supported Products (imported or local)	A) Distributor profit: 4% of the price of the plant. B) Pharmacist profit: 10% of the sale price of the distributor.
Imported Products (special import/individual requests) for packages where the public sale price is less than 500 pounds*	A) Distributor profit: 8.8% of the sale price of the importer OR 6.4% of the sale price of the public. B) Pharmacist profit: 22.9% of the selling price of the distributor OR 18% of the selling price of the public.
Imported Products (special import/individual requests) for packages where the public sale price is more than 500 pounds*	A) Distributor profit: 6.4% of the sale price of the importer OR 4.8% of the sale price of the public at a maximum of 150 pounds for the distributor with deducing the difference in price for the benefit of the patient. B) Pharmacist profit: 18.5% from distributor sale price OR 15% from the public sale price at a maximum of 450 pounds for the pharmacist with deducting the difference in price for the benefit of the patient.
Note:	*Where there are two percentages for distributors and pharmacists, the higher profit is the one used.
Source:	[112]

Patient co-payment strategy

In the public sector, co-payments are used if the patient chooses the originator medicine or a more expensive generic alternative to that dispensed in the tender [27], [33].

Education programs and information strategies

Besides marketing activities organised by pharmaceutical companies [33], there are no current public campaigns or initiatives promoting the use of generics or biosimilars in Egypt. The MoH has established a National Training Institute in partnership with pharmaceutical companies focused on upgrading the scientific knowledge of healthcare professionals [33]. Pharmaceutical companies will be sponsoring educational events and symposiums [33].

Appendix 3. Policy and practice in KSA

I. Market overview

Healthcare system organisation

The public sector in KSA covers approximately three quarters of health care offered in the country and offers universal coverage to the population [297], [298]. The government has been recently facing challenges in sustaining the public health care system free of charge [299]. The private sector is funded by private cooperative health insurance schemes and OOP payments [297]. The private sector has been growing over the last years and is now considered a key component of the national healthcare system [297], as it provides 23% of the health services [300]. Improving healthcare services is a top priority for KSA's recent strategic framework, Vision 2030 [301].

Medicine market

In 2018, pharmaceutical expenditure accounted for 19.4% of the total health expenditure of US$40.657 billion [297]. There is a steady increase in pharmaceutical expenditure in KSA, rising from US$4.894 billion in 2011 to US$7.897 billion in 2018 [297]. In 2019, 76.7 % of the total health expenditure was spent on originators while only 23.3% was spent on generics [168].

Local manufacturing

KSA depends on imported pharmaceuticals from Europe, the US and some other GCC countries to a great extent [297]. There are 19 licensed pharmaceutical manufacturers in KSA [166] and only 20% of the pharmaceuticals in the Saudi market is produced locally [44]. A significant proportion of these products are not generics but are licensed patented medicines from multinational companies, showing that foreign companies are indirectly involved in the Saudi pharmaceutical market, even if they do not have manufacturing plants in place [44]. In addition, there is an increasing focus by local manufacturers on the production of branded generics, which are considered to be of superior quality [44].

II. Regulatory environment in KSA

Regulatory authority

The SFDA is the national regulatory body in KSA responsible for the regulation of locally manufactured and imported medicinal products. The agency was first established in 2003 and oversees the import, export, distribution, advertisement, registration, approval, pricing and withdrawals of pharmaceutical products [302]. The agency is an independent body and reports directly to the President of Council of Ministers.

Regulation/policies for generic and biosimilar products

The SFDA has developed guidelines for the registration of generic and biosimilar medicines. The guidelines for biosimilar medicines was developed in line with guidance from the EMA and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) [57].

KSA has a process for abridged approvals for products approved and marketed by the FDA in the US and the EMA, applied for innovative products in circumstances of unmet clinical need (**Table 4**) [33], [41]. There are two pathways for abridged approvals for products approved and marketed by the FDA in the US and the EMA,: the 'verification process' for products that are approved and marketed by both the FDA and the EMA, and the 'abridged process' for products that are approved and marketed by either the FDA or the EMA [41]. The target process timelines of the "verification process" and the "abridged process" are 30 and 60 days respectively. KSA applies a priority review[45] for (i) medicines used to treat serious or life-threatening conditions and/or address unmet medical needs, (ii) medicines under the SFDA exempted list or (ii) medicines considered as first or second generic for an innovated product [263]. The official timeline for medicinal products under priority review[46] is reduced by 40% [41].

Bioequivalence testing for generic medicines and specific policies for biosimilar medicines are present across in KSA, which has adopted the EMA principles of biosimilar regulation [35], [36]. However, clinical study requirements are more lenient in KSA than the EU requirements (see Appendix 4).

Bolar provisions

Bolar provisions are in place in KSA.

Good manufacturing practices and quality assurance

The US FDA GMP guidelines are used by the SFDA for approval of pharmaceuticals [303]. The license of pharmaceutical factories and warehouses are issued by the Facilities Licensing Department of the SFDA which works closely with the Department of Inspection to monitor adherence to guidelines. In KSA, local product analysis to ensure safety, efficacy and quality are obligatory even if the product has been approved by the US FDA

[45] *Priority review by SFDA indicates that the review process will be expedited without altering any of the scientific standards and quality of evidence required for approval.*
[46] *"Treatment of a serious or life-threatening condition and/or demonstrates the potential to address unmet medical needs, products under SFDA's exempted list or to product considered as first or second generic for innovated product" are eligible for the priority review process according to SFDA guidelines* [322].

or EMA [44]. Quality control is conducted at the SFDA or other laboratories. Pharmacovigilance is the responsibility of the SFDA, which has a dedicated department for pharmacovigilance. The pharmacovigilance system in KSA has been developed based on European guidelines and practices. However, as the system is fairly new, implementation of all pharmacovigilance tasks has been limited [304].

Further advancements of the regulatory framework, including the pharmacovigilance system, part of the Saudi 2030 Vision plan. New policy plans for generic and biosimilar medicines were discussed during the Saudi 2030 Vision plan conference, leading to recommendations such as that generic and biosimilar bioequivalence studies should be conducted by the SFDA rather than relying on results submitted by the manufacturer, and provision of bioequivalence information should be printed on leaflets (see **Box 6** below for other recommendations adopted at the conference). Implementation of a naming strategy at the point of prescribing for effective tracking and monitoring of biologics and biosimilar medicines through the health information system has been proposed by the Ministry of National Guard Health Affairs (MNGHA) [27], [39].

Box 6 The Saudi 2030 Vision plan

The conference adopted the following recommendations:

- National regulatory bodies in the Kingdom of Saudi Arabia (KSA) such as the Saudi Food and Drug Authority (SFDA) should conduct its own bioequivalence studies rather than relying on those provided by other generic and biosimilar drug manufacturers.
- Bioequivalence information should be provided in the generic and biosimilar drug leaflets.
- Frequent and risk-based bioequivalence studies to assess the quality of marketed either generic or brand medications is important and needs future regulations to assure the quality of post-marketed medications.
- National regulatory bodies should work with industry, academia, and other stakeholders to develop better regulations and increase the transparency of manufacturing quality standards.
- The value of pharmaceutical regulations to the Saudi public and health care providers is still not sufficiently enforced through public media campaigns and scientific conferences.
- There is a lack of national standards regarding therapeutic switching of generic and biosimilar medicines in KSA.
- Current rules or regulations by the National regulatory bodies need to ensure the integrity of the generic and biosimilar drugs supply chain in KSA similarly to innovative medicines.
- Patients should be provided with information written in layman's terms about the bioequivalence of generic drugs so that they can be more informed healthcare consumers.
- There should be greater cooperation between the different entities of KSA Ministry of health as well as between the Ministry of Health and regulatory agencies to create educational outreach programs aimed at the public and the health care providers alike to educate them about pharmaceutical quality issues and how they can affect quality of care.
- Both regulatory agencies and the Ministry of Health should work together on more comprehensive and transparent regulations that govern therapeutic switching between brands, generics and biosimilars for each health condition.
- Medication leaflets have not taken into consideration the limited health literacy level of most patients in KSA. Therefore, an interdisciplinary committee of health professionals and researchers should be formed to review medication leaflets before they are released to the public.

- The Saudi generic drugs approval process should be reformed to take into more careful consideration the issue of quality.
- A clear and transparent mechanism for patients and health care providers to report quality issues of generic and biosimilar medicines (when switching from one to another) should be established.
- There is a need for a national health outcomes research centre to conduct observational studies about the quality of medications in general and generic and biosimilar drugs in particular.
- A Saudi fast-track approval process for new medications should be established.

Source: Extracted from [305].

IP rights and data exclusivity

There are currently no specific laws for pharmaceutical patents in KSA [66] but pharmaceuticals are included in the main national law related to patents (Law No. 159) [66], [67]. KSA also participates in several international treaties related to patents [66]. The main national law on patents states pharmaceutical patent protection is effective for 20 years [67] and does not allow for extensions of the protection period to account for potential delays caused during the marketing authorisation approval process [68]. Regulatory data protection is applicable in KSA as per the TRIPS agreement: a five-year data exclusivity period from the date of obtaining marketing authorisation is provided by law [67], [68]. KSA does not have specific provisions for data and market exclusivity protection periods for orphan medicines.

There is a centralised route available for obtaining patent protection in all six GCC countries, including KSA, by submitting an application at the GCC Patent Office [16]. Moreover, each of the GCC countries has established their own patent office; therefore, an application for obtaining patent protection in KSA can also be directly submitted to the Saudi Patent Office through the national route [67]. According to primary evidence, previously all types of pharmaceutical products were eligible to apply for patent protection through the GCC route, however, the GCC Patent Office is not accepting applications temporarily [33]. Since its launch, the Saudi Authority for Intellectual Property (SAIP) has become the common route for obtaining patent protection [33]. Pharmaceuticals which obtained patent through the GCC pathway still remain protected in KSA [33].

In 2018, KSA was identified by the Office of the United States Trade Representative as one of the trading partner countries where IP rights for pharmaceuticals are not adequately or effectively protected [67]. There have been several IP infringements since 2017 where the SFDA authorised domestic pharmaceutical companies to produce generic versions of innovative medicines produced in other countries during the patent and data protection period [70] or the Ministry of Health proceeded to procure infringed products despite appeals from the relevant innovator companies and, in one case, despite a favourable

court decision in Saudi Arabia [70]. In another case, the SFDA granted marketing authorisation to a generic, locally produced version of an originator product which was patented by the GCC Patent Office a few months earlier [307]. There have also been multiple instances in which data protection was not honoured for imported branded medicines that were not directly patented in KSA [33], [44].

Since then, targeted efforts have been made by the government; in 2018 SAIP was established as a new authority responsible for the regulation, promotion and protection of IP rights [308]. SAIP is working towards the development of a national IP strategy and the coordination of its implementation in collaboration with all relevant authorities [309]. The ongoing efforts by SAIP to set up a mechanism to protect IP and move towards patent linkage may strengthen patent protection depending on how effective the mechanism being devised will be [33]. More specifically, the proposed system seeks to enhance transparency on the therapies that are protected by a patent in KSA/GCC by creating two lists: (i) list of patents registered in KSA, and (ii) list of pharmaceuticals under registration [33]. Generic companies will be responsible for reviewing the first list to ensure they don't infringe patents and innovator companies will be responsible for reviewing the second list to detect potential infringements [33]. An objection mechanism is going to be available for innovator companies in case they detect a potential infringement and within 60 days they would need to either resolve the issue with the generic company or initiate a court case [33]. In the latter scenario, the final registration is withheld until the court decision and, if the court decision is in favour of the innovator, the generic registration is rejected [33].

Time to entry

Once a generic or biosimilar medicine is approved it enters the national market quickly, though, according to primary evidence, the time to entry may vary across the public and the private sector [27].

Generics. The KSA regulatory framework [310] outlines decisions for marketing authorisation application for generic medicines should be issued within 165 days. The time taken to issue regulatory approval in KSA ranges between 12 and 18 months for generic medicines. Local producers experience far shorter product registration times than foreign producers; the registration process often takes years for imported products, compared to as little as three months for locally manufactured pharmaceuticals [44].

Biosimilars. The time to market for biosimilar medicines is 18 months in KSA [24], though some reports state 24 to 36 months for biosimilar medicines in practice [27].

