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NEW REGULATION AND GENERIC MEDICINE SHORTAGES: IMPACT AND SOLUTIONS

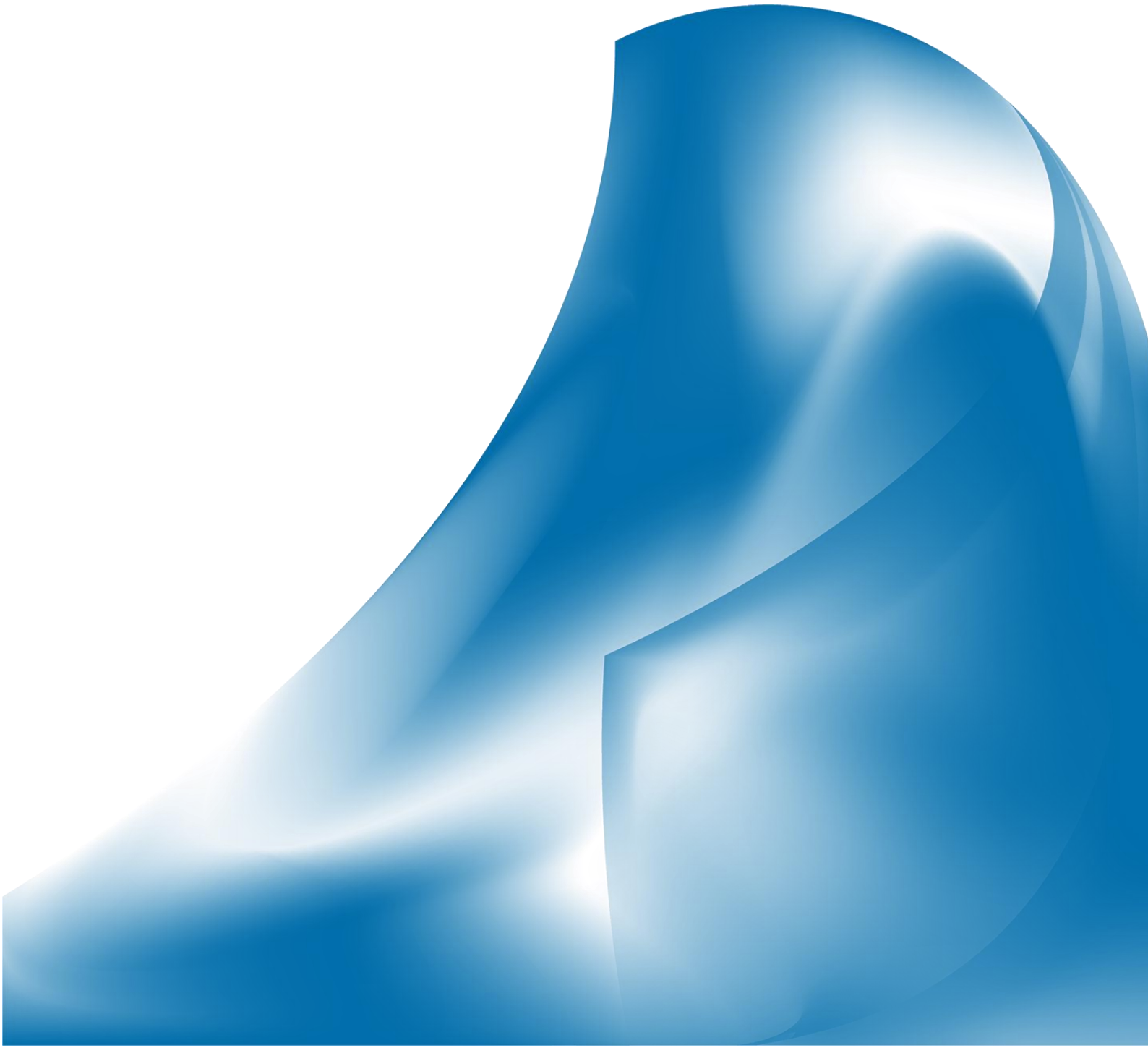

Table of Contents

EXECUTIVE SUMMARY

Background to the study

The pharmaceutical market contributes to the health and well-being of European citizens. The medicines provided are highly important for treating patients and improving their quality of life. Within the pharmaceutical sector, generic medicines account for 67% of dispensed medicines and 29% of pharmaceutical expenditure at list prices, in Europe in 2018.

The pharmaceutical sector is one of the most highly regulated industries, with regulation affecting all parts of the development, production, distribution, commercialization and utilization process of pharmaceuticals to ensure effective access to safe medicines.

New legislation and regulations are continuously being developed in Europe. While new laws and regulations have specific policy goals, they often also come with unintended side-effects that may impact the pharmaceutical sector's ability to ensure affordable and timely supply of medicines. A major bottleneck arises if industry is unable to absorb or pass-through the operational cost increases caused by new regulation.

In Europe, pricing is regulated and there are limitations to the ability to adjust pricing of medicines to account for increased operational costs. The intention of regulating pricing is to protect patients' access to medicine and manage public health budgets. Access to generic medicines is essential for that purpose. At the same time, market-authorization holders (MAHs) of generic medicines, are particularly vulnerable to the combined effect of increased cost due to new regulations, incremental price reductions and price cutting measures, strong competition and price regulation that in most cases doesn't allow increases in the price of pharmaceuticals, even if there is an increase in operational costs.

These circumstances can lead to some product margins becoming negative and these medicines no longer being marketed. Negative societal impact of medicines not brought to market is an increased risk of supply shortages, which have already been recurrent in Europe in the past few years. That makes it especially relevant to explore possible solutions to reduce the risk of negative impact from new regulation on the reliable supply of affordable and high-quality medicine.

In this research, we assess the potential unintended impacts of regulation on generic medicines and identify new flanking measures that may provide a solution for the additional supply risk caused by cost increases driven from new regulation. The aim of this research is to develop possible policy solutions to ensure the stable supply of high-quality, safe and affordable prescription medicines for human usage.

Findings of the study

Regulatory initiatives include both initiatives specifically targeted at the pharmaceutical industry, such as the Falsified Medicines Directive, and initiatives that have an impact on the pharmaceutical industry but are not specifically targeted at this industry, like the EC's New Green Deal.

Regulations impose obligations on producers and MAHs, leading to cost increases. We distinguish four categories of compliance costs:

- Monetary costs – direct payments to government;
- Production costs – cost related to adjustment of the production line;
- R&D costs – cost related to the need for new R&D to meet new regulatory obligations;
- Labour costs – cost related to time spent by employees to ensure compliance.

To examine the potential impact of regulation-based cost increases, a stylized business model for a MAH was developed with individual contribution margins for product lines. In this modelled situation, using actual data from MAHs, almost half of the product lines have good profitable (>10%) margins, a quarter has fair profitable (5-10%) margins, while the remaining quarter has low profitable (0-5%) margins, see figure 1, 'original situation'. Product lines with good profitable (>10%) margins might help to subsidize production of product lines with low profitability during a period of time, but it's not sustainable in the long-term to keep these product lines active.

To illustrate the potential unintended negative impact on availability of medicines due to regulation, the cost of an urban wastewater treatment fee is analysed. The introduction of this fee may be a potential interpretation of the Extended Producer Responsibility, relevant under the Pharmaceuticals in the Environment initiative. Cost assumptions were based on real-world findings from Swedish wastewater treatment plants; the cost of implementing techniques for advanced purification of drug residues was found to vary widely, but to be in the range of 0.5% to 4.5% of the total expenditure on pharmaceuticals.

Allocation of the costs of the advanced purification techniques solely to the MAHs may, in the worst case, lead to up to 24% of the product lines falling below the cost of production, as illustrated by figure 1, posing challenges to MAHs' ability to continue marketing the products.

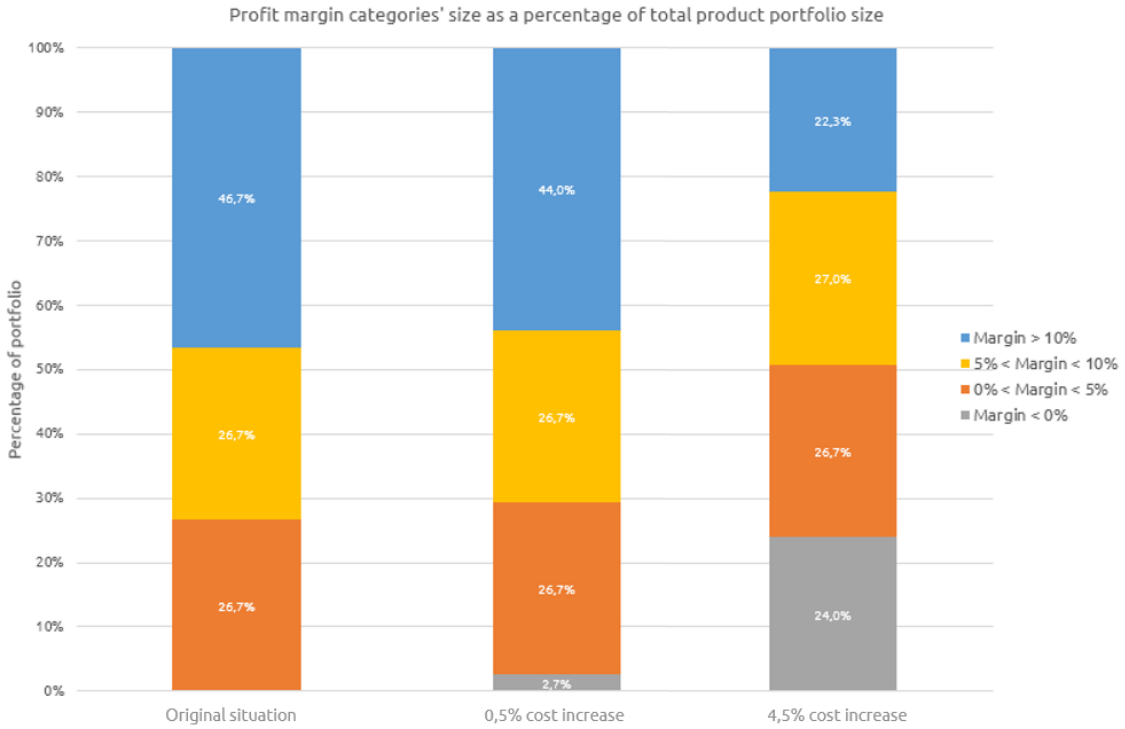

Figure 1: Impact of 0.5% (middle) and 4.5% (right) cost increase compared to the basic situation (left)

To mitigate the unintended negative impact of regulation on availability of medicines, a wide range of policy measures is available for consideration. This study focuses on measures ('financing models') addressing the impact on medicines. Comparing financing models in terms of effectiveness (the extent to which the solution reduces supply shortages risks), and feasibility (the expected acceptability of the solution), led to four promising financing models for consideration in the European market context:

1. One-In-One-Out (alleviate other obligations) – balance cost increases of new regulation by eliminating existing regulation, leading to a net zero cost effect. New regulation can also be introduced to create efficiency and reduce costs of business, like introduction of e-leaflets, replacing the need for paper leaflets in the medicine boxes;

2. Cost allocation model – allocation of regulatory compliance cost increases to different stakeholders in the supply chain according with their responsibility in the process. One example is through a Green Fee that would allocate part of the environmental regulation implementation cost to patients in line with the Polluter Pays Principle.

3. Tax credits for marketing at-risk medicines and/or implementation of new regulation – incentivise MAHs to market at-risk medicines (medicines with near negative or negative margin levels), by offering tax credits to continue marketing these medicines. New regulation can also be implemented with the aid of tax credits, if aligned with the political agenda, such as for the European Green Deal.

4. Guaranteed fee – setting price levels for at-risk medicines and indexation of these fee in line with cost changes in order to ensure a minimum positive margin on the product line, and thus sustained marketability.

Based on assessment of effectiveness and feasibility, the most preferred financing model is the OIOO model, where all the benefits of maintained supply of medicines are achieved without any major financial drawback. Hence, wide support for this financing model is expected to be likely. The main restriction is the decision on the present regulations that can be withdrawn to compensate the impact of new regulation.

The cost allocation model, as exemplified by the Green Fee, is the next-best alternative. In addition to a high level of fairness (Polluter Pays Principle), a cost allocation model such as a Green Fee puts the economic incentives for behaviour change at the level of highest control over the action - in the case of the Green Fee, entry of pharmaceuticals to the environment from human and animal excretion, which is by far the main driver of pharmaceuticals entering the environment.[1]

With tax credits, the government uses financial means to support the marketing of at-risk medicines, guaranteeing supply financed from general means. Like the previous solutions, this system is effective in addressing the risk of supply, albeit against expected higher execution costs than OIOO and the cost allocation model.

The system of a guaranteed fee, like already exists for pharmacy and wholesaler dispensing services, would guarantee that product would remain viable and available for patients. Alternatively, a tiered-pricing system, like in Canada, adjusts the level of mandatory discount of generic medicines to the number of competitors in the market, creating space for sustainable competition.

It should be noted that these alternatives are also complementary, meaning multiple models may be used in parallel to offset supply risk.

About the study

This study was commissioned to Capgemini by Mylan. Any views or opinions expressed are solely those of the authors. The analysis, conclusions and recommendations have all been developed independently and neither Capgemini nor any of the authors has a financial interest in the results of the study. The study was conducted between December 2019 and July 2020.

[1] This report does not seek to review the current regulation for pharmaceuticals, but to advise on minimizing impact of new regulation.

1. BACKGROUND TO THE STUDY

1.1. THE PHARMACEUTICAL MARKET

The pharmaceutical market contributes to the health and well-being of European citizens. The medicines produced are highly important for treating and healing patients or improving their quality of life. The European pharmaceutical market is the second largest global pharmaceutical market after the United States, with sales of €183bn in 2018 [1]. The pharmaceutical market value includes the remuneration of all supply chain actors, like wholesalers and pharmacies In 2018, the European pharmaceutical industry was directly responsible for 765.000 jobs, and additionally generated about four times more indirect jobs [2]. Additionally, the research-based pharmaceutical industry is a key asset of the European economy, having the highest percentage of R&D spending to net sales in comparison to all other European sectors [2] [3].

The value chains

The pharmaceutical market consists of numerous stakeholders, such as pharmaceutical producers, market-authorization holders (MAHs), wholesalers, pharmacies and the patients who use the medicines. The interlinkage of all stakeholders is depicted in figure 2 below. The normal arrows represent the flows of medicines. The dotted arrows represent money flows, with government and health insurance expenditure flowing through the entire value chain, and the broken arrows display other relations between the market stakeholders. The government interacts with all stakeholders displayed in the figure.

