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Regulatory density as a means to refine current regulatory approaches for increasingly complex medicines

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The continuous scientific, societal, and technological advancements have shifted drug development toward increasingly complex and ever more targeted treatments. This creates new and unprecedented challenges for global regulatory systems. To address the increased risks and uncertainties of increasingly complex medicine, we advocate for a more tailored and flexible regulatory approach, which is explained here with the concept of 'regulatory density'. In the context of this paper, 'regulatory density' describes the relative amount of obligatory standards, measures and procedures applied to certain medicinal products or product classes and the resources required to meet these requirements. Given that risk and uncertainty are dynamic variables that can change over time, with this paper, we want to stimulate (re)thinking of regulatory approaches for managing the challenges of future complex medicines.

Keywords: Complex medicines; Medicine regulation; Regulatory density; Biologics; Non-biological complex drugs; Advanced therapy medicinal products; Adaptive pathways

Introduction

Historically, medicines regulation is the result of scientific and societal developments. For example, specific regulations for biological medicinal products (i.e., biologics) as well as recent regulations for advanced therapies were put into place by the arrival of recombinant DNA technologies and developments in the field of cell and gene therapy.[1] Regulations for orphan medicines were prompted by the societal push to increase the incentivization of medicines research for rare diseases. Therefore, the current state of medicines regulation is not designed as such, but it rather is the amalgamated end-state of technological, societal, and political drivers. The overarching goal of pharmaceutical regulation remains constant, and is to ensure that only safe and efficacious medicines of good quality are approved for marketing, while also ensuring timely access to novel medicines.[2]

There are inherent limitations to both preclinical and clinical research, such as the relatively limited number of subjects that can be studied, the relatively short clinical trial duration, and a study population that is not fully representative of the real-world population. Given these limitations, residual uncertainties will always remain about the benefit–risk ratio estimate provided at the time of the marketing authorization. For the purpose of this paper, uncertainty relates to: (i) those risks of a medicine that are known, but for which the probability with which they occur is unknown ('known unknowns'); and (ii) serious unknown (i.e., unidenti-

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fied) risks that only become visible once they actually materialize ('unknown unknowns').[3]

At the same time, the continuous scientific, societal, and technological advancements have shifted drug development toward increasingly complex and ever more targeted treatments, which contribute to the additional risks and uncertainties of modern medicine that need to be appropriately managed. The scientific and regulatory community needs to fit these novel therapeutic medicines into existing regulatory frameworks or create new regulatory categories and pathways. In this paper, we reflect on how regulatory systems create different regulations for different groups of medicine, and wish to stimulate (re)thinking about regulatory approaches for managing the challenges of future complex medicines.

Complexity as an important driver for risk and uncertainty

Regulatory frameworks are traditionally organized around overarching product categories, usually based on common product characteristics. These characteristics usually relate to a certain degree of risk and uncertainty, which is inherently determined by the complexity associated with the product. Biologics are a pertinent example of a product category, which is defined by the manufacturing process (the active substance is derived from living organisms). Compared with 'traditional' chemically produced small-molecule drugs, biologics generally face a higher degree of risk and uncertainty because of challenges related to their structural complexity and sensitivity to changes in the manufacturing process.[4,5]

Here, we distinguish between three sources of complexity that impact medicines regulations, referred to as the 'three P's': (i) the complexity of the 'product', which refers to highly complicated molecular structures and sophisticated manufacturing processes. In the array of current complex medicines, biologics are a pertinent example of a product class that faces a higher degree of risk and uncertainty from challenges related to their structural complexity and manufacturing methods;[6] (ii) the complexity of the 'process', referring to challenges for the healthcare delivery process. As an example, gene- and cell-based therapies come with scientific and technological challenges for manufacturing and healthcare delivery as the production process shifts from centralized large-scale manufacturing sites toward 'final assembly' in increasingly decentralized manufacturing-sites;[7,8] and (iii) the complexity of the 'patient', referring to the more refined and detailed approach for describing the target patient population for increasingly personalized treatments. For example, future drug development is expected to yield increasingly personalized treatments, targeting biological networks and applied in a pre-emptive manner to modify disease progression. This tailored approach to treating patients, sometimes referred to as 'precision treatments' or 'systems therapeutics', creates yet more challenges for regulatory and healthcare systems, for example because of limitations for (pre-) clinical testing.[9,10]

These three sources of complexity are not mutually exclusive and, therefore, can contribute, individually or combined, to an increased risk and uncertainty about medicines. To address these increased risks and uncertainties, regulatory systems can increase, what we call the 'regulatory density' (Fig. 1).