III. Supply-side policies

Pricing

This section covers current pricing policies for generic and biosimilar medicines in KSA. A summary of the previous pricing method implemented before the introduction of the new pricing policy in January 2021, can be found below**.**

Previous generic and biosimilar pricing policy in KSA (in use before 14th of January 2021)

Generics:

At loss of exclusivity, the originator product's price is discounted by 20% by the first entry of a generic product [153], [311]. The first generic drug to enter the market is then priced 35% lower than the reduced price of the reference product and generics entries thereafter are then reduced by 10% by each entry until the fourth generic enters the market [312].

Biosimilars:

Pricing of biosimilars follows the general rules of pricing with a price celling of 60% of the price of the originator biological drug [313].

Generics. A summary of criteria used for determining the price of generic medicines in KSA is presented in **Figure 18**. These criteria should be considered when pricing generic medicines through the following mechanism: on the first entry of a generic, the originator product's price is reduced by 25%. The price of the first generic to enter the market is priced as such to not exceed 70% of the initial price of the originator before generic competition, after which the second generic to enter is priced accordingly to not exceed 65% of the originator's initial price. All following generic entries are priced to not exceed 60% of the originator's initial price [113].

Figure 18: Pricing rules for pharmaceutical products in KSA

The medicine shall be priced at an appropriate price, provided that the following data shall be considered when pricing:

1. The therapeutic value added by the medicine.
2. Prices of registered alternative treatment in KSA.
3. Pharmacoeconomics (Economic Evaluation studies) of the medicine.[1]
4. The ex-factory price of the medicine in the Country of Origin's (COO) currency.
5. The wholesale price of the medicine in the COO currency.
6. The price proposed for the Kingdom submitted by the company in the COO currency.
7. The ex-factory price or export to all countries in which the product is marketed in its local currency.

[1] This criterion is not applicable for mature brands and generics [33].

Source: *Extracted from The Saudi Food and Drug Authority Guidelines* [113].

The first imported generic to enter the market with existing local generic competitors receives a price 10% less than locally manufactured generics [130], [153], [165], [314]. Subsequent entries are priced 10% less than the latest preceding generic [130], [153], [165], [314]. If there are no locally manufactured generics on the market, the imported generic is priced 30% below the originator (for the first entrant) and following entrants are priced 10% below the price of the first generic [130], [153], [165], [314]. ERP using 20 reference countries is applied for pricing of locally manufactured generics in circumstances where the originator is not available in the local market [33], [108]. Prices of generics are reviewed every five years at the time of renewal of product registration [165].

B*iosimilars.* Biosimilar medicines in KSA are priced using price capping with managed competition based on sequential entry. The current pricing policy applies a 20% reduction on biological products on market entry of a biosimilar product. The first biosimilar product to enter the market is priced so its price does not exceed 75% of the initial price of the biological product's before biosimilar competition, the second biosimilar then priced to not exceed 65% and the third to not exceed 55% [113]. Prices of biosimilar medicines are reviewed every five years at the time of renewal of product registration [165].

Preferential practices for local manufacturers in pricing. Primary and secondary evidence suggested that favouritism towards locally manufactured medicines is present in the KSA pricing system [27]. Local producers receive support by the government through subsidies, exemptions and price concessions e.g. access to interest-free capital, subsidised utility costs, lower percentage markdown of originator prices [130].

Reimbursement

The Pharmacy and Therapeutics Committee of KSA is responsible for the decision on reimbursement and formulary listing for public coverage [44]. However, reimbursement differs between health sectors [108]. In the public sector, all Saudi citizens receive medicines listed on government formularies free of charge in all governmental healthcare facilities [27]. While, private health insurance schemes are required to provide at least partial coverage for medicines on the Saudi National Formulary [166].

According to primary evidence, IRP is used to price imported generics where the reimbursement price cannot exceed the lowest price of similar registered products on the market [33], [130].

Tendering is widely used for generics and cover both the in-patient and out-patient markets and is applied at molecule level using the INN [27]. Currently, tenders are used in the centralised public sector and take place on an annual basis as per the public sector

procurement policy [166]. Awarded tender contracts can last for a maximum of three years, but practically they usually last for one or two years according to primary evidence [27]. The criteria used to award tenders include SFDA approval, price, quality, and manufacturer capacity to cover the quantities required [27]. To ensure availability of supply for the tendering period, tender contracts are usually awarded to two to four bidders [27]. Tender awards are not made public in terms of volume supplied, but NUPCO tender prices are shared with distributors and other bidding companies [33].

The preferential pricing policy in the Netherlands serves as best practice example for KSA, according to primary evidence, where the CCHI trying to implement a similar approach [33].

Preferential practices for local manufacturers in reimbursement

Preferential practices for local manufacturers against imported products over locally produced products are present in formulary listing, the tendering and procurement process. Local manufacturers in KSA can win a tender even if their price submitted is up to 10% higher than the lowest submitted price by an oversee manufacturer price [311]. This preference in tendering procedures for local manufacturers aims to help local manufacturers to expand their production according to local experts [27].

The support towards domestic industry, is also prevalent in the procurement of medicines where locally produced products are preferred over imported products through 'obligatory lists'[47] [315]. According to primary evidence, the regulatory framework around data exclusivity in KSA further encourages local manufacturers to launch generics, even for drugs that are still under patent, as locally manufactured generics have priority in public procurement contracts [27].

Procurement

Currently KSA has both decentralised and centralised procurement processes. However, the system is moving towards becoming more centralised, led by NUPCO [27], [108]. Based on primary evidence, NUPCO is currently responsible for approximately 70% of the total pharmaceutical budget [27].

The LCGP is the national authority for procurement and is responsible for designing and refining government procurement processes of products purchased by the government including generics and biosimilar medicines [315]. NUPCO is further involved in the

[47] *Obligatory lists are lists of products created by National Unified Procurement Company for Medical Supplies (NUPCO), which will only be purchased from local manufacturers.*

procurement process by supporting hospitals and health care facilities in the public sector with procurement, storing and distributing medicines and equipment [27], [316].

There are three pathways to medicines procurement all within NUPCO: (i) a main NUPCO tender, (ii) a small scale tender for Wasfaty—KSA's e-prescribing programme—and (iii) a marketplace platform for local purchase orders [33]. The Wasfaty tender's objective is to utilise partnerships with private pharmacies while the marketplace platform is for procuring medicines whose needs are sporadic, not included in the formulary, or formularies that have add-on tenders[48] [33].

To encourage the use of generics, NUPCO is likely to purchase generics instead of originators when more than three generic suppliers bid for a tender [27]. On occasion where an originator supplier is awarded a tender, the originator is only provided to a proportion of patients based on a decision of the Pharmacy and Therapeutics Committee operating into each hospital [27]. Products which are not available in the Saudi market - such as orphan medicines or old medicines which are no longer manufactured in the country - are directly purchased from overseas markets [27].

In the private sector, there is a list of Good Distribution Practices (GDP)-certified wholesalers and distributors from whom private hospitals and health care facilities can directly purchase medicines [153].

IV. Demand-side policies

In KSA, there is scepticism about generic medicines, with a general preference for originator medicines [27], [297], [303] or branded products. According to the local industry, this preference may be explained by the current direction and vision towards domestic manufacturing and privatisation [33]. Brand loyalty is more prevalent in the private sector [27], while generics are widely used in the public sector. The use of biosimilars is less frequent [27].

Generic prescribing

Generic prescribing is allowed in KSA [160], and a 2017 regulation made INN prescribing mandatory for physicians. However, if a medicine is on the SFDA's list[49], the medicine is listed with the brand name [27], [154]. In addition, medications which are "highly sensitive", such as orphan medicines and cell therapies, should be prescribed using their brand name [27].

[48] *Add-on tenders may occur later if necessary to account for possible shortages if a medicine on the formulary needs an additional supply.*
[49] *A list of medicines issued by the SFDA* [154]*, including medicines such as narrow therapeutic index medicines, inhalers, and some oncology medicines* [27].

Generic and biosimilar substitution

Generic substitution by pharmacists takes place in both the public and private sectors in KSA [166]. Generic substitution is not mandatory; the pharmacist is free to choose whether to dispense a generic or an originator if both options are available [27]. However, there is limited evidence available on whether there is a specific regulation in place that allows the practice of generic substitution, while evidence in the literature varies between sources. Specifically, it has been reported [167] that pharmacists have been given the right through regulation to substitute for generics, and that a generic substitution policy has been in place in the country since 2005 [165]. However, according to a more recent source [168], there is "unregulated or limited governance" on pharmacists regarding generic substitution.

Primary evidence reported that, due to NUPCO's promotion of the use of generics, pharmacies in the public sector are incentivised to mainly dispense generics leaving patients without a choice on whether to choose generics or not, unless they choose to pay out-of-pocket to receive the originator [27]. When pharmacists practice generic substitution, they are not legally required to ask for permission or approval by the prescriber, but patient agreement is necessary [166]. It should be noted though that generic substitution for Narrow Therapeutic Indexed[50] drugs is not permitted [166]. Moreover, according to primary evidence, most private pharmacies have become part of the WASFATY programme, which mainly involves procurement of generic medicines; therefore, the majority of patients who obtain their medication from private pharmacies receive generics [27].

Efforts to increase generic substitution are being made through the national campaign "it is just a name, it is the same" [108]. In addition, a new strategy targeting the private sector has being endorsed but is not implemented yet; this includes the establishment of a national formulary for private insurance under the CCHI to shift towards generics through full or partial replacement of brands with generics [33], [168]. Moreover, it is common that private health insurance companies require pharmacists to perform generic substitution as a means to limit utilisation of originator medicines [108]. In private hospitals, generic substitution is encouraged and controlled through the use of formularies including products which are reimbursed. This effort aims to achieve healthcare savings which can be further used to capitalise profit [33].

Automatic substitution of biosimilars is not permitted in KSA [35]. Guidelines state that pharmacists are not allowed to switch a patient from the original biologic medicine to a

[50] *Defined as drugs for which small differences in blood concentration can cause significant toxicity* [323].

biosimilar product, unless they consult and receive permission from the prescriber, who must first discuss this option with the patient [35], [57]. When both the original biologic and biosimilar are available through tender, it is the physician's choice to prescribe the biosimilar and the pharmacist can only dispense the prescribed option [33]. Moreover, according to primary evidence, it is the decision of the Pharmacy and Therapeutics Committee of each hospital whether existing patients should be switched to biosimilars and/or whether patients newly initiated to treatment should use biosimilars [27]. Pharmacists have substantial impact on updating the formulary; through the Pharmacy and Therapeutics Committee they decide only one option (either the originator or a biosimilar) which will be available on the formulary in the majority of cases [33]. Pharmacists may switch biosimilar products for patients from one manufacturer to a different manufacturer only if they use the same reference product to compare biosimilarity but, in this case, patients should be closely followed up [35].

Incentives for physicians

Currently, there are no financial incentives targeting prescribers in KSA in the public sector [27]. However, some non-financial incentives for physicians are in place. These include the launch of a mobile application by the SFDA [193] called "We care for you", which shows the available generics for each originator and, at the same time, aims to educate prescribers about the quality of generics. Moreover, a generics campaign on social media has been launched, aiming to increase healthcare professionals' awareness [39]. In addition, physicians in the public sector use a centralised electronic prescribing system for prescribing [27]. Finally, government-funded educational programmes are being organised in hospitals for physicians, aiming to educate them on and improve their perceptions of generics [27]. The insurance regulator in the country also organises generics campaigns [27]. Academic initiatives to support the use of generics and biosimilars are also taking place [27].

Regarding incentives to prescribe biosimilar medicines, the MNGHA has implemented a naming strategy policy for biosimilar medicines included in the MNGHA formulary [39]. This policy provides that the brand name is included in addition to the international non-proprietary name of the medicine in the order entry of the computerised prescribing system in order to enable tracking and pharmacovigilance monitoring and to increase trust in these medicines [27], [39]. In addition, the term 'biosimilar' is added next to the name of any biosimilar product in the order entry to indicate its status [27], [39].

Incentives for pharmacists

Beyond allowing pharmacists to practice generic substitution, there are no government incentives in place to encourage pharmacists to dispense generic medicines [27]. Only pharmacists in some chain pharmacies are encouraged to dispense generic medicines through financial deals and discounts available for generics [33]. Pharmacists based in hospital pharmacies reportedly prefer to dispense only what has been prescribed, and are more confident about the quality of medicine when they dispense an originator [314]. Additionally, pharmacists based in hospital pharmacies have been found to be more influenced by prescribers' instructions and they only opt for an alternative when the prescribed medicine is unavailable [314].

