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The challenges of regulatory pluralism

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ABSTRACT

Countries with small and/or less-resourced regulatory authorities that operate outside of a larger medical product regulatory system face a regulatory strategy dilemma. These countries may rely on foreign well-resourced regulators by recognising the regulatory decisions of large systems and following suit (*regulatory reliance*); alternatively, such countries may extend formal decision recognition to regulators in multiple other jurisdictions with similar oversight and public health goals, following a system which we call *regulatory pluralism*. In this policy comment, we discuss three potential limitations to regulatory pluralism: (i) regulatory escape, in which manufacturers exploit regulatory variation and choose the lowest regulatory threshold for their product; (ii) increased fragmentation and complexity for countries adopting this approach, which may, in turn, lead to inconsistent processes; and (iii) loss of international bargaining power in developing regulatory policies. We argue that regulatory pluralism has important long-term implications, which may not be readily apparent to policy makers opting for such an approach. We advocate for the long-term value of an alternative approach relying on greater collaboration between regulatory authorities, which may relieve administrative pressures on countries with small or less-resourced regulatory authorities, regardless of whether countries pursue a strategy of domestic regulation or regulatory pluralism.

1. Introduction

Regulatory systems encompass a set of standards and processes which aim to ensure the quality and safety of medical devices in a given jurisdiction. Recently, two European countries have taken steps towards simultaneously adopting regulatory systems from more than one country in parallel for recognising the market access pathways of medical devices. In Switzerland, a proceeding to recognise medical devices from non-European Union (EU) regulatory systems was adopted by parliament [1], and in the United Kingdom (UK), a proposed reform introduced a new regulatory model which would allow for "rapid, often near-automatic sign-off for medicines and technologies already approved by trusted regulators in other parts of the world" [2]. These activities were triggered by the UK's withdrawal and Switzerland's exclusion from the jointly regulated European single market, which challenged policy makers in both countries to secure domestic supplies of medical devices.

Often, small countries and/or those with less-resourced regulatory authorities adopt a policy of conforming with larger regulatory systems, which is known as ***regulatory reliance*** [3,4]. Under regulatory reliance, regulatory pathways and product definitions from (typically) larger, well-resourced regulatory authorities are adopted by a less-resourced regulatory authority to form a unidirectional framework for facilitating market entry of new therapeutics, such as drugs and medical devices. Scarce resources of a regulatory authority may reflect a country's economic capacity or may be the result of a well-considered resource-optimisation decision. Reliance on the decisions of an external renowned regulatory authority allows judicious use of scarce

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resources and facilitates a transfer of regulatory expertise to the reliant regulatory authority. In addition, decision-makers may recognise the fact that firms prefer to enter the biggest market(s) first. Consequently, smaller countries opt for policies that lower the barriers to entry for their own domestic markets, thereby increasing the likelihood of patient access to new therapeutics. Regulatory reliance dramatically lowers the cost of entry into "reliant" markets, while still ensuring product quality and patient safety. A version of this phenomenon was seen in Switzerland and the UK until the suspension of negotiations on the mutual recognition agreement between Switzerland and the EU in 2021 and the entry into force of Brexit in 2020, respectively. Until earlier this decade, these two countries were fully integrated into the European market and adopted the EU's Medical Device Regulation (EU MDR) [5]. Today, Switzerland and the UK are considered third parties to the EU and no longer part of the European single market.

To ensure availability, product range, and quality of medical devices, both countries are now seeking to extend recognition of regulatory decisions from *multiple* other jurisdictions with similar (but far from identical) regulations, following a system which we call ***regulatory pluralism***. Regulatory pluralism allows therapeutics—in these cases, medical devices—to access a given market through multiple distinct regulatory pathways. In concrete terms, this means that manufacturers that have successfully completed the authorisation or registration procedure in a reference country may sell their products in a country that accepts multiple regulations (i.e., the pluralistic country). This pluralistic country would consider foreign documentation to be requisite evidence for fulfilling safety and performance requirements and would rely on the post-market surveillance activities of the reference country.