Regulatory density: a dynamic regulatory approach proportionate to risk and uncertainty

With regulatory density, we mean the relative amount of obligatory standards, measures, and procedures applied to certain medicinal products or product classes and the resources required to meet these requirements.[11,12] These requirements can range from (additional) clinical studies that need to be performed during the pre- or post-marketing phase, to certain procedures to ensure the safe use of a medicinal product, to administrative requirements or regulations for the appropriate manufacturing and safe handling of medicines. The pharmacovigilance legislation for biologics, which requires the recording of specific product information, is an example of an obligatory measure that contributes to an increased 'regulatory density' for this regulatory product category.[13] Here, we present regulatory density as the cumulative state of all regulatory measures that apply to an individual product or product class, without differentiating between individual regulatory domains.

Thus far, regulatory thinking is habitually based on identifying categories within the diverse arsenal of medicinal products and then applying regulatory frameworks to strictly defined medicinal product categories. To this end, the type of manufacturing process is the determining criterium in defining the regulatory approach for (recombinant) biologics, vaccines, and blood products. The Directives and Regulations relating to medicinal products for human use (Directive 2001/83/EC), human blood and blood components (Directive 2002/98/EC) or genetically modified organisms [Regulation (EC) No. 1394/2007] are examples of such distinctive legislative frameworks.[1,14,15] However, from a broader regulatory perspective, this strict categorical approach might not be able to account sufficiently for product-to-product differences in complexity (which, hence, define the degree of risk and uncertainty) that might exist between medicinal products falling within the same regulatory category. This is particularly the case for medical fields that evolve quickly over time and encompass a range of different medicinal products.

On the one hand, take the biologics for example, a regulatory product category comprising of a diverse array of products with different complexities, from rather small-sized recombinant peptides to large complex recombinant monoclonal antibodies or recombinant coagulation factors, facing different degrees of risk and uncertainty. On the other hand, we see that the fast-developing field of synthetic chemistry is already catching up with biotechnology, yielding increasingly complex synthetic medicines, sometimes referred to as nanomedicines or non-biological complex drugs (NBCDs). Examples of NBCDs are complex liposomal formulations and heterogeneous mixtures of polypeptides, which are currently regulated under the traditional paradigm of chemically-derived medicinal products. An interesting example that shows how advances in synthetic drug development are starting to 'blur the lines' between regulatory product categories is the recent European Union (EU) approval of a chemically synthetized generic version of teriparatide as a reference to a biological originator product.[16] In contrast to the approved teriparatide biosimilars, the gen-