There are no payment strategies likely to promote generic dispensing in KSA, as pharmacists receive fixed salaries set by the government [27]. On the contrary, pharmacists prefer to dispense originators as they generally obtain a higher revenue [27]. The profit margin gained from dispensing originators and the effect of marketing by manufacturers of originators are two factors that probably disincentivise community pharmacists from practicing generic dispensing [314].

Pharmaceutical detailing practices

Pharmaceutical detailing practices are common in KSA. Representatives from drug companies visit physicians to inform them about their products. There are reports that physicians are likely to experience more visits from representatives from originator drug companies and are being given significantly more medicine samples, compared to representatives from generic drug companies [182]. However, according to primary evidence, this is a the common practice [33].

Key factors influencing generic substitution by Saudi community pharmacists are advertising and product bonuses offered by pharmaceutical companies, in addition to consumer choice and consumers' demands [189]. Reportedly, 62% of participants in a study evaluating community pharmacists' perspectives and practices concerning generic medicines substitution in KSA, believed that advertisements by the drug companies influence their dispensing patterns [165].

Patient-level policies and behaviours

Patients do not face co-payments in the public sector in KSA [24]. However, according to primary evidence, the use of co-payments is being reviewed by the government and is expected to be introduced. Depending on the individual's monthly income, the beneficiary of the insurance policy may be required to pay a proportion of the cost if they choose to use the originator than the generic medication [33].

As patients are the end-users of medicines, accurate knowledge and positive perceptions towards generics and biosimilars are likely to increase the acceptance and facilitate the use of these products [126]. In KSA, efforts to build trust in generic medicines and promote their use by patients are made by the SFDA, several insurance companies and local manufacturers [27]. These efforts usually take the form of campaigns on social media.

Appendix 4: Overview of clinical study requirements for biosimilars across global regions

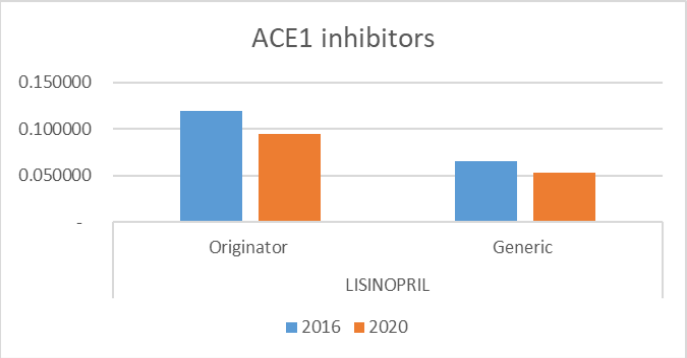
	Efficacy studies	Safety studies	Immunogenicity studies
EU			
General biosimilars	usually required	Adequate safety studies required	Required, normally in humans
Insulin-specific	No anticipated need for specific clinical efficacy studies	Confirm safety comparability	Required, including in people with T1DM, as well as for ≥12 months
Egypt			
General biosimilars	Required, basic guidance on suitable studies given	Required; basic guidance on suitable studies given	Should be conducted pre- and post-authorisation; specific guidance not given
KSA			
General biosimilars	Comparative studies required for general biosimilars; advice on study design and selection given Not required for insulin biosimilars provided that clinical comparability can be concluded from PK and PD data	Not specified	Rationale for proposed immunogenicity testing should be presented; guidance on study design and selection given Required for biosimilar insulins; basic guidance given on study design
Insulin-specific	No anticipated need for specific clinical efficacy studies	Confirm safety comparability	Comparative study (duration ≥12 months) required to evaluate immunogenicity
Source:	Adapted from Table 3 "overview of clinical study requirements for biosimilars across global regions" [35].		
Abbreviations:	EU: European Union; KSA: Kingdom of Saudi Arabia; PD: Pharmacodynamic; PK: Pharmacokinetic; RCT: Randomised controlled trial; T1DM: Type 1 diabetes mellitus		

Appendix 5: Simulation exercise results

Abbreviations used: Angiotensin converting enzyme (ACE), angiotensin receptor blockers (ARBs), proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs)

Figure 1: Originator vs generic prices by product class in Egypt (2016-2020)

A.



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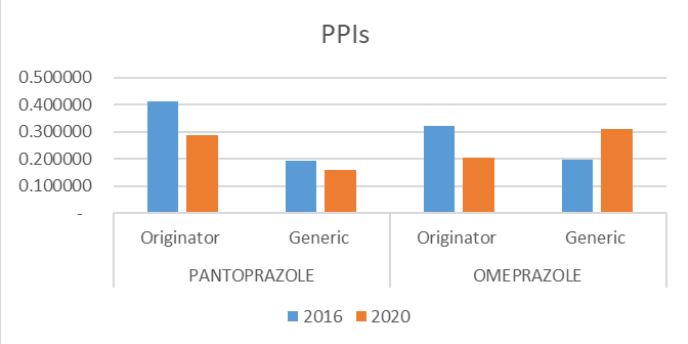

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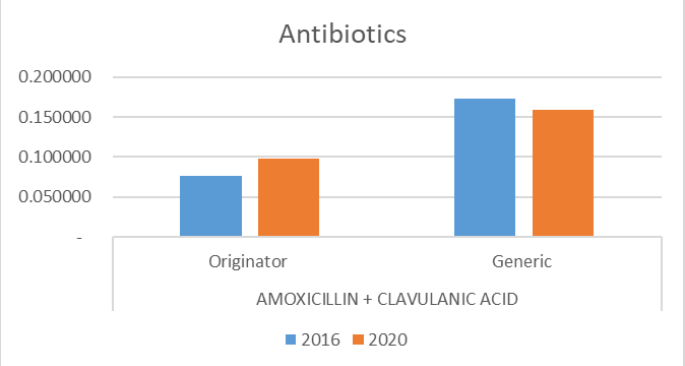

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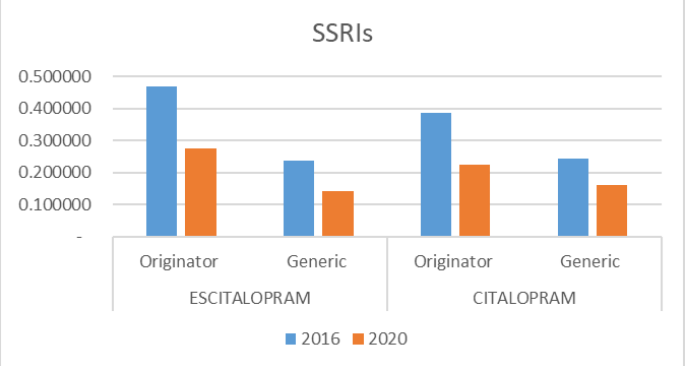

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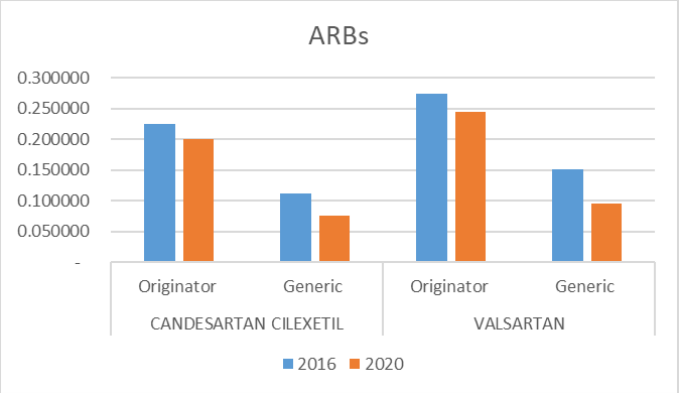

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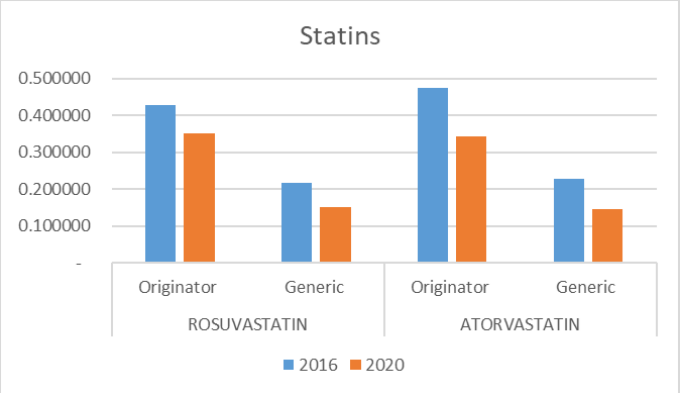
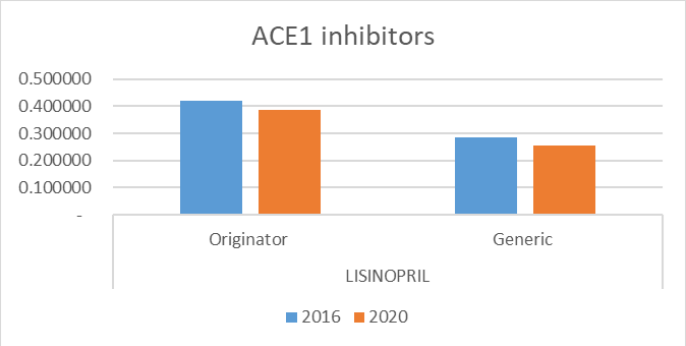


Figure 2: Originator vs generic prices by product class in KSA (2016-2020)

A.



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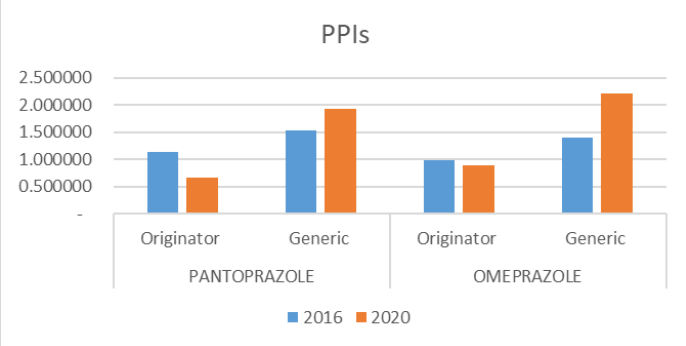

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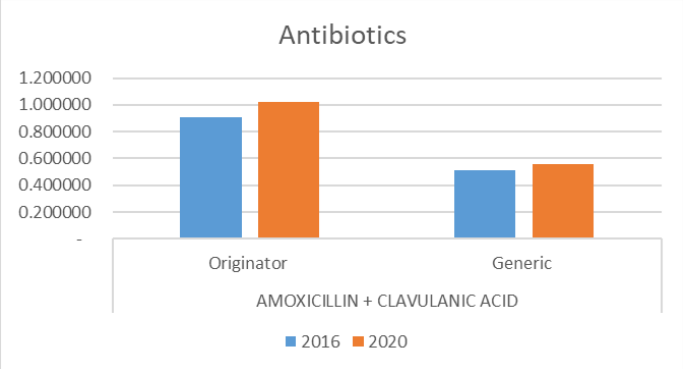

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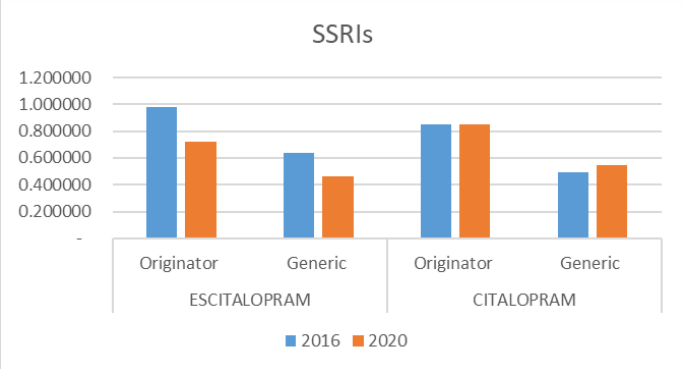

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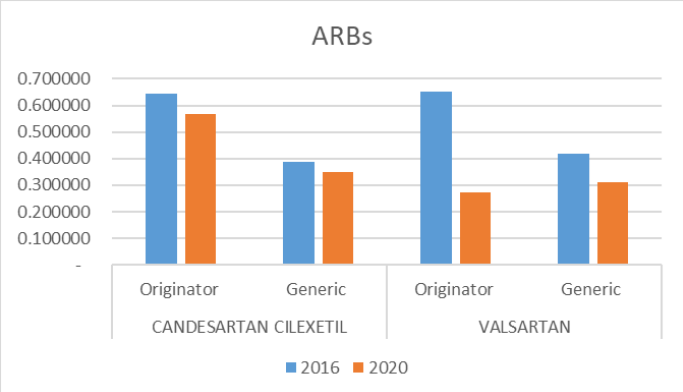