Of course, pluralism can be interpreted in different ways. In the most liberal case, the pluralistic country could simply require the appointment of an authorised representative, a sales notification and—for consumer products—a translation of the instructions for use into the national language. A more restrictive approach could require the manufacturer to provide some additional evidence or adaptations in the quality management systems before placing the product on the market.

Although regulatory pluralism comes with implementation challenges, it offers substantial advantages for pluralistic countries. First, it promises increased flexibility compared to the pursuit of traditional regulatory reliance vis-à-vis (only) one other regulator. For instance, if one predominant regulation is perceived as too restrictive for innovation or seen to limit manufacturers' incentives to distribute products in a country, regulatory pluralism may offer a manufacturer a diversity of alternative regulatory pathways and tools for market entry. Therefore, regulatory pluralism improves access to medical products within these (typically smaller) markets. Second, regulatory pluralism reduces dependence on a single reference country. For example, the transition from the Medical Device Directive (EU MDD) [6] to the EU MDR resulted in a shortage of notified body capacity required for product certification in the EU. The option to instead reference an alternative regulatory system, such as the U.S. Food and Drug Administration (FDA), would have reduced the impact of such a shortage in pluralistic countries. Finally, regulatory pluralism has the potential to increase competition between suppliers by providing multiple options for market access. This may also lead to increased competition through parallel imports, which will improve the efficiency of the market in favour of users and patients.

2. Challenges arising from regulatory pluralism

2.1. Regulatory escape

Different regulators place different demands on medical device manufacturers, which result in heterogeneous clinical evidence requirements across jurisdictions [7–9]. This variation has historically emerged from diverging philosophical underpinnings and degrees of targeted consumer protection [10]. In markets with regulatory pluralism, manufacturers can exploit such differences between regulatory pathways and choose the lowest regulatory threshold for their device. For instance, new devices can be cleared by the U.S. FDA under the 510(k) process by demonstrating substantial equivalence to so-called "predicate" devices, without presenting the same level of evidence that would otherwise be required by the most recent regulation. Because 510(k) clearance is based on similarity to one or more previously cleared devices, some products now link to chains of predecessors that can be traced back to products brought to market as early as the 1960s or that have been recalled [11,12]. With the EU MDR that entered into force in the EU in 2017, manufacturers have to recertify all previously-marketed products according to the requirements established in the new regulation – even if these products have been safely on the market for decades. Under regulatory pluralism, a manufacturer wishing to enter the Swiss or UK market would have the choice between either an EU-level *or* FDA regulatory decision—where levels of rigor and the recency of marketing (re)authorisation will vary by product. This approach to selecting regulatory pathways is what we call *regulatory escape*. It enables manufacturers to systematically avoid more stringent regulations aimed at assuring the quality and safety of a device [13] in pluralistic countries.

It is challenging for policy makers to find the optimal level of regulation that balances the interests of all stakeholders, including patients, health care providers, and manufacturers. More highly regulated markets will attract fewer novel products and regulatory escape may be one legitimate mechanism that allows manufacturers to provide patients with access to innovative and safe technologies. As it is impossible to determine the optimal nature and degree of regulation *ex ante* or to test different configurations, the availability of different regulatory pathways may be one viable way to observe whether increased regulatory stringency translates into improved patient safety, better access to innovative products, and more efficient markets. Thus, over the long-term—and if closely monitored and thoughtfully studied—regulatory escape may inspire simplification of overregulated systems without risking a loss in patient safety or market efficiency.