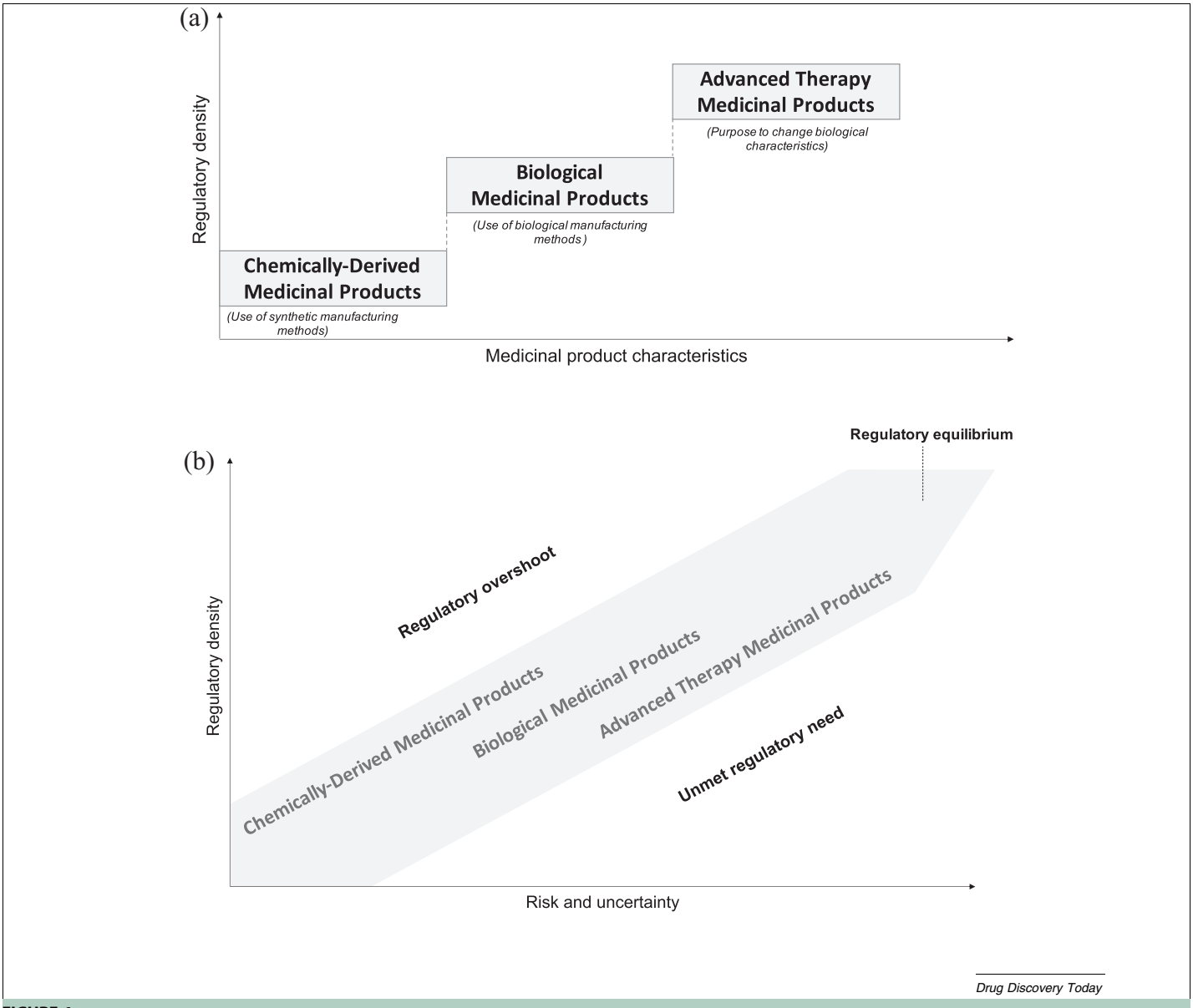

FIGURE 1

(a) The current 'static' regulatory paradigm of regulatory density applied to strictly defined product characteristics, in which medicinal products remain within their regulatory category over time. **(b)** The concept of a 'dynamic' regulatory approach, in which the regulatory density is in proportion to the risk and uncertainty of the individual medicinal product it regulates. Medicinal products can move along the regulatory equilibrium (e.g., downwards of the regulatory density spectrum), if the uncertainty has been reduced over time or if better tools are available for mitigating risks associated with the product.

eric version falls under a different regulatory framework with different requirements for documentation, prescribing, and dispensing, despite referencing the same product. Another interesting example is the recent approval of amikacin liposome inhalation suspension, which converges the regulatory fields of nanotechnology and medical devices. Therefore, the regulatory and scientific community expressed concerns about the appropriateness of current regulatory approaches to address the challenges of increasingly complex products, which might require a more tailored and flexible regulatory approach.

Depending on the levels of risk and uncertainty that exist for a certain medicinal product or product class, higher or lower levels of regulatory density might be appropriate. A higher regulatory density implies the implementation of adequate measures to ensure that: (i) known risks are appropriately managed; (ii) the uncertainty with regard to unquantified risks ('known unknowns') is gradually reduced during the postauthorization phase; and (iii) the healthcare system is sufficiently prepared to manage any unknown risks ('unknown unknowns') once they emerge.

