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Regulatory sandboxes: A new frontier for rare disease therapies

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Introduction

Regulatory sandboxes have emerged as an innovative mechanism to facilitate the development and approval of new technologies, including pharmaceuticals. Their application in the context of rare disease therapies presents a promising avenue to accelerate the development, approval, and access to disease-modifying and life-saving therapies. Given the complexities of rare diseases and the regulatory hurdles faced by orphan medicinal products, regulatory sandboxes offer a structured yet flexible environment where new regulatory approaches can be tested and refined.

Rare diseases are often chronic, complex and life-threatening conditions affecting over 400 million people worldwide [1]. The majority of rare diseases are of genetic origin and are associated with reduced life expectancy and loss of quality of life. About half of those living with rare diseases are children [2,3]. The diagnosis and treatment of rare diseases face many obstacles, partly due to limited epidemiological data and a poor understanding of the natural history across the lifespan. Additional challenges include variable disease severity and progression, limited awareness and expertise among primary health care professionals, and the high costs and risks involved in drug development. Many of these diseases require multiple and interdisciplinary expert consultation to reach a diagnosis and develop a care management strategy. Even when the disease is well-documented in the medical literature, it can take several years for patients to receive an accurate diagnosis [2,3].

Recent work has emphasized how regulatory frameworks are shifting globally to accommodate innovation, with calls for greater harmonization [4]. Evolving regulatory approaches, including sandboxes, could be leveraged internationally to better align processes and facilitate cross-border cooperation in healthcare regulation. This opinion article explores the definition, characteristics, global initiatives, challenges, and potential applications of regulatory sandboxes in the rare disease landscape.

Understanding regulatory sandboxes

A regulatory sandbox is a controlled regulatory environment that allows innovators to experiment with novel products, services, and business models under regulatory supervision [5]. This framework is designed to facilitate the testing of innovations while ensuring compliance with regulatory requirements. Regulatory sandboxes operate within a controlled environment where innovations are tested under predefined rules and conditions. They are temporary by nature, meaning participation is time-limited and designed with clear objectives. One of their most significant advantages is the regulatory flexibility they offer, allowing deviations from standard regulatory pathways to accommodate novel approaches which would not fit in any of the existing frameworks.

In the context of healthcare and pharmaceuticals, regulatory sandboxes offer an opportunity to accelerate science and health technology innovation by complementing existing frameworks and by supporting the interface between different technologies that are traditionally reviewed by different regulations [6–8]. These sandboxes also offer an opportunity to foster collaboration and learning, enabling direct interactions between regulators, therapy developers, and other stakeholders, which helps build a mutual understanding of new regulatory challenges, and refine regulatory approaches to improve future policy-making. For example, a systematic literature review of sandbox applications in health technology assessment (HTA) concluded that sandboxes can serve as a valuable tool to test flexible regulatory and reimbursement approaches in controlled environments, highlighting the relevance of sandbox principles beyond regulatory approvals and into decision-making processes such as HTA [9].

Importantly, regulatory sandboxes are not meant to be applied in research areas where existing pathways for scientific dialogue between regulators and innovators can actually resolve the problem. It is in the areas where there is no clear-cut legal path and where innovators want to experiment in controlled regulatory conditions.

Global initiatives and examples

Several countries and institutions have implemented regulatory sandboxes across various sectors, including healthcare and pharmaceuticals [10]. In Japan, a regulatory sandbox was established in 2018 to support the testing of artificial intelligence (AI), blockchain, and Internet of Things applications in healthcare and financial services [11].

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Norway has incorporated regulatory sandboxes into its national AI strategy, focusing on personal data protection, which is particularly relevant for health care data management [12]. Meanwhile, the United Kingdom has created an AI sandbox to explore voice biometrics, facial recognition, and data protection issues, showcasing how sandboxes can be adapted to address emerging technological concerns [13]. In Canada, regulatory sandboxes are used as a tool that can help federal regulators keep pace with changing technologies and reflect current business realities, challenges, and opportunities and could be used when the current rules are outdated or do not account for innovation [14]. A sandbox approach was developed by Health Canada to allow the use of foreign reviews to support drug approval [15]. Regulatory authorities are also exploring sandboxes for paediatric rare disease clinical trials to improve trial designs and enhance patient-centric approaches. In addition, the Canadian experience during the COVID-19 pandemic has shown that adaptive mechanisms for drug evaluation can function as agile reform tools, particularly in times of crisis [16]. Similarly, Lau and Rawson [17] argued that Canada may be shifting toward a more agile regulatory and reimbursement system, with real-world evidence increasingly integrated into oncology drug assessments. These examples demonstrate how sandbox principles can extend beyond rare diseases into broader healthcare contexts.