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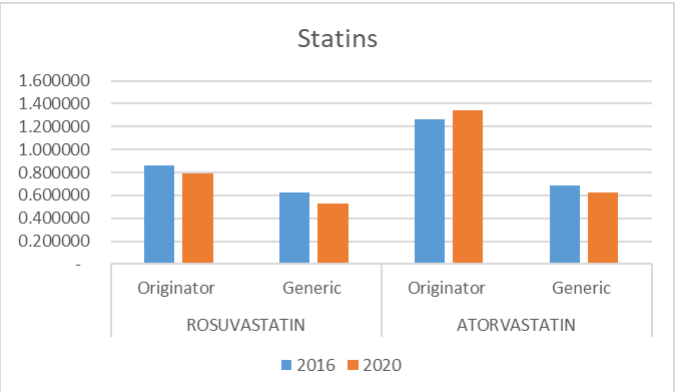
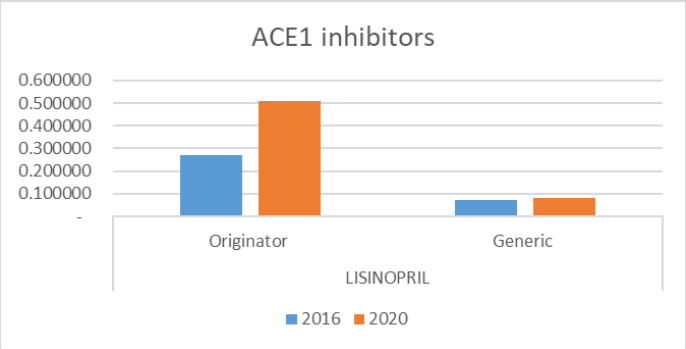


Figure 3: Originator vs generic prices by product class in the United Kingdom (2016-2020)

A.



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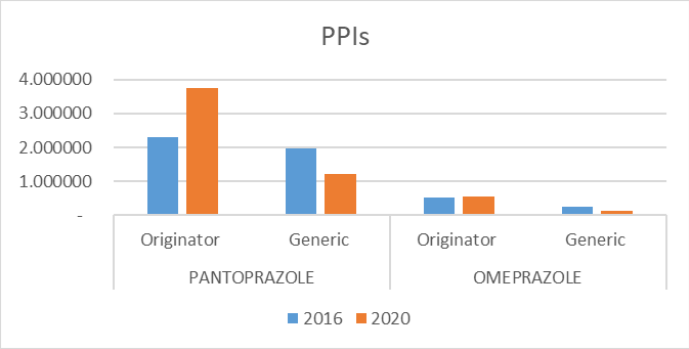

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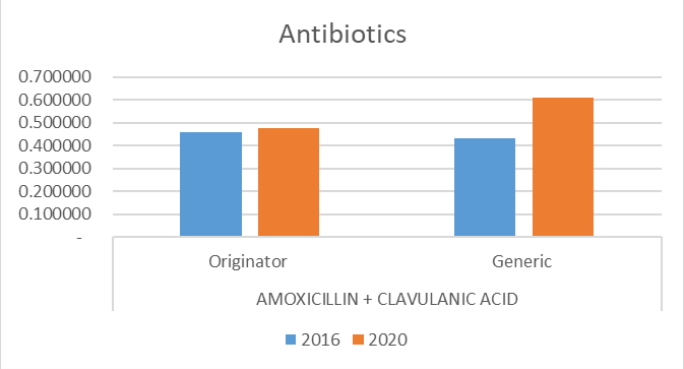

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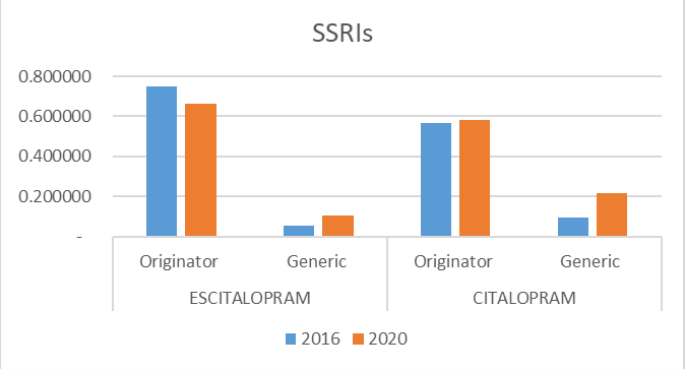

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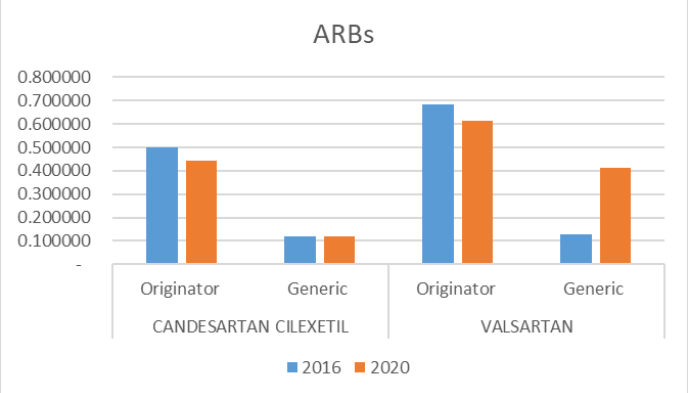

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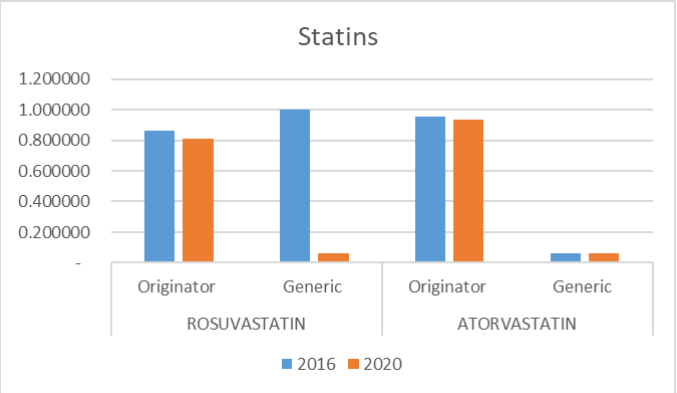
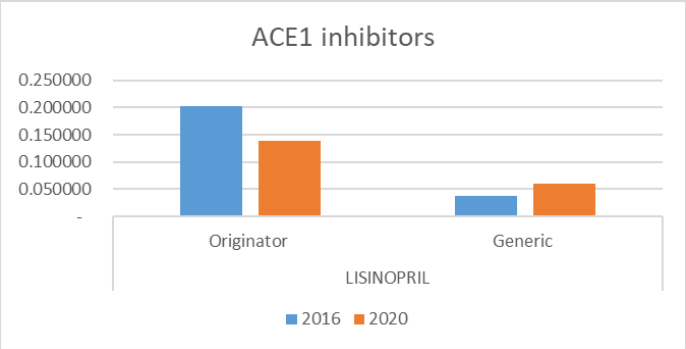


Figure 4: Originator vs generic prices by product class in the Netherlands (2016-2020)

A.



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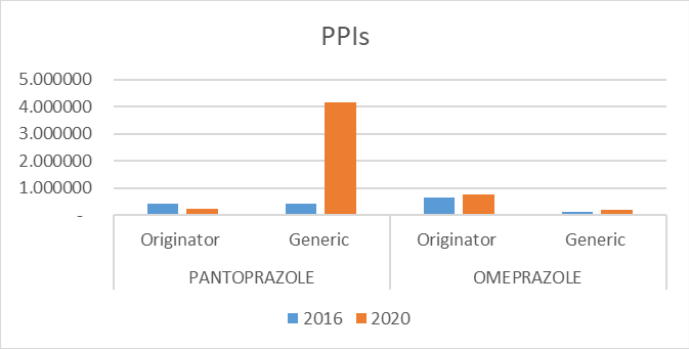

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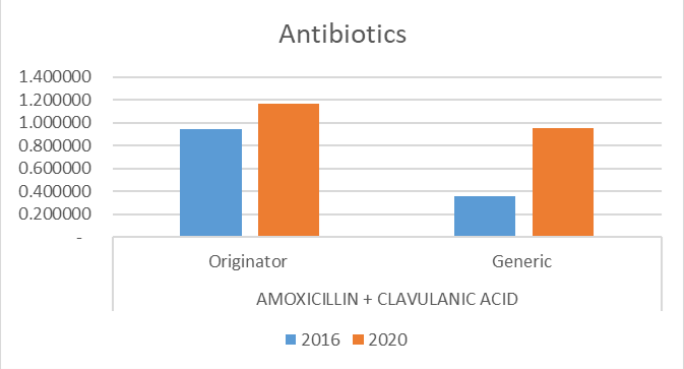

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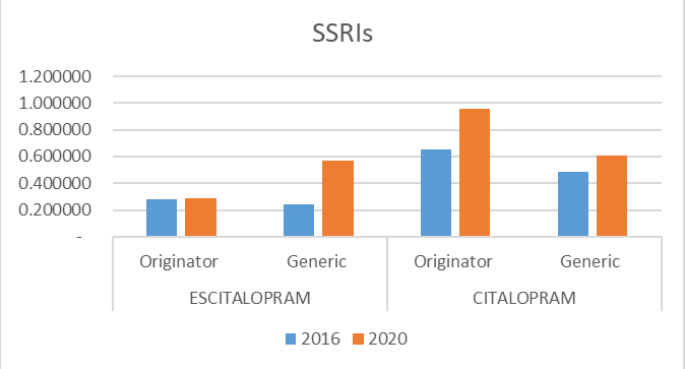

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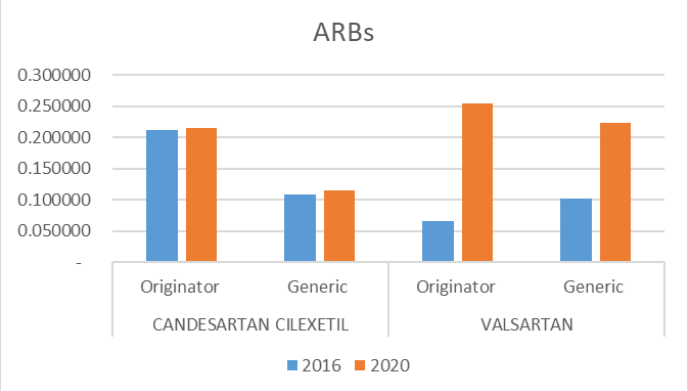

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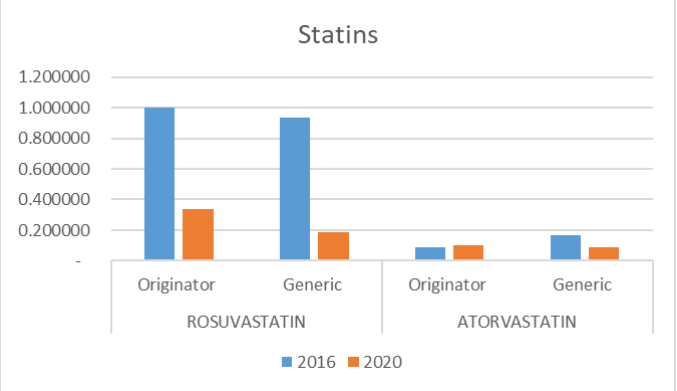
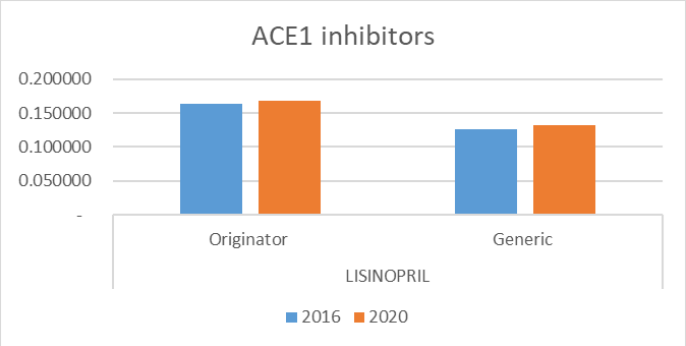


Figure 5: Originator vs generic prices by product class in Spain (2016-2020)

A.