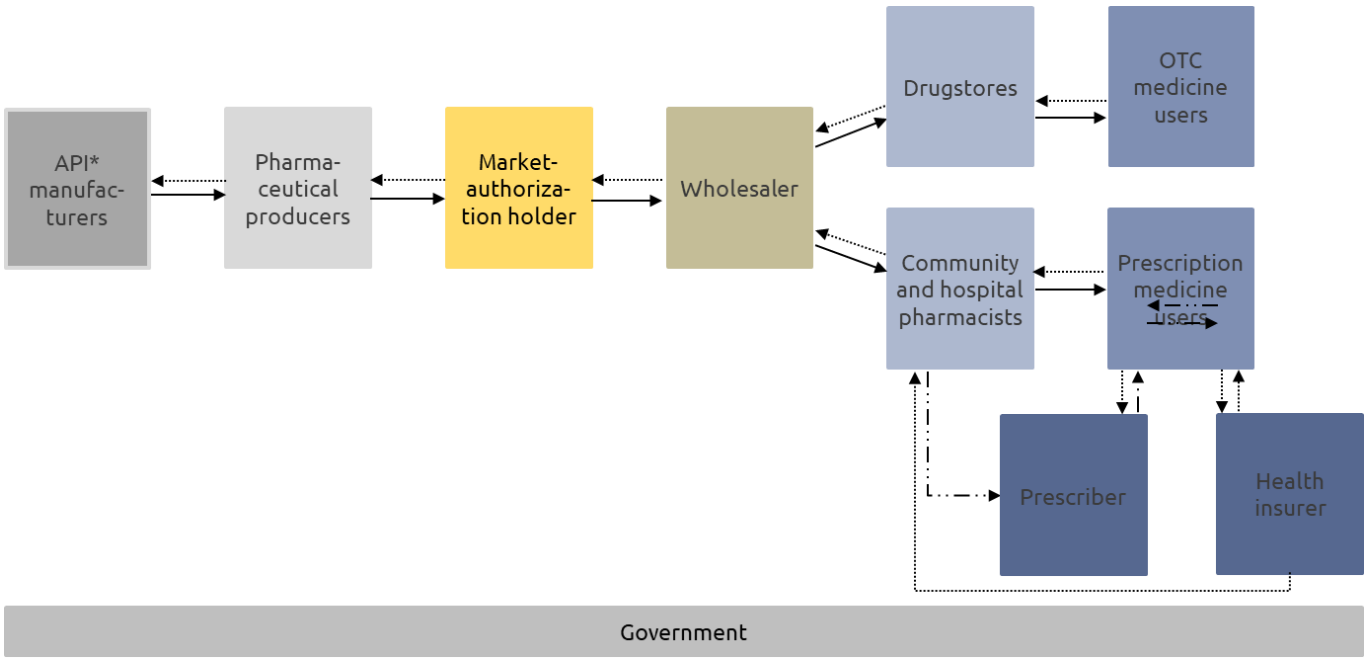

Figure 2: Value chain of the pharmaceutical market [4]

**API = Active Pharmaceutical Ingredient*

The therapeutic effect of medicines is exerted via the Active Pharmaceutical Ingredient (API), which is the active component of a medicine. Due to increasing costs of new regulation and price pressure, an increasing number of pharmaceutical producers outsource the production of APIs to contracted API

manufacturers [5]. These manufacturers are located worldwide, mainly in India, China, the US and the EU [6].

Access regulation

Before medicines may be sold in the EU, a market authorization is required, ensuring the medicine's quality and efficacy and safeguarding public health [7]. Within the EU pharmaceutical market, two main routes exist for the authorization of medicines. In the centralized authorization route, candidate market-authorization holders submit a single market-authorization application to the European Medicines Agency (EMA) [8]. Subsequently, the agency's appropriate committee submits a recommendation to the EC, which can then approve the marketing of the medicine throughout the EU. The second route is a national route, in which medicines are assessed at a national level by national competent authorities (NCAs) within the Member States [8]. MAHs may also be producers of the medicines they market, but this is not necessarily the case.

Originator medicines and generic medicines

In this research, we distinguish between two types of prescription medicines marketed in the EU: originator and generic medicines. Originator medicines are on-patent medicines. This means that the producer who developed the innovative compound to treat or prevent a disease is granted exclusivity in the form of an Intellectual Property Right (IPR) and receives market exclusivity for a period of approximately 10 years [9]. The function of IPRs is to ensure that Research & Development (R&D) for innovative medicines remains profitable. The reason being that without an IPR any other producer could recreate the medicine as soon as the medicine is marketed and consequently, previous R&D investments by the original producer will be difficult to earn back due to rapid price competition.

Generic medicines are defined by the European Medicines Agency (EMA) as "medicines that are developed to be the same as a medicine that has already been authorized—the reference medicine" [9]. Generic medicines contain the exact same API as the reference medicine and can only be marketed if they are equivalent to the reference medicine in terms of quality, efficacy and safety [10]. In general, generic medicines are priced substantially lower than their reference patented version. This price difference results from the fact that market-authorization holders of generic medicines operate in a highly competitive environment with other market-authorization holders, resulting in price reduction. MAHs of generic medicines deal with uncertainty in terms of the volumes of generic medicines they should supply, unlike MAHs of originator medicines who operate in a monopolistic environment. As prices of generic medicines decrease, profit margins become smaller, and MAHs of generic medicines become more sensitive to cost increases resulting from new regulations, or other market factors such as COVID19, inflation, or API costs increases.

Over the past several years, the prevalence of generic companies with originator medicines in their portfolio has increased. This change can be explained by the development that a business model in which solely focuses on generic medicines is becoming less sustainable, due to strong competition on generic medicines and price pressure resulting from payers cost-cutting measures [11].

Current status of the sector

Currently, the EU pharmaceutical market is facing real challenges, including demographic demand shifts, regulatory hurdles, strong increases in R&D costs, and unexpected events such as Brexit and COVID-19 [3]. The EU population is aging and an increased number of consumers of pharmaceuticals are now the elderly population [3]. To illustrate, in 2014, 129 million of medicines consumers in Europe were older than 65 years, whereas this number amounted to 191 million in 2018, showing an increase of almost 50% [12]. This requires medicines to adapt towards the specific needs of elderly patients with chronic health conditions. Additionally, increasing regulation of the pharmaceutical market has

resulted in production constraints. With each new regulation that governmental institutions implement, an investment is required to adhere to the new requirements. Another challenge is that R&D costs are rising due to, for example, a higher cost of working capital, more challenging disease areas and once again, increased regulation. Furthermore, unforeseen circumstances like Brexit and COVID-19 result in uncertainty on the MAHs' side.

All these challenges increase costs for pharmaceutical supply chain actors. At the same time, generic companies cope with significant price pressures, forcing price decreases and preventing them from increasing prices to reflect the additional operating costs [13]. The cost increases and price pressures pose a risk for MAHs of generic medicines, as the limited profit margins on these medicines may be further decreased. If profit margins on product lines continue to decrease, it becomes increasingly difficult for a MAH to continue to market these medicines [14] [15]. As a result, MAHs may need to redraw the medicine from the market. In a highly competitive market, the more MAHs stop marketing, the smaller the number of suppliers remaining. The fewer suppliers, the higher the risk of supply disruptions, which may cause an insufficient amount of medicines to reach the market.

Despite efforts of e.g. the European medicines regulatory network [16], supply shortages were increasingly recurrent over the past decade [17]. While various stakeholders have different definitions for what constitutes a shortage, supply disruptions have broad impact on the health system. For example, in 2018, 91,8% of 1.666 respondents in hospital pharmacies in 38 European countries stated that supply shortages were a problem [18]. Additionally, 75% of respondents reported that they experienced medicine shortages at least weekly [18]. These shortages have a wide range of causes and include payer procurement policies, manufacturing risks and regulatory factors [19]. Supply disruptions for generic medicines are particularly problematic as these medicines are highly important in sustaining our healthcare systems and ensuring access to medicines in terms of affordability and accessibility [20]. According to Medicines for Europe, which represents the main pharmaceutical companies in Europe, generic medicines accounted for 67 % of prescribed in Europe [21]. Additionally, generic medicines increased access to medicines by more than 100% within several key therapeutic areas over the past ten years [22]. The importance of generic medicines and the high occurrence of shortages illustrates the extent to which supply disruptions in Europe are concerning and that root causes of this problem urgently need to be addressed.

1.2. REGULATION OF THE PHARMACEUTICAL PRODUCTION SECTOR AND ITS DRIVERS

Regulation focused on MAHs

The pharmaceutical sector is one of the most highly regulated industries, with regulation affecting the production, distribution and utilization process of pharmaceuticals[23]. Examples of regulation to ensure effective access to safe medicines include quality measures both on medicines and their packaging to ensure safety of usage, and strict standards for pharmaceutical manufacturing practices including environmental management and permits.

An example of a recent directive aimed at ensuring the quality of medicines on the EU level is the Falsified Medicines Directive (FMD) [24]. This directive was put in place to guarantee that falsified medicines would not enter the market. The FMD is a highly important regulation, as it increases the ability to identify fake medicines before they are distributed to patients. However, the FMD also required large investments from MAHs [25]. These investments included, for example, adapting all manufacturing lines, changing the packaging of all medicines, and building information systems for real time registration and deregistration of a unique serial number. As a result, MAHs had to adjust packaging for each of the 10 to 14 billion medicine packs dispensed in Europe each year [25] [26]. Additionally, the MAHs had to implement tamper-proof seals on each package, which allow for verification that the medicines in drug packages are not falsified [24]. For this directive, the estimated costs of implementation were €500.000 per packaging line, which adds up to billions of euros for EU MAHs, when also taking into account the management of the system [27]. This legislation had a significant impact on the cost structure of MAHs, particularly for MAHs of generic medicines given the large volume of medicines.

Other examples of regulation that had a large effect on MAHs are various national regulations related to the stock of medicines, package size, reporting obligations and others.

Broader regulation that affects MAHs

In addition to regulations that specifically target the pharmaceutical sector, the sector can also be impacted by regulations that have a broader scope, targeting industry or society at large. A recent example of such regulation is EU Member State implementation of the EU Green Deal by enacting climate policy at national level. Potential obligations or restrictions (jointly onwards called: "consequences") for the pharmaceutical industry under the Green Deal are a carbon tax, packaging reduction requirements, additional requirements to reduce risk of environmental pollution beyond just the manufacturing process of medicine and/or mandatory investments in alternative energy sources. This Act is included here not as to critique the Act itself or its purpose, but merely to exemplify a new regulation that will drive a need for investments and increase cost of production.

A more detailed overview of recent regulation of the pharmaceutical market is presented in Table 1 overleaf. As the pharmaceutical industry is highly regulated, this overview only displays a few of the numerous regulations implemented in recent years. This overview illustrates that MAHs can be impacted by a diverse set of regulations. Each of these regulations increases costs for the MAHs, which will be further examined in chapter 2.

Examples of recent regulation	Parties involved	Geographical scope	Description of regulation	Examples of consequences on MAHs
Falsified Medicines Directive (FMD): Commission Delegated Regulation (EU) 2016/161	European Council, EMA, European Parliament	EU	New verification system that requires the end user to verify authenticity of medicines throughout the supply chain [28]. From February 2019, every pharmacy and hospital in the EU is required to have a system that will make the detection of falsified medicines easier and more efficient [26].	The FMD resulted in requirements for packaging redesign. MAHs had to include a unique identifier and an anti-tampering device onto the packaging of most medicinal products [29]. This mainly brought about investment costs in terms of adapting the manufacturing lines to change the packaging of all medicines and building information systems for real time registration and deregistration of a unique serial number.
Regulation (EU) 658/2014 on fees payable to the EMA	European Commission	EU	Regulation on fees required to be paid to the EMA by MAHs, for the conduct of pharmacovigilance activities with respect to products for human use [30].	MAHs must pay procedure-based fees for e.g. the European Union (EU) single assessment of periodic safety update reports (PSURs) and pharmacovigilance-related referrals. Additionally, this regulation entails an annual fee relating to pharmacovigilance activities, with respect to information technology systems, and the monitoring of selected medical literature [31].
GDPR Regulation (EU) 2016/679	European Parliament and the Council	EU	Regulation to protect persons with regards to collection and processing of personal information from individuals who live in the European Union (EU) [32].	Pharmaceutical companies needed to comply with stricter regulation when using data of health care professionals. Therefore, all MAHs had to adjust the way in which marketing and sales teams managed their data. As a result, this regulation mainly resulted in additional labour costs to review data owned to adhere to this regulation [32].
Health Services Regulation	UK Department of Health & Social Care (DHSC)	UK	The Health Services Regulation of 2018 aims to mitigate and manage medicine shortages as and when they arise. This regulation includes requirements for MAHs to provide information on the availability of health service medicines and on discontinuation of medicine supply or anticipated supply shortages [33].	MAHs have an increased workload in terms of documentation on the availability of their medicines, as well as giving out warnings on discontinuation or anticipated supply shortages of medicines. This results in additional labour costs and decreased efficiency.

Health Service Medical Supplies Costs Act	UK government, NHS	UK	The UK's Health Service Medical Supplies Costs Act of 2017 extends the power of the government to regulate the cost of medicines and medical supplies. Furthermore, it enables the government to collect sales and pricing information from MAHs. The main goal of the act is to regulate the spend of the National Health Service (NHS) in the UK [34] [35].	Consequences for MAHs are: 1) Partial reinstatement of branded medicines moved out of the Pharmaceutical Price Regulation Scheme (PPRS). This will reverse how some MAHs moved to an alternative statutory scheme, to avoid having to pay previously agreed upon payments to the NHS for extreme growth in NHS spending on particular branded medicines in the PPRS [34]. 2) An increase in labour costs due to intensified data documentation requirements. 3) Price control by the government for unbranded, generic medicines in case of large and unjustified price increases.
Climate Change Act	Swedish government	Sweden	The purpose of the Swedish Climate Change Act of 2018 is to create a clear and coherent climate policy for the country [36]. The act contains the national climate targets and milestones for Sweden, such as achieving zero-net greenhouse gas emissions by 2045 and to achieve negative emissions after 2045. The act obligates each government to work out specific actions to meet these goals. Furthermore, a Climate Policy Council will be set up to assess government policy against the climate targets. The act will provide long-term conditions to business and society to implement the transition needed to solve the challenge of climate change.	Although the act itself was accepted, it does not yet entail specific law changes. We expect that laws will be adjusted or adopted in the short-term, in line with the goals of the act. As the act includes ambitions to achieve zero-net greenhouse emissions by 2045 and aims for Sweden to achieve negative emissions after 2045, this act is likely to result in requirements for reducing greenhouse gas emissions amongst MAHs.

Table 1. Overview of recent regulation on the pharmaceutical market and industries in general.

Source: Capgemini research and classification

1.3. PROBLEM IDENTIFICATION

Regulation is an important tool to address policy challenges. However, it may have unintended side-effects in the form of obligations or restrictions on stakeholders. These unintended consequences of new regulation are typically translatable into cost increases, as MAHs must change their current ways of working. In turn, these consequences may impact on the pharmaceutical sector and society at large.