China's Hainan province has taken an innovative approach by implementing a "data sandbox" to generate real-world evidence for orphan medicinal products [18]. This framework allows foreign-marketed rare disease drugs and orphan devices to be tested in Chinese patients within a controlled setting before gaining broader market entry, potentially improving access to life-saving treatments. The data sandbox in Hainan province operates as a secure regulatory framework that enables real-world data collection on foreign drugs, which are not yet officially approved in mainland China. By allowing for controlled use and evaluation, regulators can gather essential evidence regarding the safety and efficacy of these treatments, helping to inform future regulatory decisions and improve patient access.

In the European Union (EU), the Artificial Intelligence Act envisages setting up coordinated AI regulatory sandboxes to foster innovation in AI across the EU, including the development of AI systems in the interest of public health [5,19]. Additionally, a revision of the EU pharmaceutical legislation is underway, with a strong focus on improving research, fostering innovation, and facilitating the uptake of novel therapies. As part of this effort, the concept of regulatory sandboxes has been introduced into the legislation, which is currently under discussion [20]. This legislative revision acknowledges the need to provide new technologies with the opportunity to prosper within a regulatory framework that can adapt to scientific advancements. Given that regulations often face challenges to keep pace with rapidly evolving innovations, these sandboxes serve as a critical mechanism to test and refine approaches that could later be incorporated into formal regulatory pathways. It has to be mentioned however that a regulatory sandbox is an experimental and temporary setting and as such, the successful outcome is not guaranteed.

Furthermore, the European Innovative Health Initiative (IHI) has launched a call for projects focused on modelling regulatory sandboxes and enabling their deployment to support breakthrough innovation [21]. This initiative aims to establish structured frameworks for regulatory experimentation, ensuring that novel therapies and technologies can be tested in a manner that aligns with evolving regulatory needs. The IHI call emphasizes cross-sectoral collaboration and seeks to facilitate regulatory reliance, particularly for orphan drugs and advanced therapies. By funding projects that develop regulatory sandboxes, the initiative is intended to accelerate the adoption of innovative regulatory pathways that can ultimately benefit patients with rare diseases.

Challenges and opportunities

Regulatory sandboxes present both challenges and opportunities. One of the key challenges is the uncertainty for a global impact, as the lack of harmonization across jurisdictions may make it difficult to scale sandbox-driven regulatory models globally. Legal and ethical concerns also arise, particularly in ensuring patient personal data protection and establishing clear rules regarding ownership of the data within a flexible regulatory framework. Additionally, pharmaceutical and medical device industry participation can be a limiting factor, as companies may be hesitant to invest resources in a sandbox if the regulatory benefits are uncertain or if the outcomes do not lead to permanent regulatory changes. Another critical issue is the post-sandbox pathway which is not well discussed and established. Clear rules for transition mechanism from the sandbox to formal regulatory approval processes are essential to ensure the success of sandbox-driven experiments.

Despite these challenges, regulatory sandboxes offer significant opportunities. They could accelerate drug development by allowing for regulatory flexibility and iterative learning, ultimately shortening the time required to bring rare disease therapies to market. Additionally, they could facilitate enhanced regulatory reliance, helping jurisdictions recognize foreign drug approvals and reducing duplication of regulatory efforts. In the realm of clinical trials, sandboxes could support decentralized and remote trial methodologies, particularly for pediatric and rare disease research, and leveraging real-world data to improve study efficiency. Furthermore, sandboxes could contribute to adaptive regulatory frameworks, ensuring that regulations remain up to date with scientific and technological advancements [22,23].

Use cases and applications in the rare disease space

Regulatory sandboxes can be applied in various ways within the rare disease ecosystem. It can be used to bridge the development gap for new and innovative medicinal and healthcare products, including medical and digital technologies. In cases where an innovative development has no precedent in the industry, a sandbox can allow for an early agreement on the most optimal product development strategy and on the type and minimum data requirements needed for (successful) marketing authorization.

Another potential application is in clinical trial innovation, where decentralized trial designs, real-world data integration, and adaptive trial methodologies can be tested to improve rare disease research. An additional application involves regulatory reliance mechanisms, where sandbox environments can be used to pilot frameworks for the mutual recognition of orphan drug approvals across jurisdictions, thereby enhancing global access to rare disease therapies.