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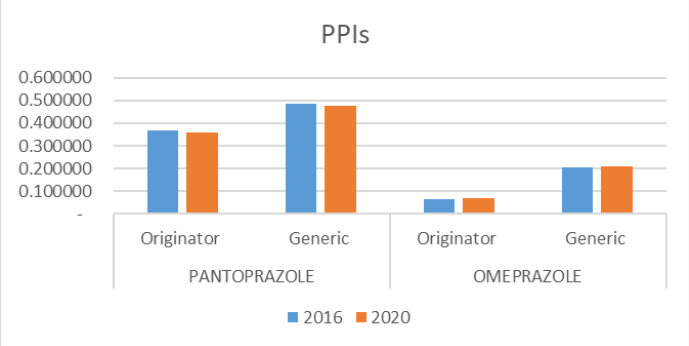

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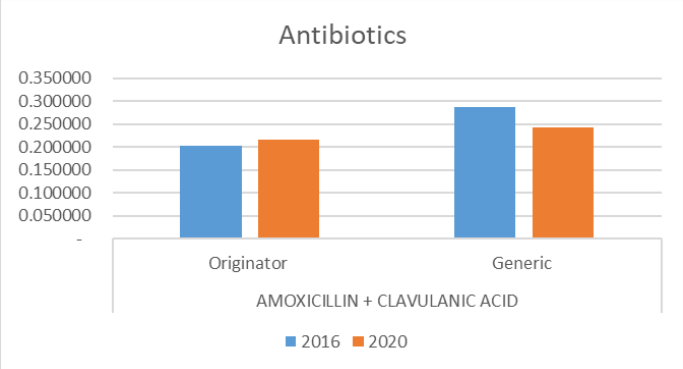

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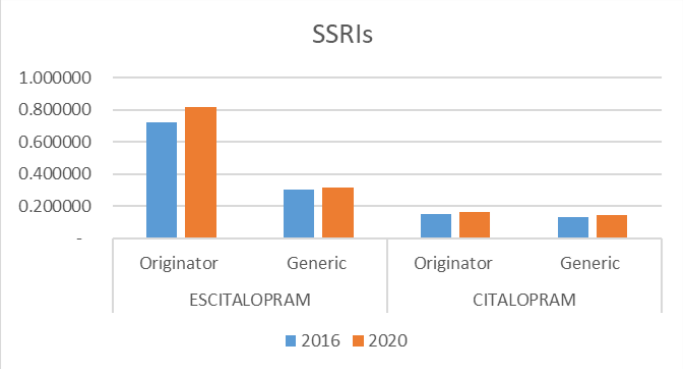

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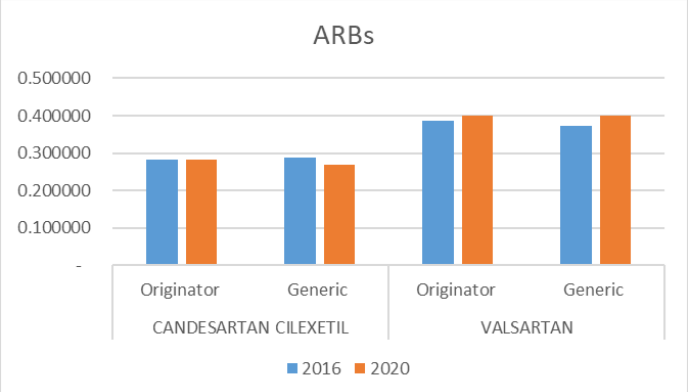

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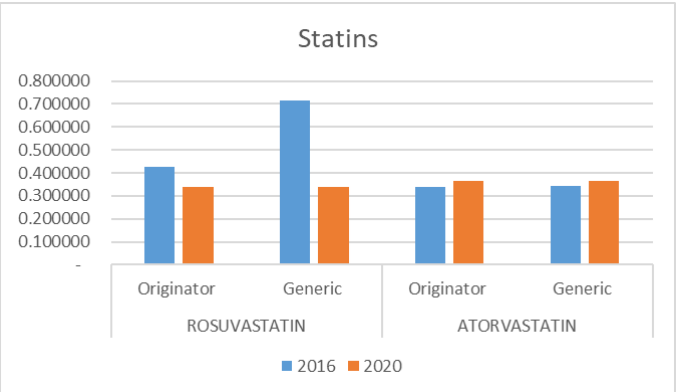
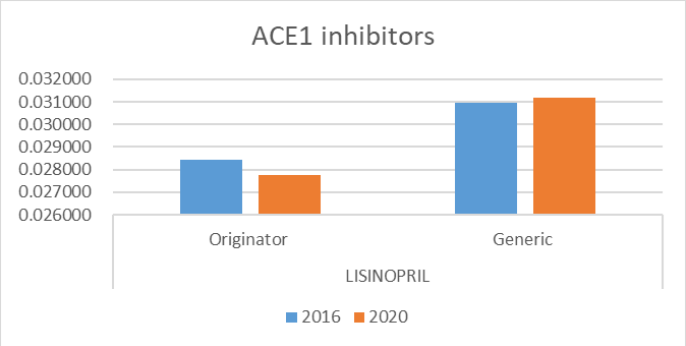


Figure 6: Originator vs generic prices by product class in Germany (2016-2020)

A.



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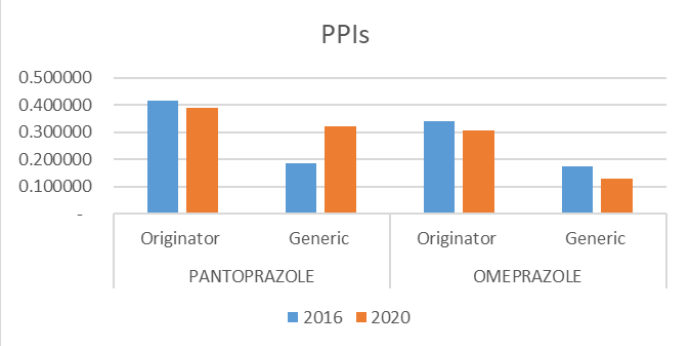

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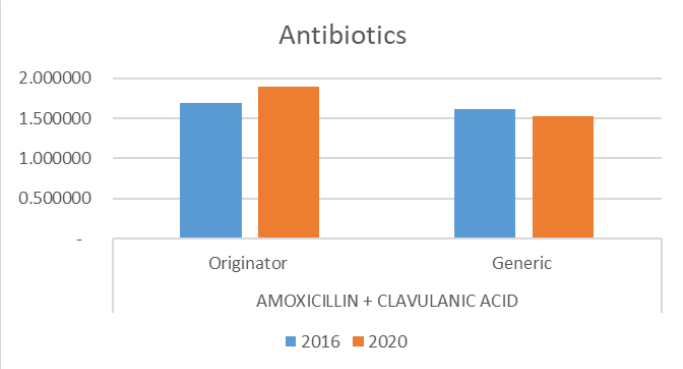

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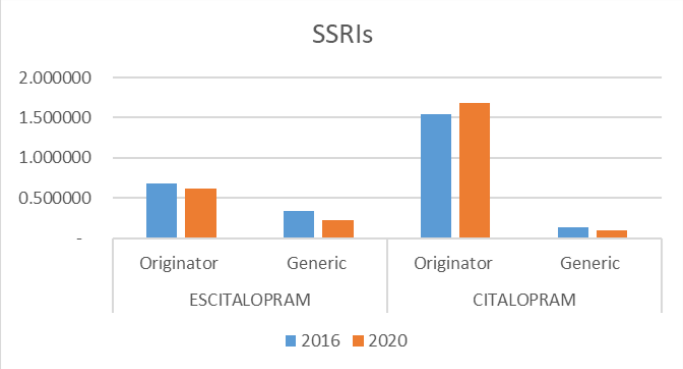

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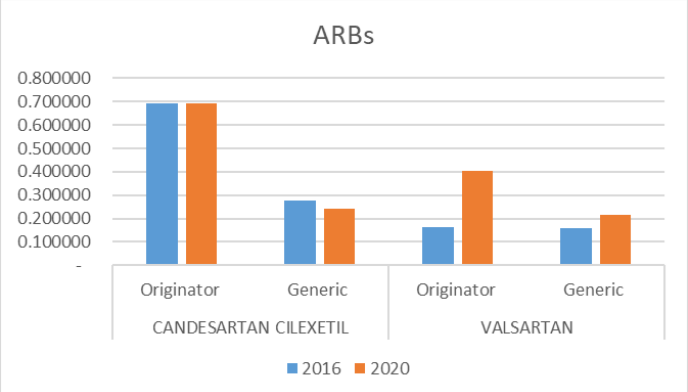

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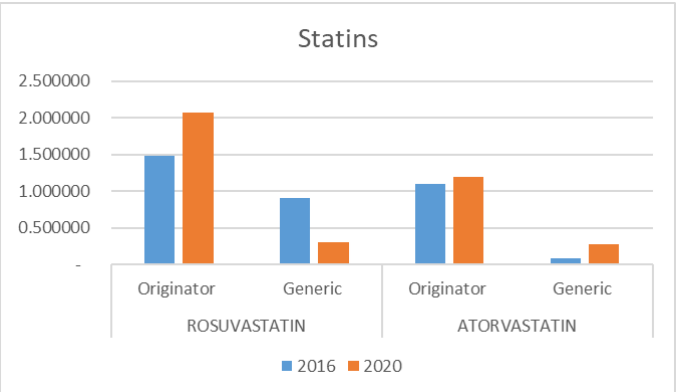

Figure 7: Originator vs generic prices of cancer drugs by country (2016-2020)

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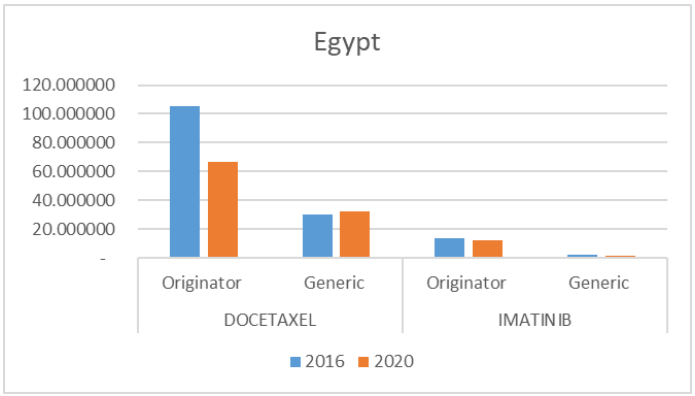

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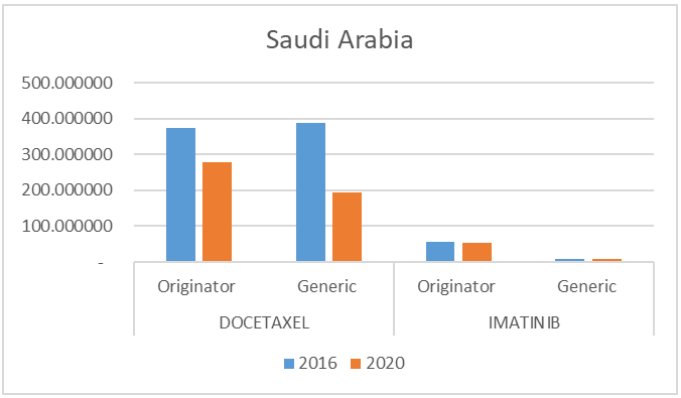

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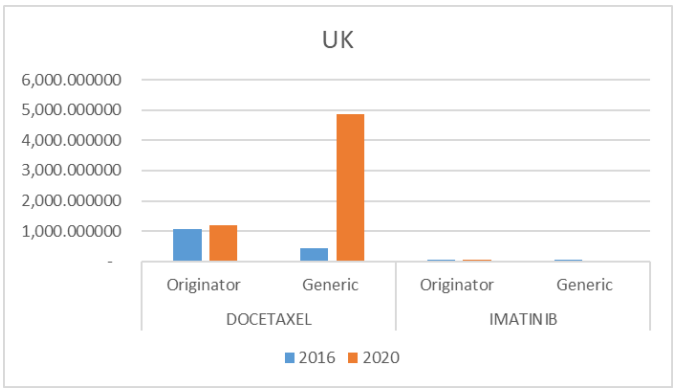
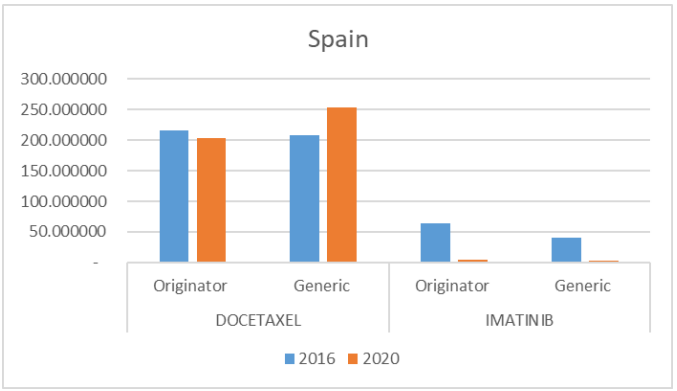


D.