For example, in case of increased cost of production, MAHs have two main lines of response. They can choose to absorb the cost increase by accepting lower margins on medicines marketed or they may decide to pass-through the cost through a price increase. A major bottleneck arises if neither option is available. That is the case when product margins are too low to remain positive after absorption of the additional costs, while the market and regulatory circumstances do not allow for a pass-through of the cost by increasing the price. In that situation, the product margin may become negative and the marketing of these medicines will become uncertain.

In Europe, pricing is regulated and there are limitations to the ability to adjust pricing of medicines to account for increased operational costs. The intention of regulating pricing is to protect patients' access to medicine and manage public health budgets. Access to generic medicines is essential for that purpose. At the same time, market-authorization holders (MAHs) of generic medicines, are particularly vulnerable to the combined effect of increased cost due to new regulations, incremental price reductions and price cutting measures, strong competition and price regulation that in most cases doesn't allow increases in the price of pharmaceuticals, even if there is an increase in operational costs.

This impact results in the risk of supply disruptions, including shortages, which have been recurrent in Europe in the past few years [37]. In 2018, the Pharmaceutical Group of the European Union (PGEU) conducted a survey, in which community pharmacists in all responding member countries (21 countries) indicated that they had experienced supply shortages[2] in the previous 12 months [37]. These shortages cause a burden on health systems, due to the costs of finding alternative medicines and the fact that often more expensive alternatives need to be used [38] [39]. Additionally, supply risks pose a significant health risk to patients who are not able to receive their required medicines [40]. To illustrate, one of the medicines most commonly affected by supply challenges are cancer medicines, resulting in significant challenges for providing high quality care to cancer patients [41].

The pharmaceutical companies represented by Medicines for Europe have expressed concern that the EU regulatory and market framework is leading to a business environment that is unsustainable for multiple MAHs to compete in the supply of essential medicines for public health [19]. Therefore, in this report, we analyse the potential risk of new regulatory initiatives, such as the European Green Deal, on the supply of pharmaceuticals. Moreover, we explore whether mitigating measures exist that can prevent the unintended negative societal consequences of new legislation and regulation. For the mitigation measures, we focus on financing models that are aimed at changing the current pricing dynamics to ensure that MAHs can cope with the cost consequences of new requirements. These financing models can help to reduce the adverse effects of new requirements on MAHs and society and to ensure a sustainable medicine supply.

[2] Shortage is defined as "every (temporally) inability for a community or hospital pharmacy to supply patients with the medicinal product requested as a result of factors beyond their control, requiring the dispensing of an alternative agent or even discontinuation of an ongoing medical therapy"

1.4. APPROACH TO THE STUDY

In this research we identify and assess solutions to the unintended negative impact of regulation on generic medicines. The aim of this research is to develop possible policy solutions to ensure the stable supply of high-quality, safe and affordable prescription medicines for human usage. To this purpose, the research consists of an assessment in five phases, illustrated in figure 3.

Figure 3. Five-phased qualitative assessment

In the first phase, we review a selection of upcoming legislation and future policy initiatives in the EU and its Member States that could impact the marketing of medicines. For each initiative, we determine potential consequences on MAHs in terms of regulatory obligations. Additionally, we determine what regulations we see in other sectors and what the consequences of these regulations are, to obtain a full view on the potential consequences regulation can have on MAHs. As the analysis includes policy initiatives rather than specific legislative proposals, a conceptual framework was created to classify the range of possible consequences of these initiatives.

In the second phase, we review the current European pharmaceutical market structure and derive a typical business model for a MAH in terms of key figures for profit and loss. Moreover, we estimate the distribution of product lines according to product margins to allow the financial impact analysis of the next phase.

In phase three, we combine the outcomes of phase 1 and phase 2 to conduct a high-level quantitative impact estimate of new legislation on medicines margins. By assuming absence of the possibility of general pass-through of cost increases and developing assumptions on the size and type of cost impact, we identify the potential risk of regulation leading to medicines not being marketed.

In phase four, we review new financial models as possible solutions to mitigate the expected negative impact of new regulation on medicines. We further review the four most promising financial models in terms of feasibility (possibility for successful implementation) and effectiveness (extent to which the solution reduces supply shortages risks).

In the fifth and last phase we compare the effects of the situation with new regulation without any flanking measures to the situations for each of the four potential finance models.

This study was commissioned to Capgemini by Mylan. Any views or opinions expressed are solely those of the authors. The analysis, conclusions and recommendations have all been developed independently and neither Capgemini nor any of the authors has a financial interest in the results of the study. The study was conducted between December 2019 and July 2020.

2. FINDINGS

2.1. REGULATORY INITIATIVES

In this section, we present a selection of upcoming regulatory initiatives, both on an EU and on a national level. These regulatory initiatives include initiatives specifically targeted at the pharmaceutical industry, as well as initiatives that have an impact on the pharmaceutical industry but are not specifically targeted at this industry. Via these initiatives, we gain insight into the challenges the MAHs will potentially face in adhering to the consequences of these initiatives.

Examples of upcoming regulatory initiatives

One major initiative at EU level expected to impact the pharmaceutical sector is the European Green Deal (EGD) [42]. The EGD is aimed at making Europe the first climate-neutral continent by 2050. With climate neutrality, the EC implies that emissions will have no net impact on the climate. Among the likely regulatory obligations on companies are a carbon tax, mandatory investments in green energy and requirements to reduce environmental pollution and micro-plastic usage [42]. These obligations are expected to come into force in addition to current regulation in place in the pharmaceutical sector to reduce its environmental footprint. The anticipated consequences may include monitoring environmental impact through Environmental Risk Assessment (eERA), introducing technology to treat public water wastage and improving the collection of unused or expired medicines [43].

On a national level, a current initiative in the Netherlands concerns the development of an "Iron Stock" policy to reduce recurrent supply shortages [44]. The Dutch government plans to implement this policy to ensure the ongoing accessibility of medicines. With this policy, the government is expected to require a minimum stock supply of at least five months across the whole supply chain. Of these five months, MAHs will probably have to provide three months of stock [44]. This increase in stock requirements would bring about consequences for MAHs, such as a rise in warehousing costs, and an increase in R&D expenses to determine and potentially increase the shelf life of medicines [44].

A more elaborate overview of current initiatives that may result in new regulation is presented in Table 2 overleaf. The nature of regulatory initiatives is that they lack fully worked-out details. Therefore, the overview presents preliminary descriptions of what we expect the regulation to entail. Furthermore, all expected consequences depend on the details of the initiatives and are therefore subject to change. As evident from the overview, the expected consequences of the current regulatory initiatives are diverse in their nature and can impact the operational process in different phases.

Current initiatives	Parties involved	Geo-graph-ical scope	Description of initiative	Potential consequences on MAHs
European Green Deal	European Commission	EU	The EC announced a European Green Deal. The EC aims to propose this deal within their first 100 days in office, starting on December 1st, 2019. The vision behind this deal is to make Europe the first climate-neutral continent and a world leader in circular economy and clean technologies [42]. The deal will contain climate and environmental laws, including the first European Climate Law to enshrine the 2050 climate neutrality target [42]. The EC will work to decarbonize energy-intensive industries and move towards a zero-pollution ambition. To achieve this, the EC wants to set more ambitious targets for 2030, for example reducing emissions by at least 50% by 2030.	Due to the EC's strong focus on addressing the climate crisis, we expect that MAHs will be affected by this new deal. For example, potential consequences of the European Green Deal could be: a carbon tax, mandatory investments in green energy, requirements to reduce environmental pollution and to reduce micro-plastic usage [42].
European Union Strategic Approach to Pharmaceuticals in the Environment (PiE)	European Commission, European Parliament, The Council and the European Economic and Social Committee	EU	The aim of the "Strategic Approach to Pharmaceuticals in the Environment" is to draw attention to the risks of pharmaceuticals in the environment and antimicrobial resistance, which is an issue of global importance. Within this strategic approach the EC identifies six areas where action is needed. The action areas cover the full lifecycle of pharmaceuticals, from design and production to disposal and waste management [45].	The six actions are: 1) increase awareness and promote prudent use of pharmaceuticals, in particular antibiotics, 2) support the development of pharmaceuticals intrinsically less harmful for the environment and promote greener manufacturing, 3) improve environmental risk assessment and its review, 4) reduce wastage and improve the management of waste, 5) expand environmental monitoring, 6) fill other knowledge gaps [46]. In practice, new legislations that will be implemented to support these actions can bring about significant cost increases for MAHs. For example, ERA as part of the EMA's benefit-risk assessment, extended Polluter Pays Principle, adding environmental aspects as part of the Good Manufacturing Practices or more 'green design', reducing emissions from manufacturing, reducing waste and improving waste water treatment [47] in

				addition to already existing initiatives in the sector to reduce the pharmaceutical footprint in environment.
A new Industrial Strategy for Europe	European Commission, European Parliament, The Council and the European Economic and Social Committee, The Committee of the regions	EU	In March 2020, the Commission presented a new Strategy to help Europe's industry lead the twin transitions towards climate neutrality and digital leadership. The Strategy aims to drive Europe's competitiveness and its strategic autonomy at a time of moving geopolitical plates and increasing global competition [48].	The Strategy sets out the key drivers of Europe's industrial transformation and proposes a comprehensive set of future actions like enhancing Europe's industrial and strategic autonomy by securing the supply of critical raw materials through an Action Plan on Critical Raw Materials and pharmaceuticals based on a new EU Pharmaceutical Strategy. Demand for raw materials is projected to double by 2050, making diversified sourcing essential to increase Europe's security of supply. Critical raw materials are also crucial for markets such as e-mobility, batteries, renewable energies, pharmaceuticals, aerospace, defence and digital applications. Access to medical products and pharmaceuticals is equally crucial to Europe's security and autonomy in today's world. A new EU pharmaceutical strategy will be put forward, focusing on the availability, affordability, sustainability and security of supply of pharmaceuticals.
EU Pharmaceutical strategy	European Commission	EU	In 2020, the EU plans to launch a new strategy to improve and accelerate patients' access to safe and affordable medicines and to support innovation in the EU pharmaceutical industry. Based on communication from June 2020 it will address: the life cycle of medicines from R&D to authorisation and patient access, how to put scientific and technological advances into practice, how to fill market gaps (e.g. new antimicrobials), lessons learnt from COVID-19 on how to better prepare for future pandemics [49].	The roadmap released by the European Commission in June 2020 as a key document in launching stakeholders ´consultation is mentioning the way environmental risks are addressed needs to be improved. According to the Commission, the regulatory framework needs to address the environmental implications of production, use and disposal of medicines to respond fully to the objectives of a green economy. One of the major challenges is increasing antimicrobial resistance.

"Iron Stock" ('ijzeren voorraad') policy	Dutch government	Nether-lands	The Dutch Minister of medical care announced a new policy, referred to as the "Iron Stock" policy. This policy concerns the recurring medicine shortages and should avoid 85% of supply shortages in the Netherlands [44]. The policy will require the pharmaceutical industry to ensure a stock supply of 5 months' worth of medicines [44]. For MAHs specifically, the Minister proposed that they are required to ensure a stock supply of 3 months. The Minister wants the pharmaceutical industry to build these stocks from 2020 onwards. He expects that it will take two years to establish the desired stock supply of 5 months in total.	Establishing this stock supply mainly results in monetary costs and is estimated to cost about 25 million euros net for the Dutch healthcare sector [44]. How these costs will be carried by the industry still needs to be discussed. Other potential consequences for MAHs are additional warehousing costs, medicine spillage and additional research to extend shelf-life of medicines [44]. Additionally, the Dutch Minister aims to go to the EC to request a law on medicine shortages on the EU level and is reviewing opportunities to move raw material and medicine production partly back to Europe [44].
Green Deal 'Care' (Green Deal 226)	Milieuplatform zorgsector (initiative taker) [48], Dutch Ministries, and other stakeholders in the healthcare sector	Nether-lands	The aim of this deal is to make the Dutch healthcare sector more sustainable, as this sector recognizes that it has an adverse environmental impact and contributes to climate change [49]. This Green Deal was proposed in 2018, after the first green deal within Dutch healthcare (Green Deal 190). 132 parties immediately signed this second deal, including Dutch Ministries and MAHs, such as Roche [50] [51].	With this deal, the healthcare sector aims to increase sustainability according to four themes: 1) reducing CO^2 emissions of the healthcare sector, 2) working in a circular manner, 3) reducing the amount of drug residues in surface water and ground water and 4) creating a living environment in and outside healthcare institutions that promotes the health of all individuals [49]. Though no specific regulation is expected, this initiative may invite MAHs to adjust their practices towards the abovementioned themes.
Medicines for the Many Policy	UK labour party	United Kingdom	The Medicines for the Many Policy is an initiative that arises from controversy about whether pharmaceutical companies may be putting their stakeholders' interest before that of the general public [52]. The main aims of the policy are 1) that patients should be able to get access to all the medicines they need, 2) the expenditure from the NHS should be sustainable and (3) that more should be invested in future innovation (e.g. CHEM21).	Potential consequences from the Medicines for The Many policy for the pharmaceutical industry are: 1) increased demand in collection and processing of data at every stage of the operational process, resulting in more labour costs and data infrastructure investments, 2) if the Crown Act is enforced, potential loss of patent and with it profits on sold branded medicines, 3) reduction in the amount of research funding that MAHs receive from the government when not complying with pre-set medicine prices, 4)

				increased competition from state-funded and state serving competitors.
Landmark Environmental Bill	UK government	United Kingdom	The Landmark Environmental Bill helps ensure that the UK maintains and improves environmental protections upon leaving the EU [53]. It does so by proposing to create an Office for Environmental Protection (OEP) that provides governance and enforcement to replace the current European Commission and the Court of Justice. The bill creates environmental improvement targets that are legally binding and contains measures to improve air and water quality, tackle pollution from plastics and to restore natural habitats. Furthermore, the bill holds the government accountable to reach a net-zero environment by 2050, like the EGD. At the time of writing, the bill is in the committee stage for review [54] [55].	Due to the similarity of the ambition of this environmental bill and the EGD the potential consequences listed for the EGD can be expected for this bill as well. Furthermore, MAHs can expect additional requirements related to: 1) increasing recyclability of the packaging used, 2) reducing overall waste in production processes (e.g. packaging material), 3) changing of labels to meet potential new requirements (e.g. label that instruct how to recycle the packaging), 4) stricter regulations on air and water pollution during the pharmaceutical production process [53].
Clean Air Bill	Green party of England and Wales, multiple UK air related authorities	United Kingdom	The Clean Air Bill is based on the human right to breathe clean air [56]. The bill requires the Secretary of State to achieve and maintain clean air in the UK. It involves making Public Health England responsible for reviewing pollutants and setting pollution limits. Additionally, the bill enhances the powers, duties and functions of the Environment Agency and several other air related authorities. Furthermore, the Citizens' Commission for Clean Air will be strengthened with the power to institute or intervene in legal proceedings.	Stricter regulations on air pollution may require additional investments from MAHs to meet stricter pollution standards. Other air related consequences such as, e.g. a carbon tax can also impact operating costs.