2.2. Increased fragmentation and complexity results in inconsistencies

Regulatory pluralism introduces considerable complexity for authorities, manufacturers, and importers, as well as patients and health care professionals. Across regulatory authorities, many devices are classified at different risk levels or are subject to unique regulatory pathways (such as the humanitarian device exemption in the United States, which allows device approval without the demonstration of effectiveness) and requirements (such as post-marketing studies and surveillance). Regulatory authorities engaging in regulatory pluralism must acquire and maintain knowledge about the different regulatory systems, enact their own multi-market surveillance systems that consolidate information from different jurisdictions, and exchange and collaborate—to the extent possible—with foreign authorities on market surveillance activities. This effort is not to be underestimated and could lead to significant increases in the work required by medical device teams working with authorities in pluralistic countries. Further, health care professionals might be challenged by different reporting requirements for adverse events or other post-marketing surveillance obligations that are specific to certain regulatory pathways. Fragmented reporting channels may also further complicate the synthesis and assessment of post-market safety information, making it more difficult to assess the quality and safety of a product. From the consumer perspective, patients, too, might become confused by similar devices that originate from different regulatory systems. For example, the same product might come with different packaging, different foreign support information, different instructions for use, or, in the case of products with a digital component, different default settings in the software.

The impact on administrative efforts of regulatory pluralism on economic operators, i.e., manufacturers, importers, or distributors, is likely to be mixed. While regulatory pluralism facilitates the operation

of manufacturers that are only active in one of the reference countries as it enables them to reuse their documentation, manufacturers that are active in several reference countries might be challenged by requirements to maintain post-market activities from all regulatory systems in the pluralistic country. To complicate matters further, it is often the case that manufacturers do not have full control over their supply chains and parallel importers will serve the pluralistic country with any authorised or registered product, although the manufacturer or its authorised representative would likely bear the responsibility and/or liability. In addition, distributors, authorised representatives, and users, such as hospitals or laboratories, will have to acquire and maintain some basic knowledge about the different regulatory systems of the products in their portfolios and workflows. Further, under regulatory pluralism, it may be demanding for manufacturers to determine which regulatory system is most appropriate or relevant for a certain product in a jurisdiction applying regulatory pluralism. This lack of *ex ante* clarity is particularly challenging, as the set-up and maintenance of parallel reporting systems is costly and complex. For example, a manufacturer that has registered a given product in the US and the EU and is selling that product in Switzerland, could feasibly be asked/expected to provide quality and safety data to Swiss and European databases for product registration and adverse event reporting (swissdamed and EUDAMED), as well as to the US equivalents (MAUDE and GUDID).

Such reporting complexity can be partially managed by electronic systems if regulations are similar, and resources are abundant. However, the medical device market includes many small and medium enterprises (SMEs) that might be unable to cope with high regulatory complexity and uncertainty [14]. Such complexity may also prove particularly burdensome for small distributors and importers, which in turn could lead to non-compliance—perhaps unknowingly—or market withdrawal. And some stakeholders might even raise prices in response to the challenge of additional reporting and administrative complexity.

2.3. Loss of international bargaining power

When individual countries participate in larger regulatory systems, they may also be able to exert some influence and shape regulations through formalised mechanisms of joint decision-making to represent their unique interests in specific contexts. Lobbying a single regulatory system may be particularly advantageous for countries with lower political resources. For example, Switzerland has used these mechanisms to defend reasonable market entry barriers for SMEs to retain its position as an innovation hub [15]. In light of their recent transitions to third-party status, however, Switzerland and the UK are currently experiencing how the loss of formal decision-making power can considerably diminish their ability to exert influence. Switzerland, for example, lost its voice in important decision-making bodies for medical device regulation, such as the Medical Device Coordination Group (MDCG), which drafts guidance that assists stakeholders in applying the EU MDR.

In particular, countries switching from regulatory reliance to regulatory pluralism lose an important bargaining chip when transitioning from dependency on the specific provisions of a single regulatory system to dispersing their international diplomacy resources across multiple settings. In the case of Switzerland, EU member states may argue that EU regulations must not further reflect or consider Switzerland's particular interests, as these interests may be served under other regulatory systems recognised by Swiss regulatory authorities. Switzerland, on the other hand, will have to distribute its regulatory diplomacy resources across two or more countries. In sum, while introducing regulatory pluralism introduces more flexibility, the recognition of a single system improves common understanding and regulatory efficiencies. Switzerland and UK authorities also lost access to the European Database on Medical Devices (EUDAMED) that administers medical devices and is an important tool for post-market surveillance. While these countries may still seek indirect influence through informal channels or bilateral ties, once regulatory pluralism is established, both formal and informal bargaining power are likely to be weakened.