E.

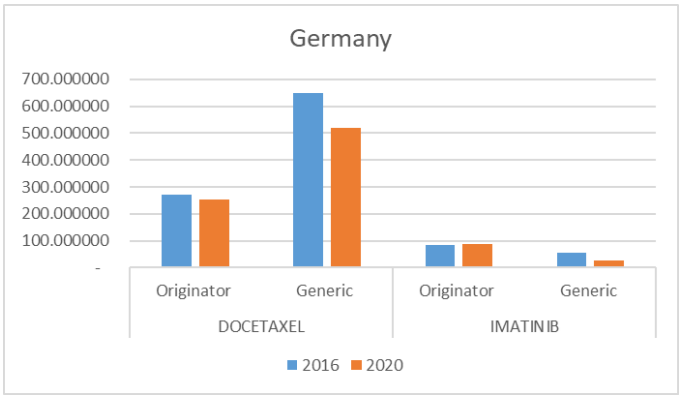
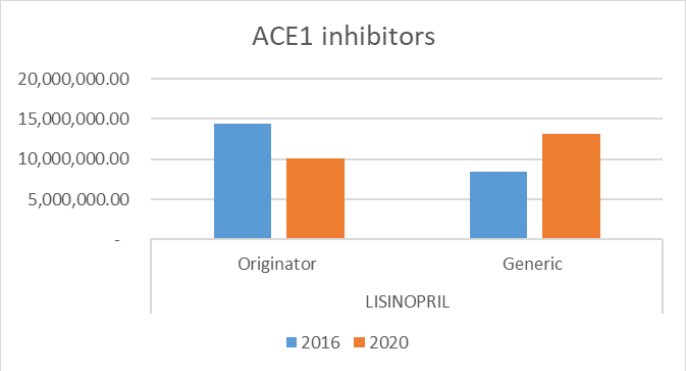
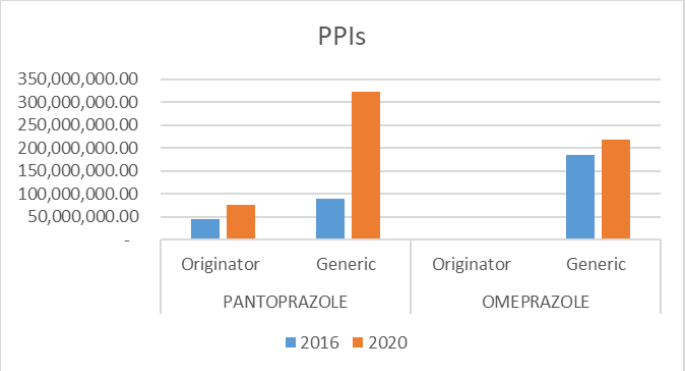


Figure 8: Originator vs generic volumes (SU sold) by product class in Egypt (2016-2020)

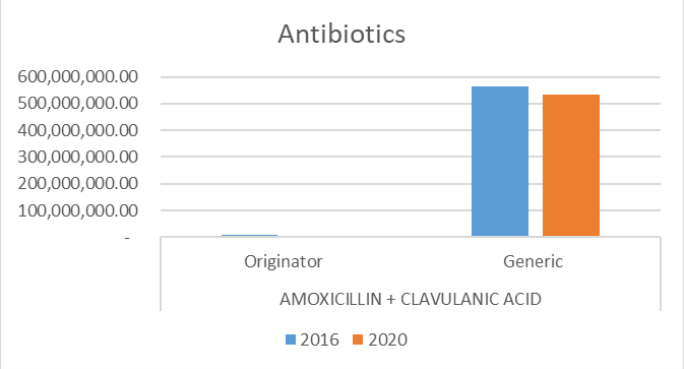
A.



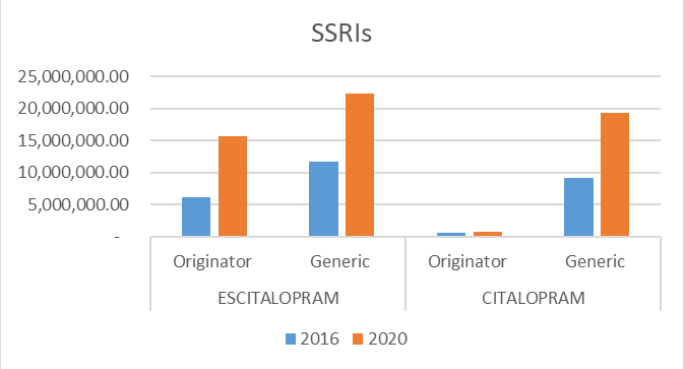
B.



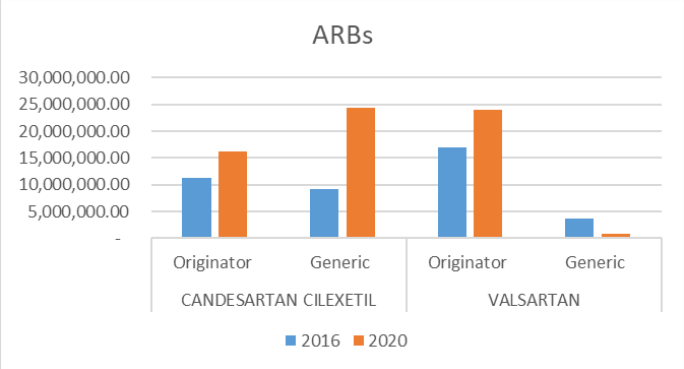
C.



D.



E.



F.

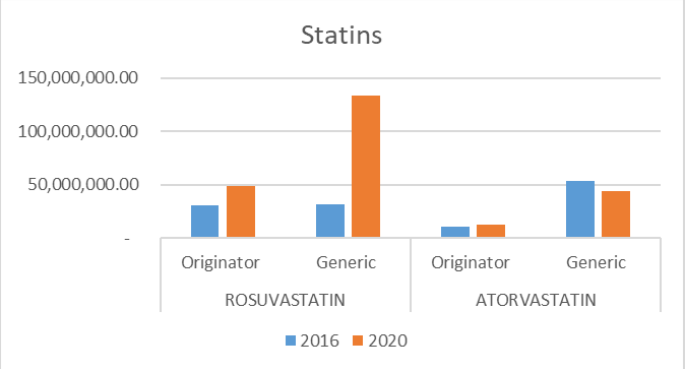
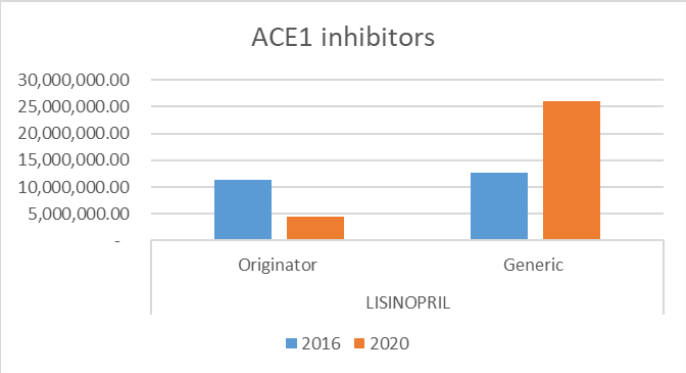
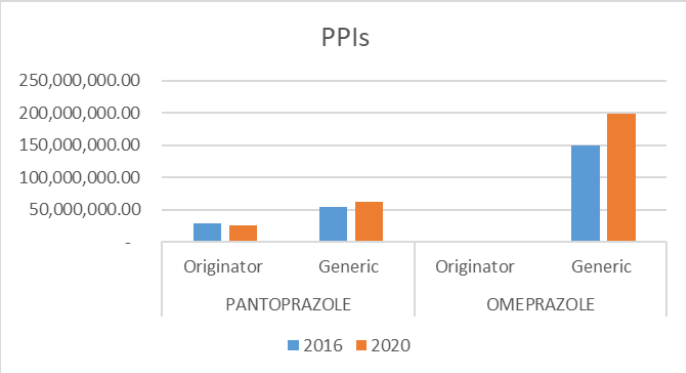


Figure 9: Originator vs generic volumes (SU sold) by product class in KSA (2016-2020)

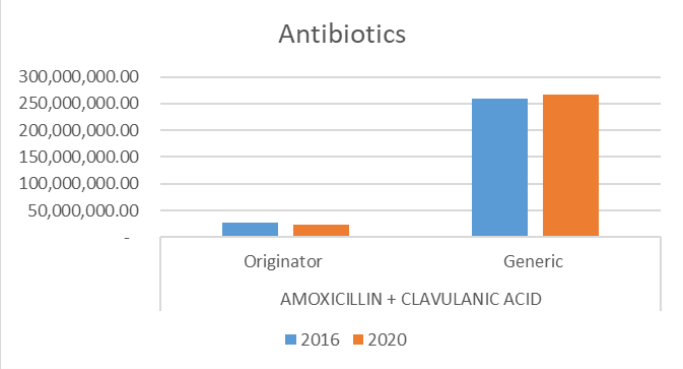
A.



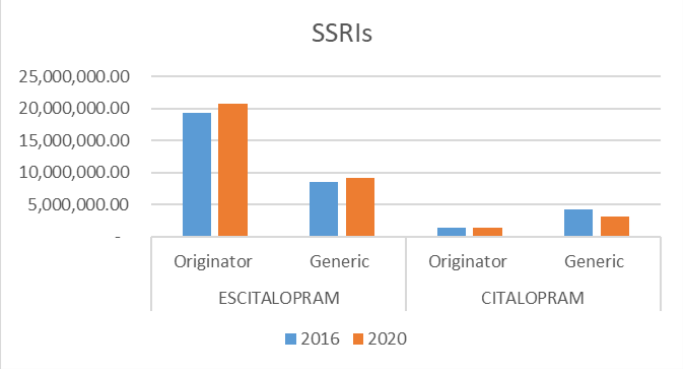
B.



C.



D.



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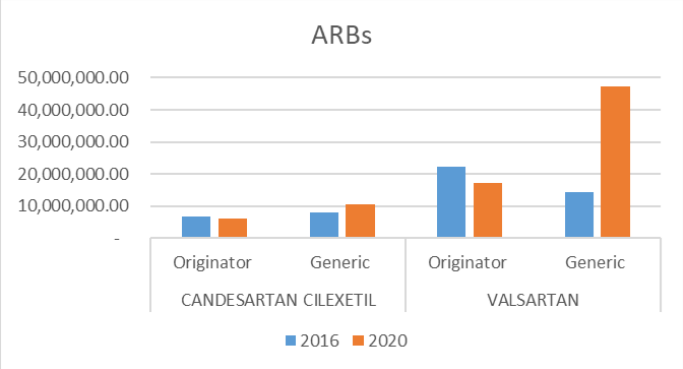


F.