Table 2. Overview of current initiatives that can result in regulation influencing MAHs.

Source: Capgemini research and classification, initiatives and consequences are subject to change.

Other factors impacting MAHs

It is notable that the above overview is not exhaustive and only concerns regulatory initiatives. Apart from these regulatory initiatives, the pharmaceutical industry can also be impacted by externalities such as significant geopolitical changes. A clear example of such a change is UK's departure from the EU ("Brexit"), which removes the UK from the jurisdiction of the EMA. This allows the UK Medicines and Healthcare Products Regulatory Agency (MHRA) to set their own requirements related to the authorization of medicines for the UK market [57]. MAHs may be required to submit their new medicines through both the approval process of the EMA and the MHRA to be able to deliver their medicines in both the UK and EU, which increases costs [57]. Moreover, after Brexit, companies will need to establish release sites, warehousing facilities and packaging requirements for both the EU and UK regulatory systems, which also increases costs and complexity [58].

MAHs can also be impacted by unexpected crises such as the COVID-19 pandemic. COVID-19 led to both an unprecedented increase in demand for some medicines in Europe, but also a strong increase in costs of products. This cost increase was mainly associated with manufacturing and distribution of medicines and was triggered by measures implemented to contain the spread of the virus, including border closures, and limitations imposed on economic activities [59] [60]. For instance, sites capacity reduced due to increased absenteeism, physical distance requirements, and more frequent cleaning of working areas. Furthermore, costs for air freight, warehousing and personal protective equipment, amongst other necessities, rose [61]. The cost increases related to COVID-19 were problematic as MAHs were not able to reflect these costs in their prices due to existing price regulation measures. Generic medicine MAHs were able to ensure current supply, but the situation is not considered sustainable.

2.2. CONSEQUENCES FOR MARKET-AUTHORIZATION HOLDERS AND OTHERS

The unintended side-effects of regulation can include consequences for MAHs and other stakeholders.

Consequences for MAHs

Regulation by governmental authorities is a significant cost factor for MAHs of generic medicines [62]. For example, before market approval, medicines are required to be tested preclinically and clinically, manufacturing is extensively regulated, and post-approval activities, such as pharmacovigilance, are subject to numerous regulations. Furthermore, regulation can increase the cost of products, when posing additional requirements on APIs and packaging materials. While the assurance provided by these regulatory requirements are important to maintain high-quality safe medicines, the costs to comply are substantial and continues to increase.

Moreover, MAH regularly face additional cost-containment measures imposed by governments and other payors. These measures include policies such as industry-wide price reductions, reference pricing systems and claw-backs [13] [63]. MAHs also argue that failures in procurement policy, such as granting tenders based on the lowest price possible without consideration of other criteria, have adverse effects on market sustainability [64].

We distinguished four categories of compliance costs due to regulation. These four categories of compliance costs are:

- Monetary costs
- Production costs
- R&D costs
- Labour costs

In these categories, monetary costs refer to direct monetary payment by the MAH, such as fees, contributions and taxes. Production costs entail required adjustments to the production process, such as changing machinery or reducing production waste levels. R&D costs refers to costs related to R&D, for example, the costs of product redesign. Lastly, labour costs imply costs such as training for employees and additional working hours to adhere to strengthened quality requirements.

For example, consequences of the Falsified Medicines Directive Commission Delegated Regulation (EU) 2016/161 resulted in three different types of compliance costs. Production costs increased as a result of a reduction in manufacturing capacity. Firstly because of a temporary halting of packaging lines to introduce the required changes, and secondly, due to a lower speed of production resulting from additional steps in the packaging process. Besides that, serial numbers have to be generated and the system needs to be maintained [24]. The FMD also brought about monetary compliance costs, as the MAHs had to pay contributions to European and national databases [24]. Lastly, labour costs increased as a result of labour effort of the employees to implement these required adjustments. In total, the additional financial costs of the FMD for a MAH of generic medicines in the Netherlands were estimated at €0,17 per medicine package [25].

In table 3 overleaf we provide an overview of the various types of compliance costs for each of the four compliance categories. This overview is based upon examples of compliance costs are identified

in a wide range of regulations, not all necessarily applicable for regulation of the pharmaceutical sector. As mentioned, each compliance cost is based on consequences of existing regulations or expected regulations. Please note that this table is exemplary and additional compliance costs may exist depending on the specific regulation.

Compliance category	Compliance cost	Examples of consequences
Monetary costs	Fees	Procedure-based fees and annual fees payable to the EMA [65], trade tariffs [66]
	Taxes	Carbon border tax [42]
	Fines	Financial punishment of heavy polluters [42]
	Contributions	Contribution to shared databases EMVS and NMVS [25]
	Investments	Investments in green energy required by regulation [42]
	IP losses	Adjustments in IP rights and incentives [65]
	Pricing	Justifying any price increase in medication, disclosing information regarding negotiations for drug discounts [67], price control in case of unjustified price increases [34], horizon scanning [68], reference country adjustments [69]
	Reimbursement	Changes in medicine reimbursement systems [69]
Production costs	Software	Purchase of new software licenses [24]
	Machinery	Purchasing new machinery and equipment [24]
	Waste management	Implementation of waste disposal according to new guidelines [42], waste reduction [42], reducing environmental pollution [42], reducing medicine spillage [44], fees per package sold for environmental waste management (e.g. Valormed) [70]
	Emissions	Reduction of industrial emissions [42], stricter regulations on air pollution [56]
	Warehousing	Renting additional storage space [44]
	Packaging	Reducing micro-plastic usage [42], packaging redesign [24], reduction of single-use plastics [42], adjustment of packaging facilities [24], enabling product tracing [71], increasing recyclability of the packaging used [53]
R&D costs	Product redesign	Extending minimum shelf life of medicines [44], bans or limitations on raw materials [42], requirements for more efficient usage of raw materials [72]
	Trials	Adjustments in preclinical testing requirements or clinical trials regulation [73]
	Authorization	Adjustments in requirements for authorization [74]
Labour costs	Training	Training of employees to work as described in the regulation [71], changing clinical and manufacturing practice to adhere to new safety standards [71]

	Project implementation	Implementing the adjusted requirements to adhere to the new regulation [25]
	Quality assurance	Conducting ethical reviews of clinical trials [73], data collection on medicine safety [25], adjustments to (environmental) risk management system [71]
	Reporting	Add clinical trial information to publicly accessible EU database [73], data collection on medicines [25], report side effects to Eudravigilance (required in 2022) [75], reporting on anticipated supply shortages [33]

Table 3. Overview of possible policy consequences in general (not limited to the pharmaceutical sector).

Source: Capgemini research and classification

Consequences for other stakeholders

This research focuses on effects for MAHs of generic medicines. However, it is important to note that these effects on MAHs can consequently lead to a large range of effects on other stakeholders. From interviews with pharmaceutical experts and MAHs, we identified the main stakeholders that are affected by the potential unintended negative impact of regulation. These stakeholders are patients, pharmaceutical industry employees, communities, and universities and pharmacists.

Patients are the key stakeholders that are affected by supply shortages, investigated in more depth later in the report. Employees are also affected, as one way in which MAHs can reduce their expenses is by decreasing their work force and laying off employees. In the past, major generic MAHs have had to lay off significant numbers of employees. The MAHs required consolidation as they were under pressure to curb expenses.

2.3. IMPACT ANALYSIS

The impact analysis consists of an analysis at the level of product lines. In this analysis, a net contribution margin per product is estimated. The net contribution margin is defined as the revenue generated by a product line minus the direct cost of marketing (including production costs).

Estimating contribution margins

As information on product margins is typically considered privileged information, estimates have been made on the average margin per product line and the distribution of contribution margins for the different product lines.

For the average contribution margin, we used the average total profitability of a range of MAHs of generic medicines as a proxy[3]. The (unweighted) average key figures are presented in the table below. Based on these findings, the average product margin for the analysis is set at 9,4%, the rounded value of the average gross profit of the MAHs analysed.

	%
Annual revenue	100,0%
Cost of sales	58,2%
Operating expenses	29,5%
Non-operating expenses	2,9%
Margin	9,4%

Table 4. Typical high-level Profit & Loss account of a MAH of generic medicines (in percentage of total annual revenue)

Note: figures are unweighted average for selected MAHs.

For the distribution of the contribution margin over the product lines, no public information is available. Based on confidential information and estimates obtained from Capgemini experts, we estimated:

1. A linear distribution of contribution margins. This means, if all product lines are ordered by contribution margin from high to low, a linear trend can be observed.
2. The lowest product line margin of 0%.

These assumptions reflect the best possible estimate of the distribution of product line margin for MAHs.

[3] The MAHs included in this analysis are: Sun Pharma; Dr. Reddy's; Krka; Stada; Cipla; Hikma; Sawai Pharmaceuticals; Mylan; Fresenius; Sandoz

In the figure below, the distribution of product lines by contribution margin is presented. The product lines are classified by level of profitability: good profitable (>10% margin), fair profitable (5-10% margin) and low profitable (0-5% margin)[4].

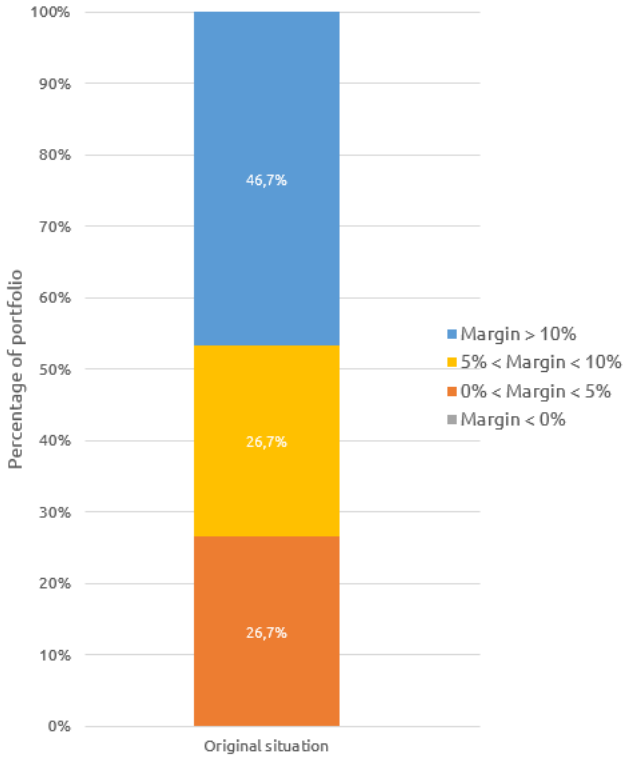

Figure 4. Profit margin categories' size as a percentage of total portfolio product size

Estimating the impact of regulatory initiatives on product lines

The obligations from regulatory initiatives (see section 2.2) can impact MAHs in a wide range of ways. In terms of impact on the product lines and the MAHs, two main types of impacts can be identified:

1. Regulation impacting the cost base of a unit (cost of goods sold)
2. Regulation impacting operating or non-operating expenses

To demonstrate the impact of the first category of regulation, we assume new regulation that increases the cost base of all products by 3% of its price. Illustrating in financial terms: a package of 20 units of medicines with a price of € 0,10 per unit, has a total price of € 2 before the new regulation. As a result of new regulation, the MAH will face a cost increase of € 0,06 cents per package. This cost increase is assumed not to be matched by a corresponding increase of price of the package (in other words: the MAHs needs to absorb the cost increase).

The result of this 3% increase is presented in the following figure. As can be observed, for 16% of the portfolio of the MAH the ability to market has been hampered. A below-zero margin means that the MAH makes a net loss on each unit marketed. From a financial point of view, continuation of the

[4] The model simulates a MAH hosting 300 product lines. Please note that the conclusions of this section, presented as relative share of the number of product lines, do not change when a different number of product lines is used.

marketing of a product line with a negative margin does not make sense, leading to a high risk that these medicines will no longer be supplied by the MAH.

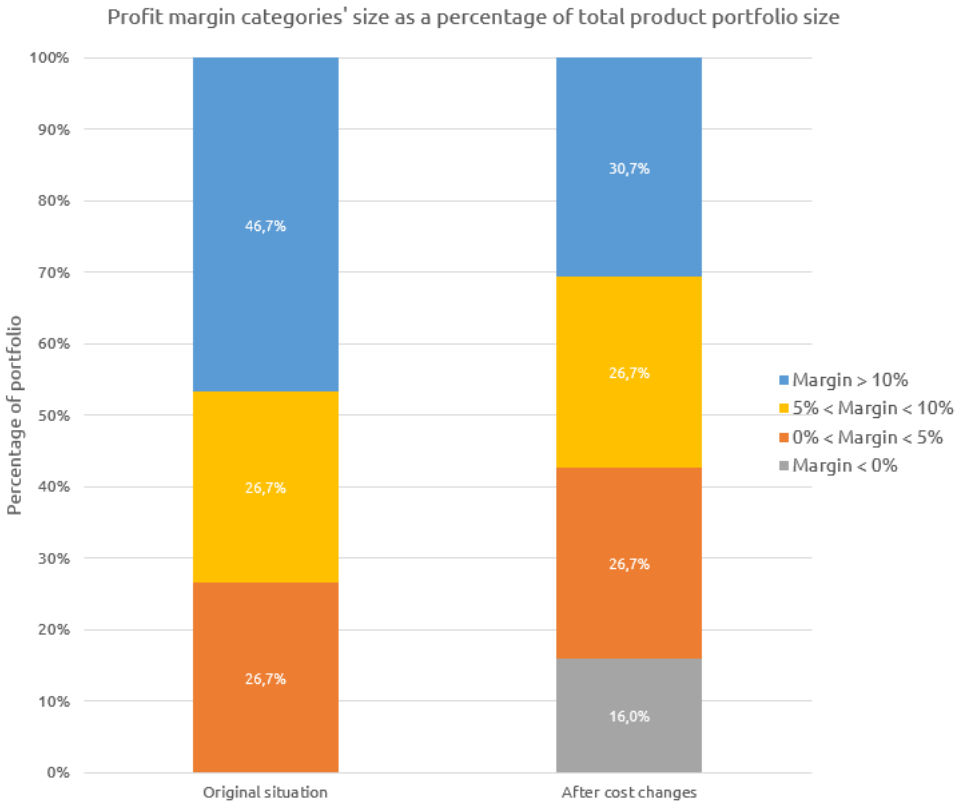

Figure 5. Profit margin categories' size as a percentage of total portfolio product size with a 3% of revenue cost increase

To analyse the impact of the second category, regulation increasing operating or non-operating expenses, the allocation of operating and non-operating expenses over the product range needs to be considered. As no specific details on cost allocation of MAHs of generic medicines could be obtained, a proportional allocation of increase in operating or non-operating costs over the product lines in line with their revenue should be assumed. As such, the dynamic becomes equal to the calculation of increase of cost of goods sold (category #1).