3. Recommendations & conclusion

Regulatory reliance is an established tool to harmonise regulatory pathways across jurisdictions and holds great potential to increase the efficiency of regulatory activities of both the regulator and economic operators in each "reliant" jurisdiction. Countries in which regulatory reliance is not attractive or feasible as well as those looking for additional flexibilities may instead turn to regulatory pluralism by admitting medical products to their domestic markets via multiple other regulatory pathways. However, a political move towards regulatory pluralism is likely to be premature if hurdles to its effective implementation have not been addressed. Countries with less-resourced regulatory authorities will require thorough knowledge of the regulatory pathways they plan to recognise and admit in order to identify important differences among relevant regulations and estimate the extent and effects of regulatory escape.

To render regulatory pluralism more feasible and overcome some of the accompanying challenges, third-party countries could establish coalitions to promote regulatory harmonisation for medical devices and other regulated medical products. Despite barriers such as different languages, bureaucratic procedures, and country-specific culture with political preferences that will always be present and may impede cross-border cooperation, policy makers might acknowledge the benefits. For instance, formalised information sharing agreements for post-market surveillance data and technical solutions to achieve interoperability between reporting systems would ease the administrative burden on both regulatory authorities and economic operators. In addition, such harmonisation would reduce the administrative burden related to product development. For example, joint early dialogues between manufacturers and different regulatory authorities on the design of clinical studies for novel technologies substantially reduce uncertainties and alignment efforts of the manufacturers [16].

Beyond regulatory alignment, work-sharing agreements and joint reviews of marketing applications or post-marketing studies could enable synergies and conserve scarce regulatory resources. Work-sharing agreements could entail the joint development of regulatory guidance documents or collaboration on information platforms and technology. Importantly, these solutions can help ensure coherence between systems and maintain access to relevant regulatory information for associated countries. Policy makers should remain aware of potential barriers to work-sharing, including language barriers, bureaucratic procedures, or opposing political preferences. Pioneering schemes in the pharmaceutical sector like the Access Consortium (Australia, Canada, Singapore, Switzerland, UK) [17], OPEN (EMA, Australia, Brazil, Canada, Japan, Switzerland, WHO) [18] or Orbis (USA, Australia, Brazil, Israel, Canada, Singapore, Switzerland, UK) [19], which provide for collaboration and data sharing across regulatory bodies already successfully overcome many such barriers and represent compelling intermediate solutions that can serve to inspire future collaboration. For example, within the Access Consortium, like-minded, medium-sized regulatory authorities share marketing application data of pharmaceutical products for joint review by a working group. In the case of a favorable recommendation by the Consortium's working groups, products receive simultaneous access to multiple collaborating markets.

In the end, regulatory reliance and regulatory pluralism are not mutually exclusive. For example, the UK is targeting full reliance with the EU's regulatory decisions combined with a system of reliance with abridged assessment and/or device-specific requirements with countries like the United States, Canada, and Australia [20]. Most importantly, the regulatory system aims to address the country's societal preferences, accounting for the advantages and disadvantages of different regulatory approaches, including domestic regulation, regulatory reliance, or regulatory pluralism.

Therefore, it is vitally important for policy makers to critically assess the challenges of regulatory pluralism before abandoning its more straightforward cousin, regulatory reliance. In the meantime, efforts are needed to maintain coherence with larger influential regulatory systems and seek collaboration for more data sharing between regulatory authorities.

CRediT authorship contribution statement

Sandra Gillner: Project administration, Writing – review & editing, Writing – original draft, Conceptualization. **Katharina Elisabeth Blankart:** Writing – review & editing, Writing – original draft, Conceptualization. **Florence Tanya Bourgeois:** Writing – review & editing, Writing – original draft, Conceptualization. **Ariel Dora Stern:** Writing – review & editing, Writing – original draft, Conceptualization. **Carl Rudolf Blankart:** Project administration, Writing – review & editing, Writing – original draft, Resources, Conceptualization.

Conflict of interest

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