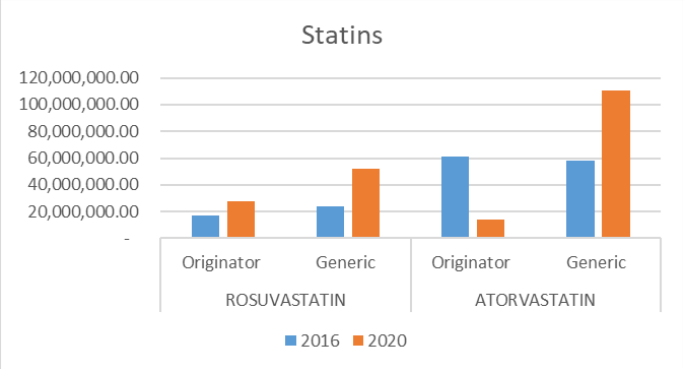
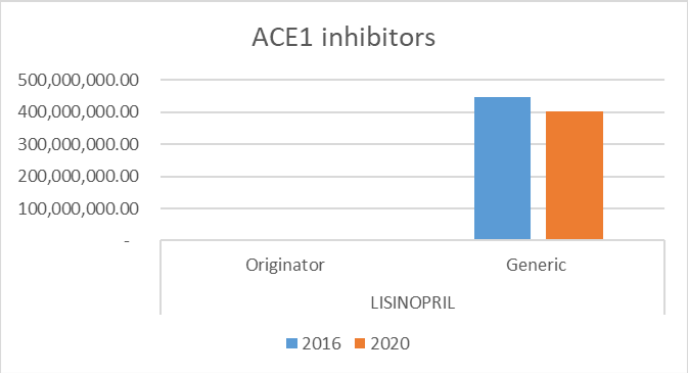
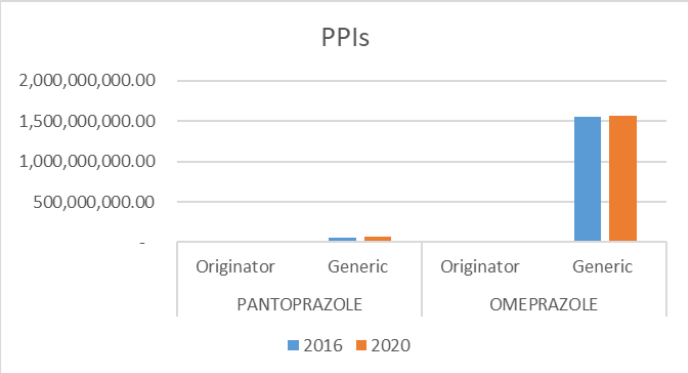


Figure 10: Originator vs generic volumes (SU sold) by product class in the United Kingdom (2016-2020)

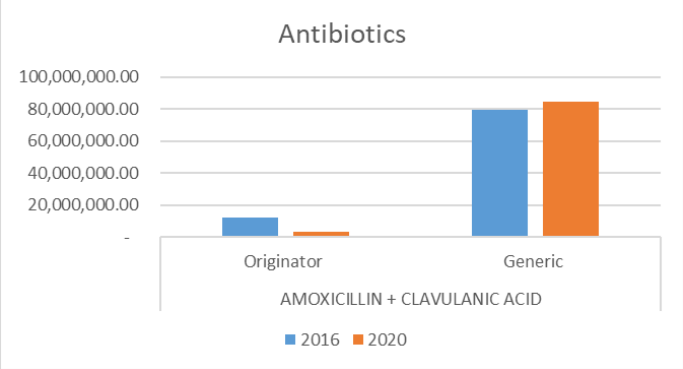
A.



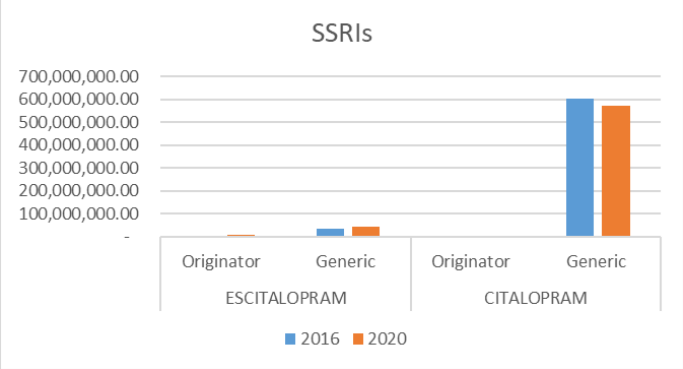
B.



C.



D.



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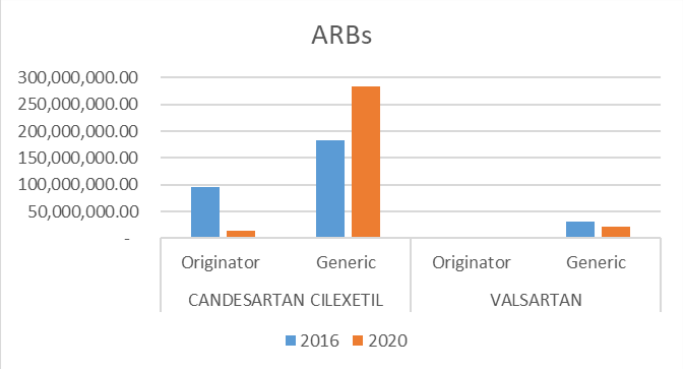

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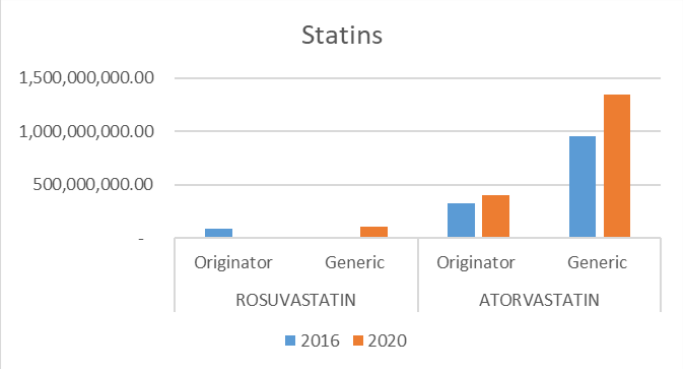
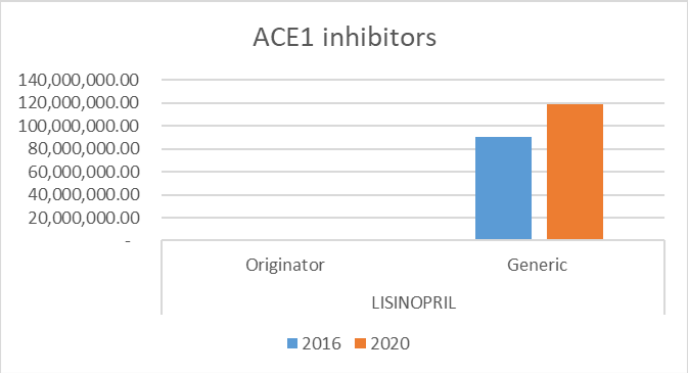
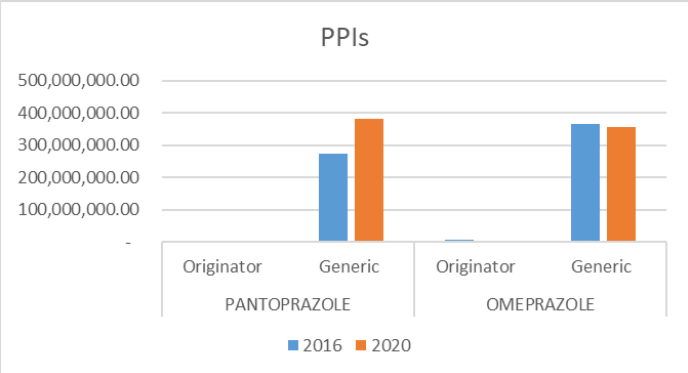


Figure 11: Originator vs generic volumes (SU sold) by product class in the Netherlands (2016-2020)

A.



B.



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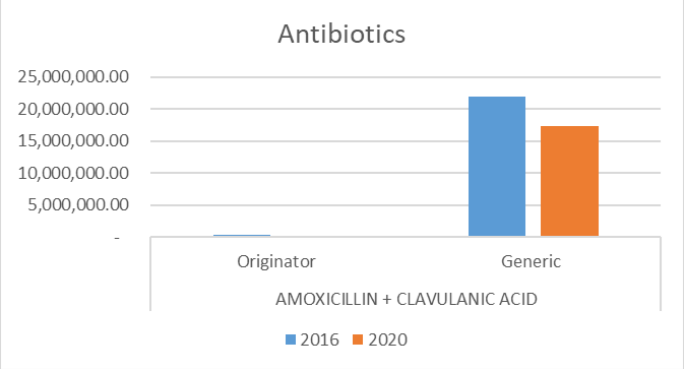

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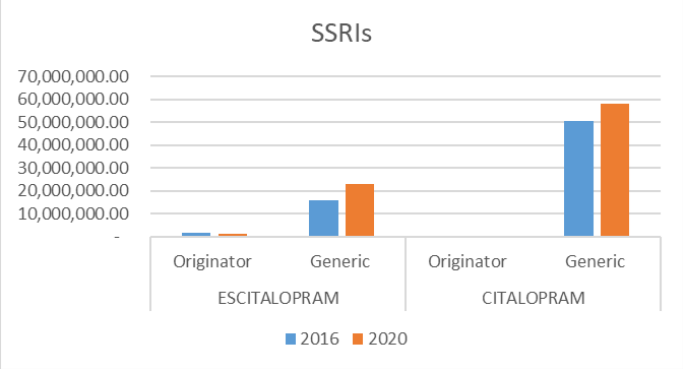

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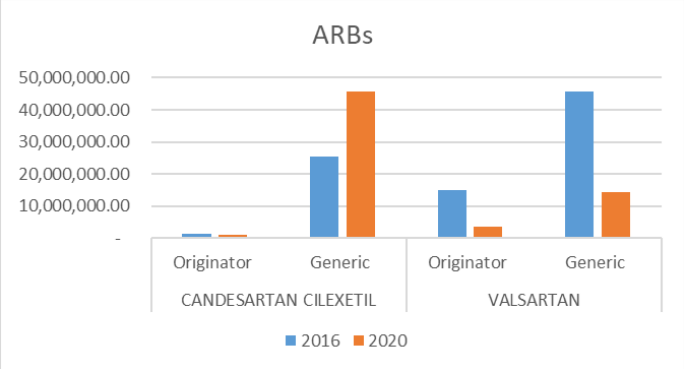

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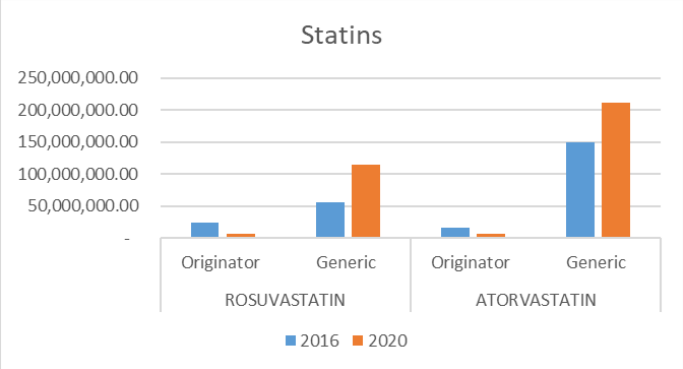
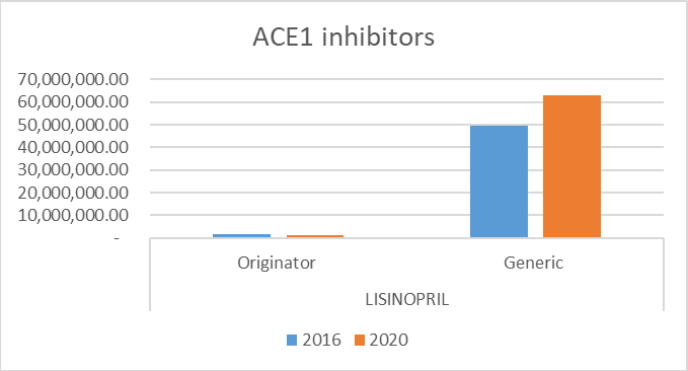
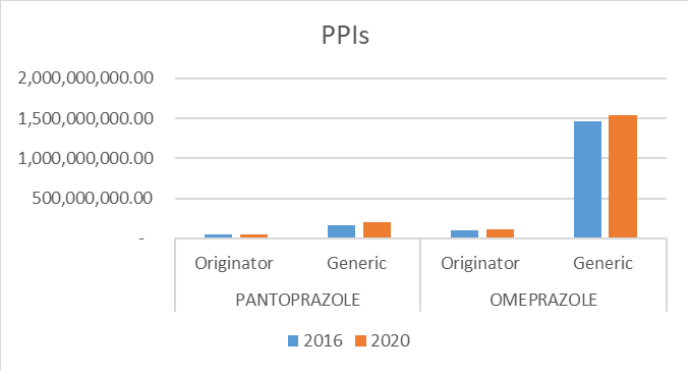


Figure 12: Originator vs generic volumes (SU sold) by product class in Spain (2016-2020)

A.