Patient-centered evidence generation is another critical area where regulatory sandboxes can play a role. By validating the use of real-world evidence for drug approvals, sandboxes can help facilitate regulatory decision-making, particularly for ultra-rare diseases where traditional randomized, double-blind, placebo controlled clinical trials may not be feasible. Additionally, regulatory sandboxes can enable cross-sectoral integration by exploring the interplay between pharmaceuticals, medical devices, AI-driven diagnostics, and digital health technologies, ensuring that all these elements are regulated in a cohesive and complementary manner [24]. Depending on the scope of the specific regulatory sandbox, multi-stakeholder involvement and participation will be critical for the efficiency of the sandbox exercise.

Sandbox blueprint

Based on the current examples of sandboxes applications authors propose the following high-level approach to the sandbox methodology, as presented in Fig. 1.

Conclusion

Regulatory sandboxes represent a transformative approach to addressing the challenges associated with rare disease therapies. Rare diseases, due to their heterogeneity, complexity and numerous

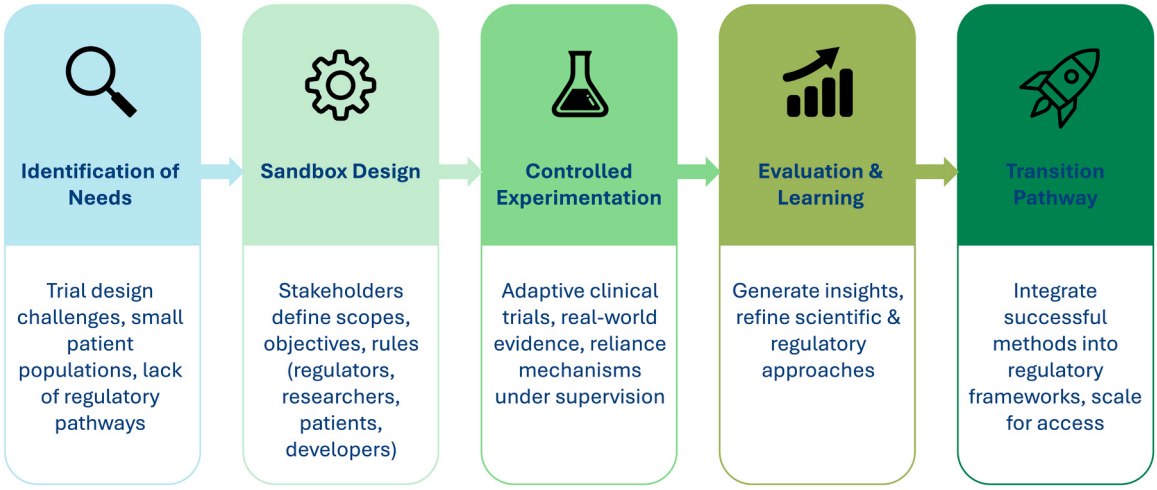

Fig. 1. Regulatory Sandbox Methodology for Rare Disease Therapy Development. The figure illustrates the high-level methodology of regulatory sandboxes applied to rare disease therapy development. The process begins with the identification of need, such as challenges in clinical trial design, small patient populations, or lack of suitable regulatory pathways. In the sandbox design phase, stakeholders—including regulators, researchers, patients, and developers—define the scope, objectives, and rules of the sandbox. During controlled experimentation, innovative approaches are tested, such as adaptive trial designs, the use of real-world evidence, or regulatory reliance mechanisms, all under close regulatory supervision. The evaluation and learning stage focus on generating insights to refine regulatory and scientific approaches, addressing the unique constraints of rare diseases. Finally, the transition pathway ensures that successful methods are integrated into formal regulatory frameworks or scaled to support broader access to rare disease therapies.

challenges in basic science and drug development, represent a good example for the application of alternative approaches in regulation. Hence the concept of regulatory sandboxes could be piloted in this domain. By creating a controlled, flexible, and collaborative space for regulatory experimentation, sandboxes can accelerate the development and approval of disease-modifying and life-saving treatments. However, their success depends on clear objectives, robust stakeholder engagement, and well-defined pathways for translating sandbox learnings into permanent regulatory frameworks. As more jurisdictions embrace this concept, regulatory sandboxes may become a crucial tool in bridging innovation and regulatory compliance, ultimately benefiting patients with rare diseases worldwide.

CRediT authorship contribution statement

David A. Pearce: Writing – review & editing. **Samantha Parker:** Writing – review & editing. **Daniel Scherman:** Writing – review & editing. **Oxana Iliach:** Writing – review & editing. **Violeta Stoyanova-Beninska:** Writing – review & editing. **Galliano Zanello:** Writing – original draft.

Ethics statement

Do not apply.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Data availability

No data was used for the research described in the article.

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