One practical illustration of the potential impact of regulation may be derived from the initiative to introduce an Extended Producer Responsibility that might be implemented in the form of urban wastewater treatment fee under the Pharmaceuticals in the Environment. The aim of the wastewater treatment fee is to finance the costs of removing pharmaceutical residues from urban wastewater[5]. Although targets still need to be set, different purification methods have different efficiencies, and local situations may differ, a rough estimate on the cost effect can be developed based on already implemented initiatives.

A study by the Swedish Environmental Protection Agency (SEPA) of techniques for advanced purification of drug residues at Swedish wastewater treatment plants finds the costs vary widely, both between different technologies and different wastewater treatment plant sizes [85]. The estimated total costs lie between SEK 1 to SEK 5 per cubic meter wastewater, or approximately SEK 241 million (€

[5] For a more elaborate discussion, see section 2.4, sub 5 Eco-fee

22 million) and SEK 2.1 billion (€ 190 million) per year in total[6]. Against a total expenditure of SEK 47 billion (€ 4.3 billion) on pharmaceuticals in Sweden in 2018 [86], this equals a cost increase of 0.5% to 4.5% of the price of pharmaceuticals. If these costs where to be fully charged to the MAHs, with no corresponding increase in price, this means that between 3% to 24% of the product lines are at risk as a result of dropping to negative margin, illustrated in figure 6.

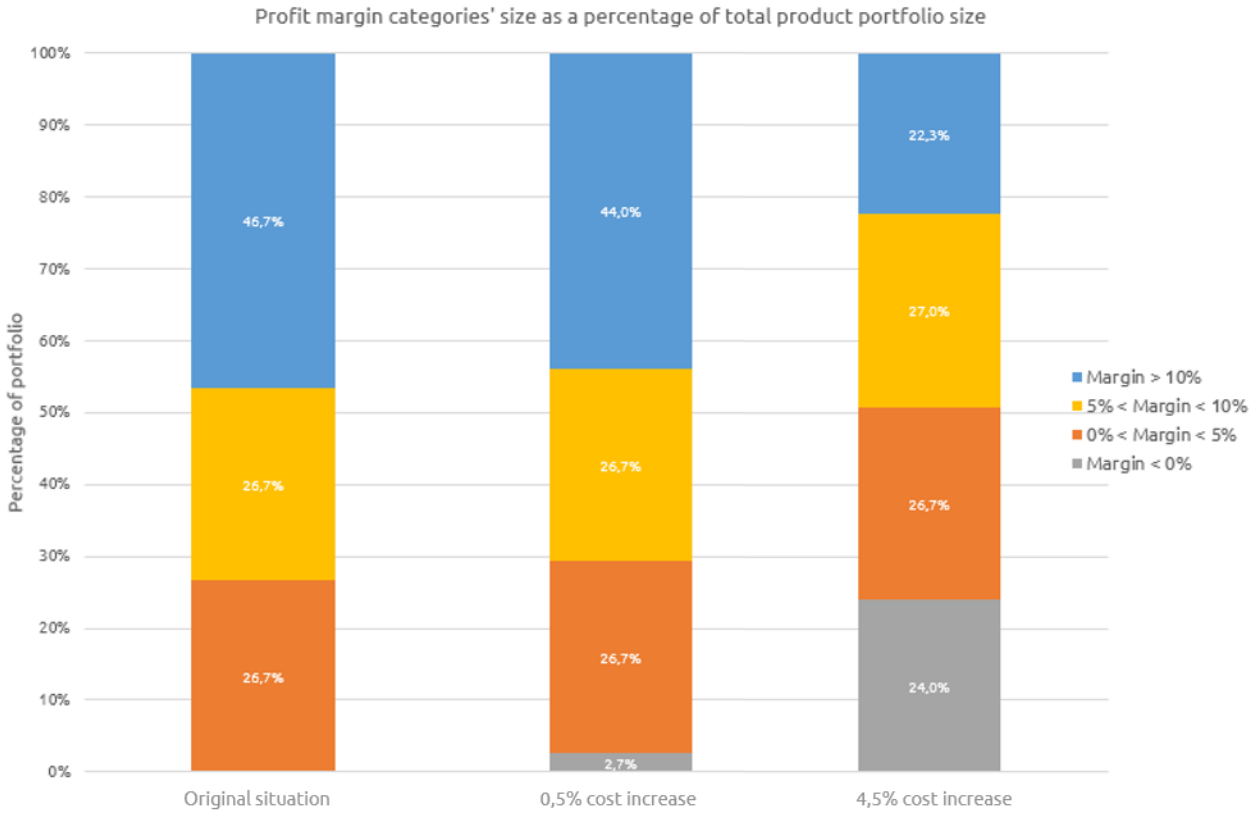

Figure 6: Impact of 0.5% (middle) and 4.5% (right) cost increase compared to the basic situation (left)

[6] Cost estimates made in Germany, the Netherlands and Switzerland indicate slightly higher costs per cubic meter wastewater.

2.4. AVAILABLE SOLUTIONS

The business impact model shows that a cost increase for the MAHs can have detrimental effects on the supply of generic medicines as MAHs do not have the capacity to reflect the cost increase in the final price. An unsustainable medicine supply is undesirable from a societal point of view and requires mitigating measures.

We identified a wide range of new mitigating measures addressing the financial impact of regulation, referred to as 'financing models'. These financing models range from establishing minimum fee for the MAH, that can reflect cost increases associated with new regulation. We determined these models via desk research and Capgemini expert interviews. From all the mitigating models identified, we created a long list of seven new financing models that have the most potential to offset the financial impact of regulation. These seven models are briefly described in table 5 below. If the financing model is specifically focused on at-risk medicines, this implies that the financing model applies to the production of medicines with profit margins <5%, meaning that they are at-risk of rationalisation, which increases the risk of supply shortages.

	Measure	Description
	Taxes & fees	
1	Cost Allocation Model, e.g. Green Fee	Allocation of cost associated with public goods or regulations with general population responsibility to the final user in the form of a user-fee. For environmental regulation passing through costs is in line with the Polluter Pays Principle. The revenue of this fee is received by an institution that would have the responsibility to finance the infrastructure required to comply with the new environmental regulation.
2	Hypothecated tax	An indirect taxation on the users by the government. The revenue of this tax provides supply chain actors with funds to introduce new technology that will to comply with new regulation.
	Subsidy & income support	
3	Subsidy	After implementation of a new regulation, the government provides a subsidy to MAHs that reflects costs increases associated with the new regulation
4	Tax credit for marketing at-risk medicines	Incentivise MAHs to market medicines that will drop to negative or near-negative margin levels, by offering tax credits for marketing of these medicines. New regulation can also be implemented with the aid of tax credits, if aligned with the political agenda, such as for the European Green Deal.
5	Income support for MAHs of at-risk medicines	With income support the government provides MAHs with income support for the sales of at-risk medicines. In case of new regulation, income support can also be offered for the new medicines that become at-risk as a result of cost increases.
	Price regulation	
6	Guaranteed fee for at-risk medicines	Setting a minimum fee for at-risk medicines and indexation of this fee with cost changes resulting from regulation, to ensure MAHs maintain a sufficient margin to ensure supply of the at-risk medicines.
	Other solutions	
7	One-In-One-Out (OIOO) - Alleviate other obligations	Compensate cost increases of new regulation by eliminating duplicative regulation or introducing regulation with a similar though opposite cost effect, leading to a cost effect of net zero.

Table 5. Long-list of financing models.

Source: Capgemini research and classification

We ordered the long-listed financing models identified according to expected impact and feasibility. **Effectiveness** depicts the extent to which a certain solution can be beneficial towards the goal of reducing supply shortages of medicines. This means that the solution either directly addresses the cost increase of regulation for the MAHs or provides a financing model that ensures that profit margins on medicines do not drop to unviable level even with a cost increase due to new regulation. Effectiveness has not been adjusted for the number of medicines the financing model applies to. For example, if the solution only applies to the production of at-risk medicines, the financing model can still have a high effectiveness if the financing model successfully sustains supply of those medicines. **Feasibility** depicts the feasibility of implementing the solution. The higher the feasibility, the more likely that the solution can be implemented successfully. An overview of the long-listed financing models and their expected impact and feasibility can be found in figure 7 below.

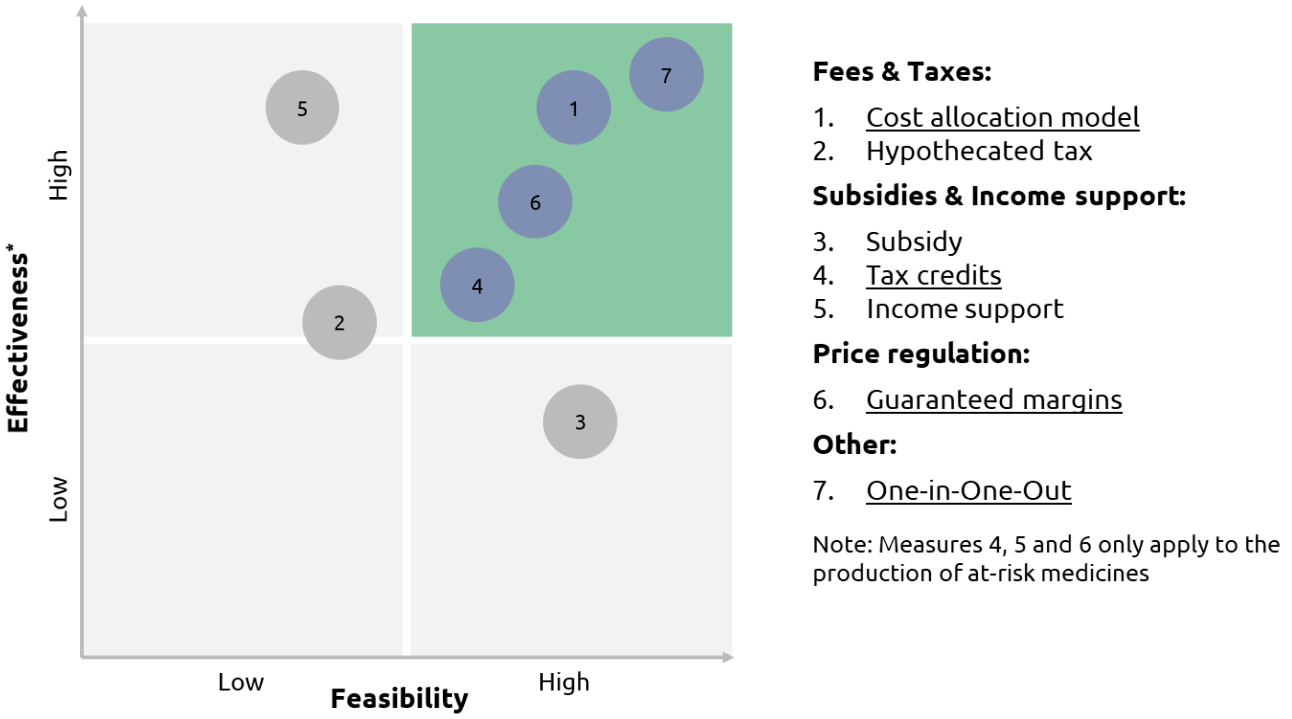

Figure 7. Overview of long-listed financing models and their potential

Source: Capgemini research and classification

From this analysis, the four most promising models based on impact and feasibility are the Cost allocation model, tax credits, minimum fee, and OIOO. A more elaborate description of the non-selected models is presented in Annex 3.

Descriptions of short-listed models

We will describe the four most promising financing models in detail below. It is notable that out of these four new models, the minimum fee and tax credit models are applicable to the marketing of at-risk medicines only. All these models have potential benefits, but also bring about challenges. Thus, the models need to be carefully considered and only illustrate potential solutions to the broad problem of decreasing profit margins on generic medicines and resulting risk of supply disruptions.

Additionally, it is important to note that each of these solutions will require an investment, either from governments, the MAHs, health insurers or other payers. The costs of inaction are not modelled, though are anticipated to be substantial. If these investments are not made, the risk increases that the number of suppliers of certain generic (and at-risk) medicines on the market will further decrease and the odds of supply shortages will increase. If these shortages occur, they also pose a cost burden on the healthcare system, alongside being harmful for patient health [38].

1. One-In-One-Out (alleviate other obligations)

One-In-One-Out (OIOO) is a new model in which governmental institutions alleviate one existing regulation for each newly implemented regulation. The regulation alleviated commonly concerns a regulation that results in red tape, meaning excessive bureaucracy [82]. Relieving a regulation as such results in a cost decrease due to e.g. a decrease in labour hours spent on adhering to these regulations. Duplicative regulation could also be considered for alleviation.

The rationale behind this solution is that the net cost effect for the MAH can be kept at zero, when new regulation is implemented and at the same time an old regulation is lifted. Ideally, governmental institutions would lift a regulation of which the positive cost effect of lifting the regulation offsets the expected negative cost effect of the newly implemented regulation. This model is attractive, as the smaller the net negative cost effect, the less the profit margins on the medicines of the MAH are affected and the more a sustainable medicine supply is ensured, which is the overarching interest. Thereby, relieving one regulation for each new regulation could result in more stable profit margins and supplies.

Introducing such a principle would also require an effective impact analysis of the new regulation, giving the regulator an opportunity to consider the holistic impact, including access.

Additionally, there is also the option to introduce regulation that aims to increase efficiency and reduce costs, like electronic leaflets or use of telematic tools in the regulatory environment that would eliminate national procedures and fees. Such cost-reducing regulation would not need to be offset but could offset new cost-creating regulation.

Similar use cases

The OIOO model is becoming increasingly well-known. In recent years, the OIOO concept was used in numerous EU Member States to cut red tape, with some countries broadening its application to include the reduction of substantive compliance costs [87]. In some countries, instead of OIOO, the measure consisted of one-in-two-out or even one-in-three-out approach. Therefore, this method is commonly referred to as one-in-X-out (OIXO).

Examples of countries that already have at least one implementation of OIXO aimed at reducing administrative burdens are Italy, Latvia, Lithuania and Spain [87]. Additionally, implementations in Austria, Finland (pilot), France, Hungary, Germany and Sweden cover both administrative burdens and substantive compliance costs. Moreover, Poland, Romania, Slovakia and Slovenia are planning to introduce an OIXO rule in the near future.