In an ideal situation, the regulatory density is aligned with the perceived risk and uncertainty of the medicinal product to be regulated. The regulatory density can also be too low and, therefore, not sufficiently able to address certain risks and uncertainties, leaving patients exposed to inappropriately managed risks from medicines.[17] This can be the case if certain

regulatory requirements are not in place, but might also exist when a certain regulatory requirement is in place but not effective, for example because of aspects that have a negative impact on compliance. This is indicated in Fig. 1b as 'unmet regulatory need'. By contrast, an unreasonably high regulatory density that is not proportionate to the risk and uncertainty it aims to address, can also have a negative impact on public health. This can result, for example, in unjustifiably hampering access to medicines, but also in inefficient healthcare systems because of the disproportionate administrative burdens. This is indicated in Fig. 1b by 'regulatory overshoot'.

Tailoring regulatory density requires a cross-disciplinary effort, a continuous learning environment, and an adaptive regulatory system

The concept of a tailored regulatory density approach relies on several aspects that will become increasingly important for future medicines to design appropriate levels of regulatory density, as discussed herein.

A cross-disciplinary approach in the process of policy formulation, policy implementation, and policy evaluation should be applied. This involves from start to end, a multistakeholder dialog, including industry, health technology assessments (HTAs), and payer and patient perspectives, to delineate key concepts of regulatory density and define operational definitions and acceptable thresholds of risk and uncertainty. This approach should also help to define individual components of regulatory density that can be separately and collectively applied to form tailored regulations that are proportionate to the aim being pursued without being overly excessive and burdensome. This cross-disciplinary approach does not stop here. It should also involve 'street-level' actors (e.g., prescribers and pharmacists) to create effective regulations that can be readily implemented, which expedites the process of compliance.[18]

A continuous learning approach is required, in which the concept of regulatory density accepts a higher level of risk and uncertainty at time of authorization and relies on 'postapproval learning' to reduce the uncertainty over time because new knowledge about the safety, efficacy, and effectiveness of the medicine will be progressively generated throughout real-world use.[19] Key components of this approach are validated prediction models for treatment response at the individual patient level, wide acceptance of the use of real-world data (RWD) to support regulatory decision-making, and the implementation of 'data science' in regulatory decision making, including the use of digital technologies, artificial intelligence (AI), and global data repositories for the real-time monitoring of medical interventions.[20–22] Of course, the use of these technologies is not expected to replace traditional regulatory approaches and many challenges, including responsibilities and ownership, need to be addressed to make best use of these technologies in the regulatory domain. However, these technologies can contribute to making regulatory systems more efficient.

An adaptive regulatory approach is also required that allows for a rational response to changes in the regulated environment in which regulatory systems can learn from new insights and experience, to maintain the regulatory equilibrium between 'unmet regulatory need' and 'regulatory overshoot'. Within the adaptive regulatory approach, regulatory systems should be able to incorporate new knowledge resulting from the continuous learning environment described earlier, and respond appropriately. This allows for the flexibility to adapt the regulatory density rapidly as a response to new knowledge (e.g., if this decreases the residual uncertainty of particular medicinal products) or new technology and tools to better mitigate risks.[17] This could also entail a response to specific circumstances, such as an emergency health crisis, including pandemics, which could increase the acceptance of risk and uncertainty in certain conditions. Periodic evaluations of existing regulations and guidelines are also crucial to maintain a desired level of regulatory density. Evaluation frameworks, such as the 'Better Regulation Toolbox' of the European Commission can help to carry out impact assessments, evaluations, and fitness checks to assess all societal, economic, and environmental impacts of new EU policies and regulations for medicines.[23] This process should help to identify to what extent public health objectives are met, if acceptable levels of cost-effectiveness can be assured to maximize regulatory compliance, what the implications are for individual stakeholders, and what potential risks exist for unintended consequences. This approach should also become an integral part of initiatives, such as the pharmaceutical strategy for Europe.[24]

Concluding remarks

The regulatory approach presented in this paper might feel counter-intuitive, because the concept of regulatory density increasingly relies on regulatory decision-making on a case-by-case basis. However, in light of the surge of expected new medical technologies putting further stress on the current boundaries of predefined regulatory categories, we feel that re-evaluating existing regulatory frameworks at some point is inevitable. This paper aims to contribute to stimulating discussion in this area.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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