B.



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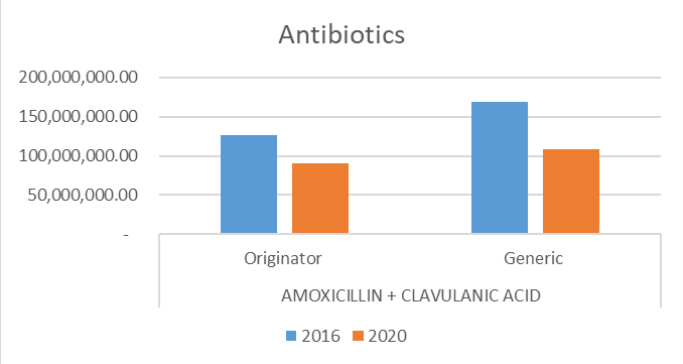
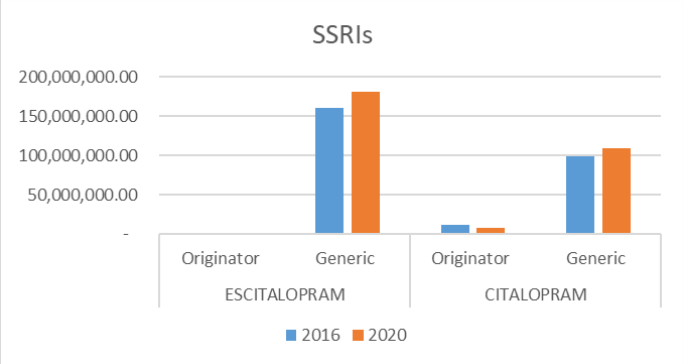


D.



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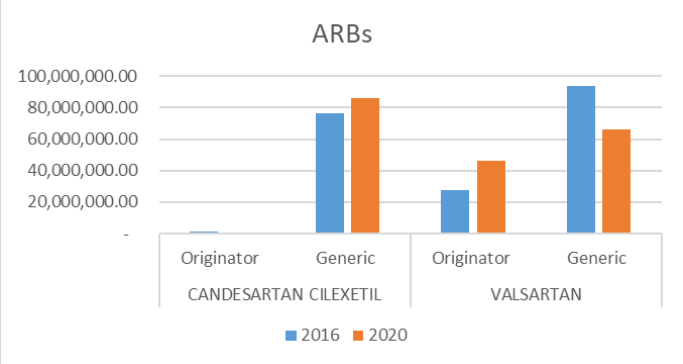

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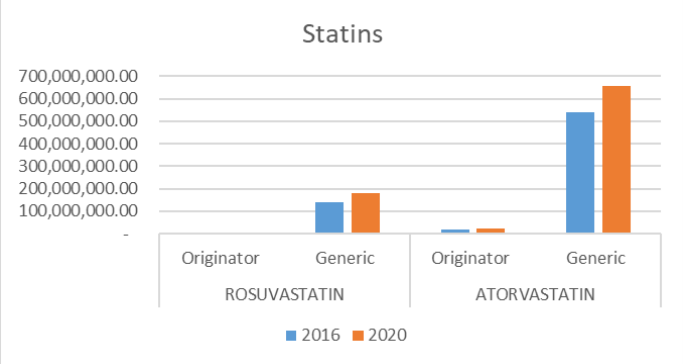
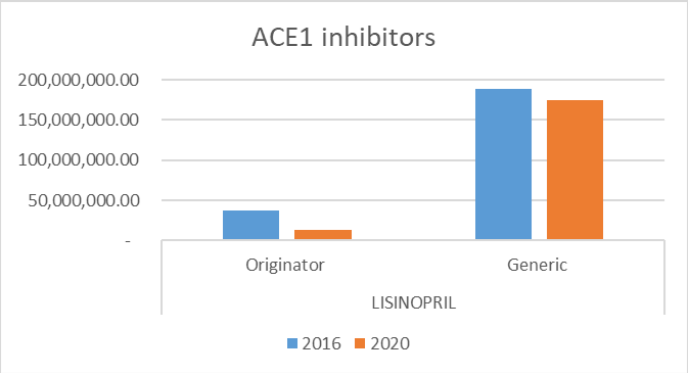
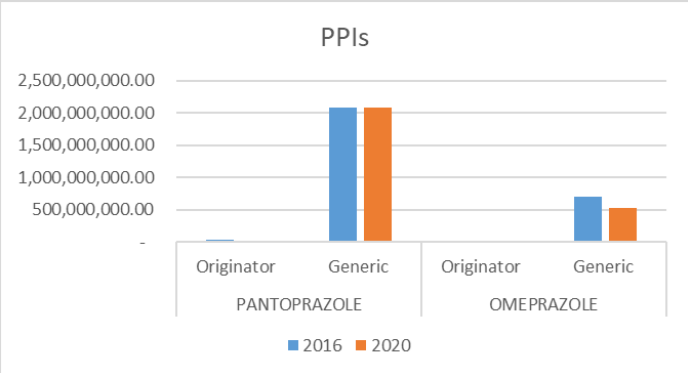


Figure 13: Originator vs generic volumes (SU sold) by product class in Germany (2016-2020)

A.



B.



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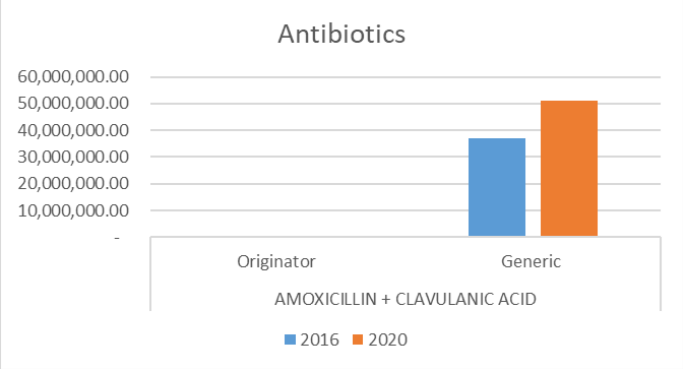

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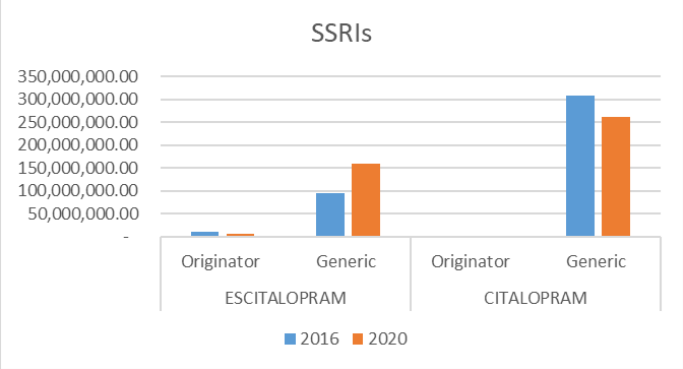

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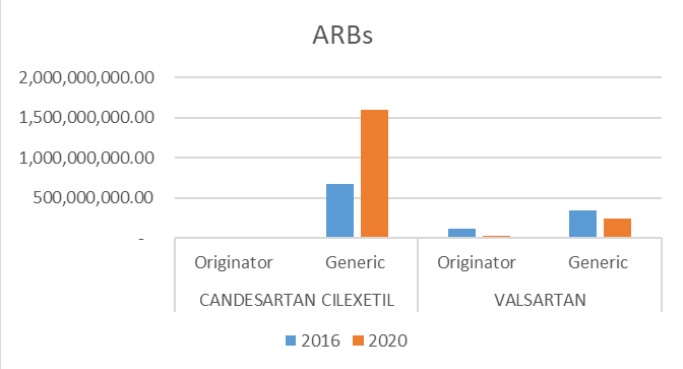

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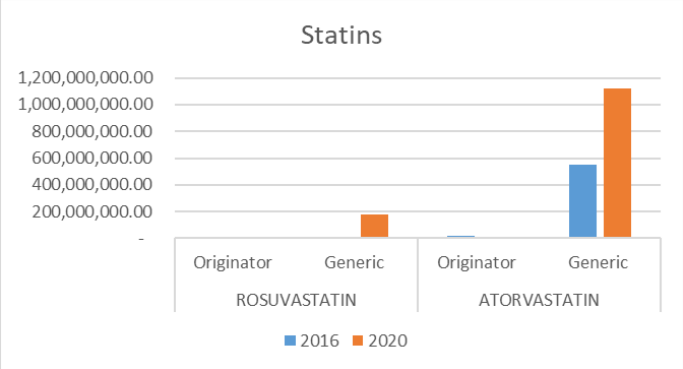
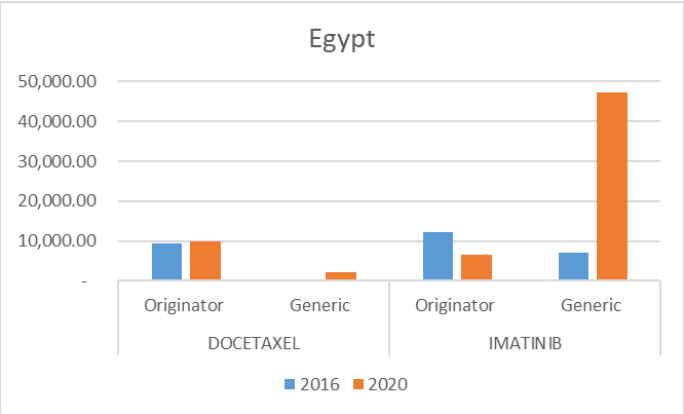
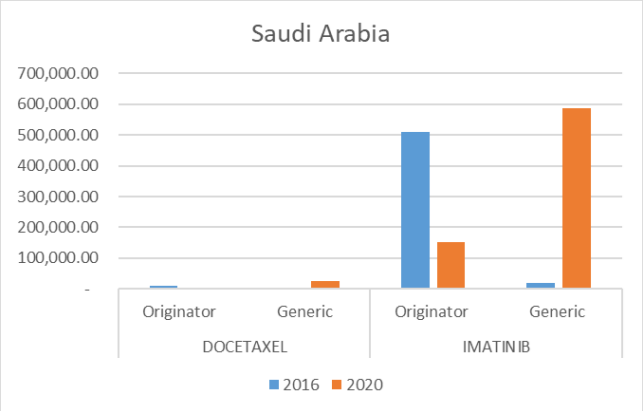


Figure 14: Originator vs generic volumes (SU sold) of cancer drugs by country (2016-2020)

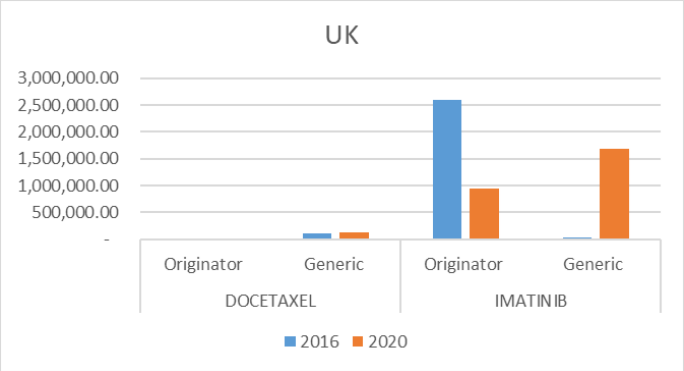
A.



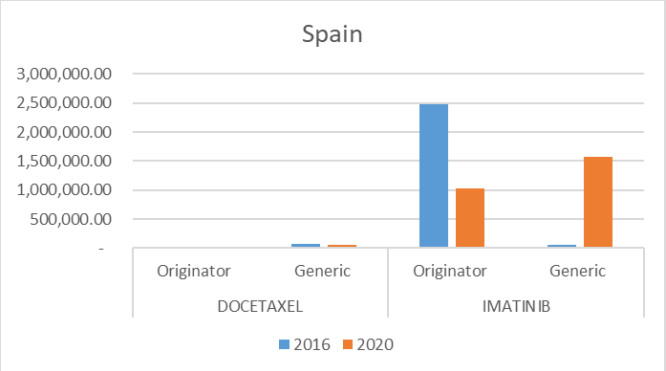
B.



C.



D.



E.