As the national experiences with OIXO are positive, the new EC announced that they will also start applying OIOO in the future [87]. The EC stated that the OIOO rule would cover all direct compliance costs, being administrative burdens, substantive compliance costs, and charges, where existing [87]. The reason for this broader application of OIOO is that the exact cost reductions were more excessive when also covering compliance costs [87]. Additionally, the proposed system only aims to repeal (or revise) existing regulations that incur recurrent costs, as no cost reductions are achieved by lifting one-off costs.

Although the EC still needs to define their exact approach to OIOO, the willingness of the EC to apply this method allows for opportunities for implementing OIOO in the pharmaceutical industry as well. Additionally, the use of OIOO or OIXO is not limited to an EU level but can still be proposed on a Member State level. On a Member State level this would imply that the Member State determines which national regulation could be relieved when implementing a new national regulation. Additionally, a relieve of regulatory burden can be achieved by harmonization of diverging national regulation across the EU.

Determining which regulation to relieve (the 'out-regulation')

With this model, it is important that the net cost effect of the implementation and alleviation of the two regulations is kept close to zero. To achieve a net zero effect (or better), an institution must conduct research on the expected cost increase of the new regulation. Additionally, they need to have insight into the currently implemented regulations, and which of these regulations cause an excessive burden and became irrelevant.

Challenges

One of the opportunities with the OIOO model is the calculation of the impacts. For this model, an independent analysis needs to be conducted to determine the average cost increase associated with the proposed new regulation[7]. Additionally, this analysis then needs to include research on the cost reduction expected from lifting a certain regulation. Besides that, it is crucial that the institution conducting the analysis has insights into the actual regulations that could potentially be lifted and come with recurrent costs.

Opportunities

Introduction of the OIOO and the need to determine average cost proposed with new regulation is the creation of an additional awareness and visibility for the regulator in terms of the real impact of the regulation.

This financing model can also be combined with the introduction of a regulatory index. This index would measure the actual cost of regulation that is in-place (index 100). The index would be assessed on a yearly basis and any increases in the regulatory index should be reflected in the price of generic medicines.

It is important to note that a limit exists to the number of regulations that governmental institutions can lift. At one point it may become a challenge for governmental institutions to identify excessive regulations, which limits the time span over which this model may provide a solution. There is also likely to be substantial work involved for government institutions to identify regulations to remove and cost implications of each.

2. Tax credits for marketing at-risk medicines

The second financing model is to offer a tax credit to MAHs who market at-risk medicines of which the profit margins would normally not incentivise continued market presence. To enable this new solution, national authorities and the MAHs need to align in terms of Key Performance Indicators (KPIs). For example, both parties must agree on which medicines are at-risk, and the volume of these at-risk medicines are required. The authorities can then offer tax credits in return for the bringing to market these medicines, up to the required amounts.

[7] In some cases, such an analysis is already conducted. For example, the EU Better Regulation guidelines request an impact assessment determining the impact of new regulation to include "the environmental, social and economic impacts, including impacts on small and medium enterprises and competitiveness.

The MAH will receive tax credits from the authority upon successful marketing of the agreed upon medicines. A tax credit is an allowance for the MAH that weighs towards a reduction of tax. To illustrate, if a MAH would need to pay a tax equal to €50.000 and the tax credit is €20.000, then the net tax the MAH needs to pay equals €30.000. With this approach, the costs of marketing of the medicines are partly earned back.

As the authorities and MAHs jointly determine which medicines are at-risk medicines, this model can mitigate the adverse effects of new regulation. If the margins on certain generic medicines decreases due to a new regulation, or other factors that could impact the viability of these medicines, the MAH can discuss this problem with the authorities. Subsequently, the authority can decide to offer tax credits for marketing these new at-risk medicines, allowing MAH to receive tax credits for these medicines. As a result, the cost reduction resulting from the offered tax credits can offset the cost increase resulting from new regulation or other factors.

It is notable that either a reduction of regulatory fees or a subsidy on at-risk medicines results in comparable outcomes.

Similar use cases

In some countries, R&D tax credits are used to promote innovation and increase the incentive for R&D spending. Governments, such as the US and the UK government, implemented this financing model as an increase in R&D spending can drive the economy [88] [89]. In the UK, the government implemented the tax credit for companies operating in the UK. This tax credit allows companies to recover up to 33.35% of its R&D spend as a cash repayment [89]. It is notable that the UK government takes an approach in which spending is repaid in cash, whereas we propose to decrease the amount of taxes the MAH is required to pay. In practice, both options have potential, though we propose to use the latter as it reduces cash-outflow for the government. Responses to the R&D tax credit are positive and implementing tax credits for the marketing of at-risk medicines may thereby provide a solution to minimizing supply shortages as well [88].

Determining the level of the tax credits

For this model, the level of tax credits offered per at-risk medicine needs to be determined, to reduce the risk of oversupply. Oversupply can occur if tax credits are offered infinitely and the MAHs' market more of these medicines than patients demand. If the supply of these medicines is too high, prices drop, and the benefits of the tax credit will be partially offset, resulting in a sub-optimal level of supply sustainability for the tax credit investments. Although the natural rebalancing of supply and demand will decrease the amounts marketed again, the risk is that too many MAHs discontinue these medicines as they become unprofitable, which results in undersupply. A fixed amount of tax credits offered tied to anticipated market demand reduce the risks of oversupply, as MAHs are aware of the extent to which it is profitable to market these medicines. Moreover, the open-ended nature of such an unrestricted tax credit may have unwanted large financial impact on the government. The amount of tax credits given out can be decided upon by authorities, in cooperation with MAHs, based on current supply levels. Additionally, the number of tax credits offered can be adjusted to match cost increases due to regulation, or to create an incentive to bring competitors back onto the market.

Additionally, the amount of a tax credit needs to be set at an amount that at least bridges the gap between the cost price and the market price of a certain medicine, plus an additional profit margin for the MAH. Without inclusion of a profit margin, the tax credit does not offer an incentive to market these at-risk medicines. The total tax credit amount a batch of medicines will bring to the MAH is equal to the given-out tax credit per medicine multiplied by the number of these medicines marketed, as long as the maximum amount of tax credits issued for that medicine has not been reached.

Challenges

One challenge with the tax credit model is the additional labour effort required to run this model. The main source of labour effort is that an institution needs to be appointed that receives input from MAHs on the current at-risk medicines. Additionally, this institution needs to determine how many tax credits are given out for each of these medicines, and what the amount of the tax credits are.

Besides that, it is important that attention is paid to the approach in which tax cuts are implemented. For example, in the U.S. the Tax Cuts and Jobs Act caused strong controversy. This act entailed tax cuts, aimed at creating more jobs and increasing investments. Nonetheless, some MAHs had little increase in R&D expenses the year after. Instead, some MAHs turned out to spend extra money on stock buybacks and investor pay-outs [90] [91]. To mitigate the risk of a similar situation in the EU, we propose that tax credits are only offered when the at-risk medicines are supplied. Thereby, the costs of supplying these medicines have already been made before the tax credits are received, and actual marketing of these medicines is ensured.

A last challenge is that the amount of tax credits offered for a medicine, as well as the amount of these medicines needs to be sufficiently high, to ensure that undersupply does not occur. If either of these amounts is not sufficient, MAHs will not be attracted to marketing these medicines, which results in a continued risk of supply shortages.

3. Guaranteed fee for at-risk medicines or tiered pricing framework

Another financing model is to implement guaranteed fee for at-risk medicines by setting and adjusting minimum remuneration for MAH. In this solution, governmental institutions of each Member State are responsible for determining the necessary value needed to ensure supply of at-risk medicine in their country.

The rationale behind this solution is that establishing a guaranteed margin – by setting a fee sufficiently above the cost price, ensures that the MAH receives a profit margin that allows for a sustainable marketing of the medicine.

The benefit of implementing guaranteed MAH fees for at risk medicines is that MAHs retain similar profit margins and marketing the medicines remains attractive. As a result, a more sustainable supply of medicines is ensured. Additionally, these medicines should automatically be excluded from any price cutting measures that would further contribute to their viability and availability.

Similar use cases

Guaranteed margins by setting (minimum) fee is a governmental measure which is already applied in other parts of the pharmaceutical value chain. For example, in France a fixed dispensation fee is included in the public price of medicines to ensure cost of dispensation are sufficiently covered. Other countries also have similar fixed price compensation in place.

Guaranteed compensation ensures that products can be offered at a sufficient margin to make marketing economically feasible and ensure that products are supplied that would otherwise be discontinued.

Determining the level of the margins and (minimum) fee

The necessary margin needed for sustained supply will depend on the specifics of the product line. As the prices of at-risk medicines differ per EU Member State, it is important that the fees are determined per country and, eventually, per product.

Accordingly, the minimum MAH fee level for at-risk medicines needs to be set carefully to ensure successful implementation of this model and viability of respective medicines. Therefore, the Member State needs to place the minimum price on such a level that enough MAHs receive an incentive to

market the required medicines. The Member State could determine this level either by using a proxy, or by determining the price level where MAH are exiting the market.

An alternative to this model is implementing a 'Ladder' Pricing Framework, which has already been implemented on the market for generic pharmaceuticals in Canada [95]. With a 'Ladder' Tiered Pricing Framework, the price of the generic medicine depends on the number of MAH marketing the product. For example, in the Canadian system the price of a generic medicine is discounted to 50% of the brand reference price, if two MAHs of the generic medicine exist [95]. In this system, the discount will increase or decrease based on the number of players in the market. If the number of players is reduced, the discount will be decreased – leading to higher prices - to incentivize other players to (re)join the market. A similar system could be implemented in EU Member States, where the exact tier levels could be determined based on current prices of generic medicines and the number of suppliers. The advantage of a ladder-style tiered-pricing system is the reduced execution costs, as no detailed analysis of MAHs' cost levels is required, but rather a simple identification of the number of suppliers active in the market.

Additionally, the approach to which the Member State accounts for cost increases due to new regulation needs to be clarified and agreed upon. The easiest approach is to determine the impact of new regulation on the cost and adjust the MAH fee accordingly (considering the mark-up for profitability). Thus, the price level will fluctuate over time.

To ensure that the price level can fluctuate, it is important that the amount of the MAH fee can easily be adjusted. New regulation will regularly appear, and without this flexibility it will not be possible to adjust the market price to a level that ensures that it is sustainable for a MAH to supply the medicines. Besides that, it is important that the government possesses data on which medicines are at-risk, and what their current prices are. Moreover, the government needs to be informed that new medicines may become at-risk and require additional fee increases after implementing a new regulation, as the regulation may have decreased profit margins.

Challenges

With any market intervention, implementation brings about challenges. Here we describe the key challenges associated with implementing a MAH fee for at-risk medicines.

It is also important to consider that there are numerous stakeholders standing in between the MAH and the patient. These stakeholders are commonly a wholesaler and a community or hospital pharmacist. The final price of the medicine reflects the margins and/or fees of these stakeholders. Therefore, the all stakeholders must receive proper remuneration to make the medicine viable.

4. Cost allocation model, e.g. Green fee

A Cost allocation model, such as the one that could be applied to a 'Green Fee', is a new financing model that offers a different type of solution than the three previously discussed models. Whereas the previous models describe financing models that can mitigate the costs of new regulation (or other costs increases), this model is aimed at allocating the additional cost of regulation to the 'correct' entity, including a split between various relevant stakeholders. As such, this financing model can be taken in combination with the previously discussed models.

This model is based on the concept of sharing costs associated with regulatory requirements across all stakeholders that contribute to the societal challenge leading to the implementation of new regulation. One of the main sources for expected future regulatory impact for the pharmaceutical sector is related to environment-related regulation, as seen in the EC's strategic approach to Pharmaceuticals in the Environment and the announced New Green Deal. The EC agenda is supported by the public opinion and industry must adapt and embrace increasing environmental regulation.

For example, among recent developments regarding policies on pharmaceuticals in the environment is the proposal to introduce Extended Producers Responsibility in the form of an urban wastewater treatment fee. The aim of the wastewater treatment fee is to finance the costs of removing pharmaceutical residues from urban wastewater. The rationale behind this fee is that under the Water Framework Directive (WFD) that is part of the strategic approach, one of the focus points is to ensure that urban wastewater containing pharmaceuticals residues is properly treated [46].

In line with the Polluter Pays principle (PPP), charging a fee at the sources where the pollution enters the environment is the optimal location to charge the fees on pollution, aligning economic incentives with ecological desirable actions[8]. Pharmaceutical residue in wastewater can come from many sources, including production effluent, hospital waste or from individual patients – either through excretion or inappropriate disposal. Excretion from human and animal use is the largest driver of pharmaceuticals in the environment. In the example of the urban wastewater fee, cost of pollution arising from the point of manufacturing should be and is addressed by manufactures of the pharmaceuticals through applicable environmental regulation (e.g. the Industrial Emissions Directive) and permits. The manufacturers are also best placed to mitigate this pollution at the point of production. Likewise, costs for pollution arising at the end users' side are best placed on the end users to stimulate responsible use and disposal of medicines, by encouraging rational disposal of medicines and preventing users from throwing left-over pharmaceuticals down drains, directly into the sewage[9].

The costs of introducing technology and procedures at the location of origin must be supported by the MAHs and are essential for companies to comply with local regulations. Additionally, MAHs get charged a fee based on discharge to the water or, if discharge cannot be properly monitored, on overall amount marketed. For the fee for end users, the pollution can be assumed to be related to the intensity of medicine usage, meaning a fee can be levied by means of a mark-up to the price of packs of medicines sold[10].

The revenues of the Green Fee should be received by an external body that transfers the revenues to European and/or national water service providers, who can use these fees to facilitate the treatment of urban wastewater and remove pharmaceutical residues. Considering the lack of liberty in pricing of pharmaceuticals and the strong competition, it is important that the fee is a of non-competitive nature, i.e., value added on top of the price and not subject to price erosion via competition. This ensures that the fee remains stable and can be used by the European and national water service providers to clean wastewater.

Similar use cases

Fees on end-users exist in other industries as well. For example, within the electronics and appliance industries in British Columbia, an Environmental Handling Fee (EHF) exists [97]. The EHF is a fee that applies to the sale of all new electronic products and is paid by the purchasers of the products. The fee reflects the costs of recycling the materials in the products, for example, the batteries. Similarly, the Green Dot, a symbol by PRO Europe, is used to identify that for packages containing the Green

[8] This principle is also captured in Article 9 of the WFD, which establishes that: "The main water uses (households, industry and agriculture) must adequately contribute to the recovery of costs of water services, proportionally to their contributions to the pressures imposed on aquatic ecosystems in line with the PPP".

[9] Research (Coalition of sustainable pharmacy et al, 2020) shows that about 1 out of 10 Dutch people throw away medicine residues at home. About 25% of these people flush the medicines down the toilet or sink.

[10] A study published by the Swiss Federal Institute of Aquatic Science and Technology (Logar 2015) finds Swiss households are willing to pay a substantial amount of money on top of their current water bill for the reduction of pharmaceuticals residues.

Dot a financial contribution is paid. The contribution is paid to a qualified national packaging recovery organization to ensure the collection, sorting and recovery of used (mainly household) packaging [98]. In the case of medicines, the EU disposal mechanisms is supported by the pharmaceutical industry and guarantees the correct disposal of medicines that are left by patients at the pharmacy.

Determining the amount of the fee

The fee would consist of a non-competitive fixed cost amount added to the market price at which a medicine is sold. The amount of the fee depends on the total costs of improved water treatment and the unit on which the fee is charged, be it individual medicines (with or without a weighted correction for pollution caused), the number of packs, or any other measure. As demonstrated in the impact analysis, the fee can be quite small, in the order of 0,5% to 4,5% price increase which should have a very limited impact on affordability, with quite a significant impact in terms of offsetting supply risks.

Challenges

Numerous stakeholders need to work together to ensure that the non-competitive cost of the cost allocation model is received by the external body. Towards this goal, it is important that all stakeholders in the value chain agree that this fee is necessary, to be certain that the fee is transferred to the external body in practice.

One possible implementation of a cost allocation model that would not have the desired effect is the introduction of an Extended Producer Responsibility (EPR). According to the OECD, the EPR is "an environmental policy approach in which a producer's responsibility for a product is extended to the post-consumer stage of its life cycle." While medicine producers should, and do, control any pollution created at the production phase and have set up systems for recycling of medicines, they are not in control of the way the patient handles medicines after purchase. Consequently, they do not have any control over the waste caused at the patient side. Today, no model that would deal with EPR at molecule level has been developed and there is still lack of clarity on potential calculations of quantitative amount of product placed on the market vs real-life monitoring of residues found in wastewater treatment plants. Moreover, due to the nature and purpose of pharmaceuticals, aside from increasing use of biological medicines, it will be very hard to transform them into "eco-friendly products" (the process to research, develop, assure intended medicinal affect, stability and quality and to produce and get approval), as the environmental benefit from enforcing EPR on pharmaceuticals is unknown. Rather, the extra financial burden only increases the risks of rationalization of product lines and supply shortages, compromising patient access.

Another challenge is to ensure proper incentivisation of the users in relation to their health insurance. In an ideal situation, this fee would make patients more aware of the risks of disposing of medicines via sewage, and thereby decrease the extent to which pharmaceutical residues occur in urban wastewater. Subsequently, with a minimal number of pharmaceuticals disposed of via sewage, the fee would only need to finance the costs of water treatment of residues coming from human excretion. However, a slight risk is that the fee works in the opposite direction, and patients neglect the fact that they should not pollute the environment with medicines. This could occur if the patients feel that they pay a fee for treating any 'damage' they are causing or if the eco fee is fully offset by the health insurance payment. Therefore, it is important to consider how this fee can be organized and marketed to the wider public in a way that assures that the fee benefits society.

2.5. EFFECT OF SOLUTIONS ON STAKEHOLDERS

For policy makers, it is highly important to understand how stakeholders in a market will react to a new intervention. We determine the expected responses of stakeholders in the pharmaceutical market to each of the four proposed solutions. Table 6 overleaf provides an overview of the expected effects on stakeholders of each of the four solutions, compared to the current situation in which no financing model is implemented. In this table, we considered the effects of the proposed models on the stakeholders most affected by the solutions. However, it is notable that the pharmaceutical value chain consists of more stakeholders, such as API manufacturers, pharmacies, wholesalers, health insurers and prescribers. When implementing a solution, the effects of the solution on these parties also needs to be considered.

Stake-holder	No financing model	One-In-One-Out	Tax credits for at-risk medicines	Guaranteed MAH fee / ladder tiered pricing framework	Costs Allocation model e.g. Green Fee
Summary	MAHs eliminate products that are not viable Government to decide between acceptance of shortages and increased costs for purchase of alternative medicines that are still marketed Patients dependent on government choice	MAHs can continue existing marketing Government needs to find offsetting measures. Aligned with political agenda, digitalization. No drawback for patients	MAHs can continue existing marketing Government to fund from general means, meaning society pays. Aligned with political agenda (EU industrial Policy) No drawback for patients	MAHs can continue existing marketing Regulator to set appropriate prices	MAHs can continue existing marketing Government to set fee on users (aligned with political agenda. Green deal) Patients keep access to medicines, but will have to pay an additional fee
MAHs of generic medicines	Cost increases from new regulation will squeeze the margins of MAHs and thereby increase the risk of rationalisation of medicines. The number of product lines at risk is dependent on the size of the impact of the new regulation.	When implementing OIOO, the cost reduction of removing an old regulation offsets the cost increase of the new regulation, balancing out to neutral impact on the cost for MAHs. Consequently, negative impact of new requirements on viability of product lines is prevented, and risk of rationalisation of medicines is mitigated.	With this model, the tax credit ensures that marketing at-risk medicines will result in sufficient profit margins to sustain marketing. Furthermore, tax credits can be offered for new medicines that become at-risk because of new regulation. Therefore, this approach sustains the MAHs' profits and revenues as they do not have to rationalise medicines due to lacking profit margins. Moreover, the MAHs are better able to contribute positively to public health, by marketing the medicines that society requires.	Minimum fee enables governmental institutions to set the market price above the cost and enable indexation of these minimum prices with cost changes resulting from regulation. Like the other solutions, this model thereby supports profit margins of product lines, which decreases the risk of rationalisation when costs increase due to new regulation.	This model supports the distribution of financing costs of new environmental regulation between the patients, which decreases the risk of rationalisation of medicines, since the costs associated with new environmental regulation are distributed fairly across the users. This results in a reduced cost burden of new environmental regulation on MAH and avoids rationalisation of medicines.

Governmental institutions	Governments will be faced with a decision to either accept the shortages (and the associated impact on health of its citizens) or turn to higher priced alternative medicines that are still marketed. Choosing for originator medicines means a significantly higher cost level with an associated financial impact on either the government budget or the budget of its citizens.	As with tax credits, the model mitigates the problem of supply shortages. As the main 'cost' of this model is the elimination of regulatory burdens on companies, no significant direct effect on government is foreseen other than the cost of ensuring a proper identification of regulation to be relieved, as well as its costs and incorporation of any critical components in other regulations It should be noted that this model is restricted: when policy makers have no more regulations available that they can alleviate, this solution will only be an option for introduction of new cost-saving regulation paired with cost-incurring regulation Government can find political and economic support from EC, considering the digitalization agenda	The benefits of this model for governments is that it mitigates the problem of supply shortages. However, the tax income of the government will reduce, as tax credits result in a tax reduction for MAHs. The government also must determine the amount of tax credits offered and given out to MAHs. This results in an additional financial burden for the government. Government can find political and economic support from EC, considering the industrial policy agenda	This model requires effort from the governments, as they need an institution that can respond to claims for at-risk medicines by assessing these claims and setting appropriate fees for these medicines. A tiered pricing framework is easier to implement and is adaptable to all product lines and market conditions.	For the model Fee governments only have to ensure that the fee is properly implemented. For pharmaceuticals, this entails allowing for an additional cost to be placed upon current medicine prices and ensuring that this cost is distributed directly to relevant entities. Additionally, the governments need to assess the amount of the fee, depending on the cost effects of new regulation. Government can find political and economic support from EC, considering the green deal agenda
Patients	Patients of generic medicines are the main victims of recurring supply shortages. Without generic medicines access and capacity,	Patients will benefit from a sustained medicine supply. Also, with net costs to government turning out quite low, no significant financial	Patients will have access to the required medicines. The cost of the tax credits will be transferred to society at large, as the funding of the tax credits will be provided	Patients will continue to have access to the required medicines. Under the tiered pricing framework, the number of	Patients will receive better access to their required medicines. Though, as a result of the cost allocation fee, the medicine prices will increase. If the patient is the cost-carrier of its

ability to finance new medicines will decrease	impact is expected for patients.	from the government overall resources, prioritizing health and patients access over other political options	MAHs will vary to guarantee stable supply to patients.	own medicines, this results in a higher prices and increased costs for the patient. However, the patient will be co-responsible for the disposal and will be directly contributing to a greener world.

Table 6. Expected effects of financing models on stakeholders on the pharmaceutical market.

Source: Capgemini research and classification

Evaluation of financing models, including effect of financing models on medicine supply

Table 6 provides insight into the expected responses of different stakeholders on the new financing models proposed. It should be noted that in this section, expected effects are presented. Actual opinions on these models may differ and need to be further researched.

The most obvious financing model is the OIOO model, where all the benefits of maintained supply of medicines is achieved without any major financial drawback. Hence, wide support for this financing model may be likely. The main restriction is the decision on the presence of regulations that can be used to compensate the impact of new regulation. Successful applications of OIOO in Member State countries are primarily focused on businesses, meaning that the exact applications of OIOO on the pharmaceutical industry still need to be explored, mainly on an EU level. However, according to pharmaceutical companies, there are regulations, particularly at a national level, that have limited value given the EU role in regulating medicines, and that are identified in the MFE Regulatory Efficiency report [99].

The Cost allocation model, such as the Green Fee, is the next-best alternative. In the case of a Green Fee, as the fee is charged on the entity where the medicines enter the environment, this measure is in line with the Polluter Pays Principle. As a result, there will be an economic incentive at the party where the ecological effect is realised. The solution prevents unwarranted burdening of MAHs, thus preventing negative impact to supply and makes the end user aware and responsible for the correct disposal of medicines. The main drawback is that this model is only applicable to regulations targeting societal challenges with broad stakeholder responsibility.

With the financing models for tax credits, the government uses financial means to support the marketing of at-risk medicines. Depending on the health finance system in place and the choice for model and detailing by the government, the burden may be put on the patients or, more likely, society at large (directly or via the health insurer).

The system of guaranteed fees relies on MAHs receiving a guaranteed (minimum) fee for product lines. The ladder-style tiered-price system may help to identify the products that require such fee implantation and to set the fee level that would make marketing these products viable to companies. In this system, only the number of suppliers needs to be checked, thus relieving the execution costs to a significant extent.

For both the tax credit model and the fee model, the effectiveness will be correlated with the amount of efforts put into the detailed analysis of the height of the required burden or fee level. The more detailed the analysis conducted to assess the necessary financial support – either in tax credit form or via fee – the better the intervention will be to address the supply risks without over- or undercompensating. However, such a detailed analysis will incur costs[11]. The main exception is the ladder-style tiered-price system, with only limited analysis required.

[11] See, for example, the cost of national regulators regulating prices in regulated sectors, like energy, telecom and the postal sector.

The financial impact of both the MAH fee and tax credits is expected to be significantly less than the option of non-action. In the case of non-action, the negative impact of new regulation and the associated reduction in supply will lead to increased risks to public health.

3. CONCLUSION

The aim of this research was to propose new financing models that could mitigate the risk of medicine shortages by reducing the potential for adverse effects of new regulation in the generic sector. Our findings show the unintended effects of new regulation on medicine supply can be quite impactful, as new regulation increases costs, while MAHs of generic medicines cannot subsequently raise prices to accommodate the additional costs. Relatively modest cost increases can already result in a significant part of the product lines becoming economically unsustainable. Consequently, there is a significant risk of MAHs of generic medicines ceasing marketing of certain medicines. The fewer suppliers, the higher the risk of supply shortages. Especially in the current situation with existing supply disruptions, additional shortages would be highly undesirable from a public perspective.

With new regulation on the way, such as the EGD at EU level and climate policies in Member States, the sector requires solutions to mitigate the unintended adverse effects of new regulation on patient access to medicines. Only then can Europe ensure a sustainable generic medicines supply and safe-guard public health. In this research, we propose four new financing models to mitigate the adverse effects of new regulation. These models are MAH fee for at risk medicines (and ladder-style tiered pricing framework), tax credits for at-risk medicines, OIOO and a Cost allocation model, such as a Green Fee, for generic medicines. All four financing models provide opportunities to address the problem of negative margins amongst MAHs and can therefore be beneficial to public health. The most prominent candidate is OIOO, although it does require elimination of other regulation. The Cost allocation model, as exemplified by a Green Fee, is a good alternative to implement new regulation that impact a wide range of stakeholders. In addition to a high level of fairness (Polluter pays), a Green Fee puts the economic incentives at the party where the ecological effect is realised and prevents unwarranted burdening of MAHs, thus preventing negative impact on supply. Tax credits and MAH fee are good market alternatives to address supply issues of at-risk medicines.

It is important that pharmaceutical companies, trade associations and policy makers jointly address this problem and agree on solutions, to ensure that root causes of supply shortages are addressed. This research is only the first step in identifying suitable solutions. To fully assess the potential of each proposed solution, a detailed quantitative research needs to be conducted. In that research, the exact effects of each model on the supply of medicines needs to be calculated, to determine the benefits to society. Additionally, a cost assessment of each financing solution is required.

ANNEX 1 – DETAILED METHODOLOGY

To establish this report, we conducted desk research and interviews, and engaged in modelling and analysis. In this annex we provide a more elaborate description of the activities conducted and the methodology used for this research.

In our desk research we consulted an extensive number of sources. These sources were all publicly available, such as the website of the European Medicines Agency (EMA), Medicines for Europe and governmental websites. We conducted desk research on a wide number of topics, namely: 1) the current status and characteristics of the European pharmaceutical market, 2) recent regulations on the pharmaceutical market on EU and Member State level, 3) regulatory initiatives on EU and Member State level, 4) the consequences of new regulation on MAHs, 5) different business models among MAHs 6) positioning and stability of MAHs of generic medicines and 7) potential financing models, which mainly consisted of research on models implemented in other markets.

For this research, we also conducted interviews with internal Capgemini pharmaceutical experts. In these interviews, we engaged in conversations on the stability of originator MAHs, as well as MAHs for generic medicines. This input was used to gain insight into the extent to which MAHs cope with small profit margins on generic medicines. Therefrom, we were able to review the impact of regulation on numerous MAHs and gain insight into the prevalence of margin squeeze related to new regulation. We also gained input on which other stakeholders are affected by cost increases at MAHs. Once we determined the effects of regulation on MAHs, we also asked for the experts' input on financing models that could potentially help finance the growing costs of new regulation. The experts proposed potential models and engaged in determining the potential and attractiveness of each model. Moreover, we discussed the most promising solutions to gain their thoughts on success factors and challenges associated with each of the four models.

Another extensive part of this research consisted of modelling and analysis. First, we conducted a business model analysis to roughly determine the differentiation in the business models used by MAHs. For this analysis, we reviewed the annual reports of 19 MAHs to determine differences among MAHs. Via this analysis we determined that the most obvious distinction was visible in the Profit & Loss (P&L) statements between MAHs that focus on originator medicines and MAHs that focus on generic medicines. The main differences were that originator focused MAHs typically had higher R&D expenses and higher profits margins, whereas MAHs of generic medicines coped with smaller profit margins. Comparing the P&L statements of both types of MAHs thereby gave us a good insight into the main bottlenecks for MAHs of generic medicines. The focus of the remainder of the research was on MAHs of generic medicines, due to the low profit margins and thereby higher risk of medicine shortages amongst these MAHs.

From all MAHs analysed, thirteen MAHs belonged to the category of MAHs of generic medicines. Subsequently, we developed a typical P&L statement of an MAHs of generic medicines by analysing the P&L statements of these thirteen MAHs. All P&L statements were retrieved from public figures. The following thirteen MAHs were reviewed in this analysis:

1. Sun Pharma
2. Dr Reddy's
3. Krka
4. Stada
5. Cipla

6. Hikma
7. Sawai Pharmaceuticals
8. Mylan
9. Fresenius Kabi
10. Sandoz
11. Teva
12. Zentiva
13. Par Pharmaceuticals

From these thirteen MAHs of generic medicines of whom we analysed the P&L statements, we did not include Teva, Zentiva and Par Pharmaceuticals, as their P&L statements showed significant outliers.

From this analysis, we developed a typical P&L statement of an MAHs of generic medicines to use as input for our business impact analysis. In this analysis we measured the impact of new regulation on MAHs of generic medicines. We started off with the typical P&L statement and simulated how the typical MAHs of generic medicines may cope with shocks. Examples of these shocks include a variable cost increase in the production costs or a fixed cost increase in R&D expenses. The model that we developed allows the user to give a cost increase as the input, such as a 3% cost increase in cost of goods sales, where after the model calculates and displays how the margins decrease per product line. From the output, the user can determine the number of product lines that end up with negative margins due to the cost increase, and therefore may need to be rationalised.

Once we understood how regulation impacted MAHs of generic medicines, we conducted research on solutions to mediate the adverse effects of new regulation. From the interviews and desk research we first created an extensive list of 15 potential financing models. We reviewed all 15 models and removed all models that were too far-fetched or had too limited impact. This resulted in a reviewed long list of seven potential financing models. Drawing on existing models used in other sectors, such as agriculture, we determined what these models would exactly entail. From these seven models, we created a short list of the four most promising models, in cooperation with our internal pharmaceutical experts. Subsequently, we determined the proposed form, as well as the key challenges of each of the short-listed models.

For each of the potential financing models, we aimed to determine the impact on different stakeholders via a stakeholder analysis. We selected several stakeholders to include in this analysis, by first considering all stakeholders of the pharmaceutical industry and, subsequently, deciding which stakeholders were most affected by the short-listed models. In this analysis, we compared the impact of each model on each stakeholder to the situation as is, in which no solution exists, and supply shortages are increasingly common.

To finalise this research, we determined of each model whether it had a positive impact on medicine supply, and evaluated each model based on their attractiveness. This led us to bring about a proposal for four models, that can potentially mitigate the adverse effects of regulation on MAHs and medicine supply.

ANNEX 2 – FINANCIAL FIGURES OF MAHS

In paragraph 2.3, table 4, we describe a typical high-level Profit & Loss account of an MAHs of generic medicines. Below we provide the figures of the MAHs used to generate table 4.

First, we determined the absolute values of 10 MAHs for annual revenue, cost of sales, operating expenses, non-operating expenses and net earnings. We then converted all absolute values to USD and determined the values as percentage of the annual revenue.

The figures in table 7 display the absolute values in local currencies, and the figures in table 8 illustrate these values in percentage of annual revenue of each MAH.

	Sun Pharma (in mill. INR)	Dr Reddy's (in mill. RON)	Krka (in mill. EUR)	Stada (in mill. USD)
Annual revenue	101.342,90	142.028,00	1.331,86	2.330,82
Cost of sales	22.101,20	65.724,00	561,13	1.139,49
Operating expenses	72.556,10	64.387,00	538,28	813,28
Non-operating expenses	3.883,10	2.424,00	30,11	35,18
Net earnings	3.056,40	9.806,00	173,77	310,53

	Cipla (in mill. INR)	Hikma (in mill. USD)	Sawai Pharmaceuticals (in mill. YEN)	Mylan (in mill. USD)
Annual revenue	117.796,90	2.076,00	184.341,00	11.433,90
Cost of sales	33.033,10	1.004,00	107.204,00	7.432,30
Operating expenses	97.788,70	612,00	39.399,00	3.096,00
Non-operating expenses	119,00	52,00	5.207,00	607,20
Net earnings	15.460,40	335,00	32.531,00	352,50

	Fresenius (in mill. EUR)	Sandoz (in mill. USD)
Annual revenue	33.530,00	10.098,00
Cost of sales	23.696,00	5.530,00
Operating expenses	4.583,00	3.236,00

Non-operating expenses	2.274,00	150,21
Net earnings	2.027,00	944,23

Table 1: Individual P&L statements of MAHs of generic medicines, in absolute values.

	Sun Pharma	Dr Reddy's	Krka	Stada
Annual revenue	100,00%	100,00%	100,00%	100,00%
Cost of sales	21,81%	46,28%	42,13%	48,89%
Operating expenses	71,59%	45,33%	40,42%	34,89%
Non-operating expenses	3,83%	-1,71%	2,26%	1,51%
Net earnings	3,02%	6,90%	13,05%	13,32%

	Cipla	Hikma	Sawai Pharmaceuticals	Mylan
Annual revenue	100,00%	100,00%	100,00%	100,00%
Cost of sales	28,04%	48,36%	58,16%	65,00%
Operating expenses	83,01%	29,48%	21,37%	27,08%
Non-operating expenses	0,10%	2,50%	2,82%	5,31%
Net earnings	13,12%	16,14%	17,65%	3,08%

	Fresenius	Sandoz	Total
Annual revenue	100,00%	100,00%	100,00%
Cost of sales	70,67%	54,76%	48,41%
Operating expenses	13,67%	32,05%	39,89%
Non-operating expenses	6,78%	1,49%	2,49%
Net earnings	6,05%	9,35%	10,17%

Table 2: Individual P&L statements of MAHs of generic medicines, in percentage of annual revenue

ANNEX 3 – ADDITIONAL FINANCING MODELS

In paragraph 2.5 we extensively describe four financing models: OIOO, minimum prices, tax credits and a cost allocation model. Below follows an overview of the three remaining models on the long list of potential solutions.

1. **Hypothecated tax**
    a. Regulation specificity: Specific to environmental regulation
    b. Medicine types: Generic medicines
    c. Description: A tax on the patient of which the revenue is dedicated as a subsidy to the MAH to support the MAH in adhering to new environmental regulation. Paying this fee can illustrate the recognition of the patient in e.g. the value and importance of protecting the environment.
    d. Rationale: If the patient pays a tax to reflect the additional costs for the MAH to adhere to environmental regulation, the tax can be used to subsidize the MAH and thereby help the MAHs become more environmentally friendly. The fee can be increased to account for cost increases due to new regulation.
    e. Approach: Member State governments place a tax on generic medicines, where the tax reflects the additional costs new regulation for MAHs brings about. The cost effects of new regulation need to be quantified to determine the amount of tax. The MAH then uses the hypothecated tax revenues to reduce its environmental externalities.
    f. Cost-carrier: Patients, via increased prices
    g. Similar use cases: In the UK tax system National Insurance contributions (NICs) were used, of which the majority of the revenue was automatically spent on social security benefits [100].
    h. Challenges:
        i. The exact amount of the tax needs to be determined, which needs to reflect the cost increase for the MAHs as a result of new regulation.
        ii. It is difficult to track where exactly the MAH will use the received subsidy for.
    i. Feasibility: Medium
    j. Impact: Medium

This model was not included in the selection as this model is comparable to the cost allocation model, but the hypothecated tax model is less efficient. In this model, the tax needs to go via governmental institutions to the MAHs. Additionally, a downside of this model is that it is hard to track where exactly the MAH will spend the received subsidy on.

2. **Subsidize cost increase of regulation**
    a. Regulation specificity: Not designed for a specific type of regulation
    b. Medicine types: Generics
    c. Description: Provide MAHs with a subsidy to reflect the cost increase of new regulation.
    d. Rationale: If MAHs receive a subsidy that reflects their additional costs to adhere to new regulation, the cost effect of new regulation becomes net zero. This ensures that profit margins on pharmaceuticals remain unaltered and supply is sustained.
    e. Approach: The government pays a lump sum to the MAH. This lump sum should reflect the increases in fixed and variable costs due to new regulation for the MAH.

f. Cost-carrier: The government, by paying a subsidy
g. Similar use cases: Subsidies for fossil fuels, where MAHs of fossil fuels receive subsidies from governmental institutions as a means of support [101].
h. Risks:
    i. The exact amount the lump sum should entail is hard to determine, especially when variable cost increases over future years are involved.
    ii. A subsidy is burdensome for governmental institutions.
    iii. Subsidies could be used by MAHs for purposes they are not meant for.
    iv. Other sectors may want a subsidy as such as well, which may result in governmental institutions refraining from providing this subsidy. Therefore, the subsidy would need to be framed in such a way that it reflects the importance of the MAHs for public health.
i. Feasibility: High
j. Impact: Low

This model was not included in the selection since it has similarities with the tax credits model, but with less impact. The main reason being that this subsidy can be used by the MAH for other purposes than adhering to new regulation. Additionally, a subsidy brings about a significant cash-outflow for governmental institutions.

3. Income support for MAHs of at-risk medicines

a. Regulation specificity: Not designed for a specific type of regulation
b. Medicine types: Medicines at-risk
c. Description: Providing MAHs with income support on the sales of pharmaceuticals with low profit margins in case new regulation that negatively impacts their margins is implemented.
d. Rationale: The benefits of marketing at-risk medicines with low profit margins are small for MAHs. Income support for those medicines could incentivize the MAHs to market these medicines nonetheless and ensure they have a sustainable income.
e. Approach: The government gives income support to MAHs that market at-risk medicines. The income support is dependent on the number of at-risk medicines they market.
f. Cost-carrier: The government, via income support
g. Similar use cases: Payment for sustainable farming methods ("greening") [102]. The difference with this existing model is that income support is usually only given in case the income of the MAH is not enough at all, whereas here we propose only giving income support for the at-risk medicines that MAHs bring to market.
h. Risks:
    i. Oversupply of at-risk medicines, due to the ability to obtain income support when marketing these medicines. This would occur when the income support provides a relatively high profit margin. Governmental institutions subsequently cope with a cost burden, as they promised to provide income support to MAHs of these at-risk medicines.
    ii. On the other hand, a lack of supply of at-risk medicines occurs when the income support is too low, and therefore provides little incentive to the MAH to market these medicines.
i. Feasibility: High
j. Impact: Low

This model was not included in the selection since it has similarities with the tax credits model, but it is less feasible. The reason being that income support can lead to oversupply, which will result in a burdensome cost on governmental institutions.

ANNEX 4 – MODEL DESCRIPTION

In this annex we describe how users can work with the impact analysis tool provide alongside this report.

Introduction

This tool computes and visualizes how cost changes, possibly due to regulatory effects, can impact the profitability of products in a company portfolio. The inputs required are company financials and relative and/or absolute cost changes for specific types of compliance costs. The output of the tool contains a graph that visualizes the change in profitability of product lines when cost changes occur. The tool has a frontend and a backend interface.

Frontend

The frontend worksheet is named "Tool" and contains the required input fields and the generated output. A more elaborative description of the input and output is provided below.

Input

The tool needs several information inputs. First, the end user needs to select an answer either by using drop-down menus of by entering data for the following questions:

1. Do you want to manually input company financials, or do you want to use pre-defined industry average numbers?
2. Are you only entering relative cost changes, absolute cost changes or both?
3. How are the relative cost changes defined? As a percentage of annual revenue, cost of sales, operating expenses or non-operating expenses?
4. How would you like to define the product categorization boundaries (based on which exact product profit margins)?

Second, if the user chooses to manually input company financials the following fields should be filled out:

- Total annual revenue
- Cost of sales
- Operating expenses
- Non-operating expenses
- Number of products in portfolio

If the user chooses to use the pre-defined pharmaceutical industry average numbers, no data needs to be filled in under the "Company financials" heading. The data with which the aggregated financials were calculated can be found in annex 2 of this report.

Third, the perceived/expected cost changes need to be entered. These cost changes can either be entered as relative numbers, absolute numbers or as a combination of the two. Based on the users' answer to question 3 from above, the relative cost changes will be converted to absolute numbers in the backend, using the corresponding financial metric. Note that some fields may be blocked from editing based on the answers given to input question number 2.

Output

The output consists of a graph that visualizes the results from computations performed in the backend on the input. It displays how the profitability of products in a company portfolio changes as a result

of certain cost changes. For interpretability reasons, products have been grouped into certain categories based on their profit margin. Each coloured block in the graph represents a different profit margin classification. The blocks on the left-hand side show the profit margin category sizes in the original situation, whereas the blocks on the right-hand side show the margin category sizes when costs change. An important note is that it is possible for the profitability to become negative for certain products when costs increase.

Backend

To get from the input to the output, several transformations are conducted on the provided data. The computations performed on the data from the input sheet can be found in the "Backend" worksheet and are, in order, as follows:

1. Net earnings are calculated by subtracting the sum of the cost of sales, operating expenses and non-operating expenses from the annual revenue.

2. The total profit margin is calculated by dividing net earnings by the annual revenue.

3. Basic metrics required to simulate the profit margins for the products in the company portfolio are then created. These metrics are as follows:

    a. Minimum and maximum product profit margins. These are set at 0% and 2*total profit margin, respectively.
    b. Margin step size, using the following formula

$$\text{Margin step size} = \frac{\text{Total number of groups}}{(\text{Max margin} - \text{Min margin})}$$

4. The relative cost changes are transformed into absolute cost changes using either the annual revenue, cost of sales, operating expenses or non-operating expenses. These cost changes are then summed with all the absolute cost changes to form the total cost change.

5. The total profit margin decrease is computed using the calculated total cost change.

6. Each of the products gets assigned an integer product ID ranging from 1 to the total number of products. Then, a product specific profit margin is calculated for each of the products using the following formula:

$$\text{Group profit margin} = \text{Max margin} - ((\text{Group ID} - 1) * \text{Margin step size}) - \frac{\text{Margin step size}}{2}$$

7. The products are categorized based on their profit margin into categories defined by the user.

8. Sizes of all profit margin categories are expressed as a percentage of the total portfolio for each category. These percentages sum up to 100%. This is done for both the original case (where no cost changes are considered) and the case where there are cost changes.

Assumptions

To allow the tool to produce the output, several assumptions are made. These assumptions are as follows:

- The cost change impacts every product equally
- The differences between product profit margins are linearly
- No product in the original portfolio has a negative return
- The maximum profit margin is 2*total profit margin

ANNEX 5 – SOURCES

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