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Research Article

Research and analysis of regulatory framework and harmonisation of repurposing

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Abstract

Drug repurposing is a modern and successful mechanism for discovering new therapeutic indications for authorised medicinal products. There is an absence of a clear definition of the term "drug repurposing" or its synonyms in regulatory frameworks, which clearly shows the need for inclusion and definition of the process. The main regulatory documents show a greater absolute number of repurposing options for European Medicines Agency (EMA) (5) versus Food and Drug Administration (FDA) (4) and the need for harmonisation because of different authorisation procedures and their benefits. While the EU Agency focusses on regulating and improving the interaction between pharmaceutical companies, academia, and non-profit organisations, the U.S. drug regulator directs the generation of candidates for repurposing using digital technologies.

Keywords

drug repurposing, regulatory framework, marketing authorisation, EMA, FDA

Introduction

Despite advances in many scientific, technological, and managerial areas that should accelerate drug development, in recent years there has been a serious decline. Scannell et al. (2012) describe the so-called Eroom's law, which describes the decline in the number of new drugs approved relative to money spent. According to data from annual surveys of the U.S. R&D industry, the authors show that the ratio of the number of approved medicinal products (MPs) per $1 billion spent declines by half approximately every 9 years. Ashburn and Thor (2004) defined the term "drug repurposing" (also referred to as repurposing and reprofiling) as a mechanism to discover uses for approved medicinal or investigational products beyond their original indication and that this method can lead to lower risk and higher reward compared to de novo development. Repurposing is based on two main scientific foundations: the discovery, following the sequencing of the human genome, that some diseases share common biological mechanisms and, on the other hand, the concept of pleiotropic drugs (Jourdan et al. 2020). From a regulatory point of view, drug repurposing is performed as the addition of a new indication to an already authorised medicinal product, using accumulated data on the medicinal molecule after its authorisation. On the other hand, the so-called „drug rescue" of investigational molecules that have not presented satisfactory efficacy in clinical trials is more of a marketing approach to repurposing and follows the traditional route of filing a marketing authorisation application (MAA).

Repurposing offers advantages in lowering the risk of failure, as the repositioned drug is already proven safe in preclinical models and in humans. Secondly, repurposing

reduces the time required for drug development because preclinical studies, safety evaluation, and, in some cases, dosage form development can be skipped because they have already been completed (Pushpakom et al. 2019). Combating health crises is also a field for the preferential application of repurposing, in which cases the reduction in development time is very clearly demonstrated (Shende et al. 2021). Last but not least, in the course of searching for new indications for a drug product, new target molecules or signal pathways can be discovered.

An inherent disadvantage of repurposing arises from the fact that drug products are traditionally the result of a long optimisation process aimed at increasing affinity and selectivity for the primary target. As a consequence, repurposing is mainly limited to the therapeutic area of the originally approved indication (Oprea and Mestres 2012). The use of already generated data also raises drawbacks in terms of the accuracy and consistency of the models analysing the databases. Moreover, there is a clear need for quality control of the information and the methods by which it was collected (Sharma et al. 2021). Another disadvantage, namely data overload, arises from the need for more information to mediate more effective repurposing. For example, Hanisch and Rake (2021) identify as a problem the generation of too many and too similar clinical trials and spending resources that could otherwise be used to generate diversity in the search for an effective way to impact a health condition.

In spite of the shortcomings of the repurposing approach, it is proved to be successful and relevant, as demonstrated by many successful examples. Common examples of banned molecules that have successfully used repurposing are dimethyl fumarate and thalidomide. The former has been used as a process inhibitor for mould development, but due to the development of allergies, it was banned from usage in Europe. However, in the first decade of the XXI century, the molecule received approval for treatment of multiple sclerosis. Thalidomide, used as an antiemetic for morning sickness in pregnant women, was banned because of the development of phocomelia in neonates but was subsequently approved for use in leprosy and multiple myeloma (Jourdan et al. 2020).

Based on the potential benefits of the drug repurposing, the aim of our study is to evaluate and compare the current regulatory framework in the EU and U.S. for adding new indication(s) to an already authorised medicinal product. In addition, we analysed the efforts and measures taken towards further regulation and harmonisation of this mechanism.

Methods

We performed systematic and chronological analysis of electronically available documents with a primary focus on the regulatory framework of drug repurposing. The applied strategy was content analysis with processing and organisation of data from the documental review. We established different themes and categories per reference to the main question of our research. By using this method, we analysed three groups of documents. The first one consists of current and preceding main regulatory documents in the field of medicinal products in EU (Directives and Regulations) as well as in USA (Code of Federal Regulations). The second group consists of the draft proposals for Regulation and Directive from 2023 (EU so-called Pharma Package), which will lay out the future of drug legislation in the EU. As part of the third group, we analysed working documents of different national and international (supranational) institutions and organisations in which work we have identified drug repurposing as a topic.

Results and discussion

European Union state-of-arts 2024

The EMA, through Directive 2001/83/EC, provides five different options for drug repurposing for adding a new indication to an authorised medicinal product. The first is adding new indication upon demonstration of significant clinical benefit compared to existing therapeutics during the first 8 years after the authorisation of a medicinal product. This approach adds one extra year of marketing exclusivity for the product. Article 10(5) of the Directive proposes the addition of a new indication for an established active substance (EAS) using literature data. In order for a medicinal product to qualify as EAS, it is required to demonstrate efficacy and safety for a minimum of a 10-year history of drug use in the EU. The other three approaches involve adding a new indication through exceptional circumstances, conditional use, and orphan medicinal product authorisation procedures. The possibility of providing a smaller data package due to the inability to collect a comprehensive amount of information can be considered an advantage for the first two options. Challenges to these procedures are the shorter validity of authorisations (1 year) and the need to re-evaluate subsequently generated data. The addition of a new indication as an orphan medicinal product is a widely used mechanism due to the clear advantage in cases of insufficient return on investment in the diagnosis, prevention, or treatment of serious diseases. A strong limiting factor is the relatively small number of indications and therapies to which the conditions of Regulation (EC) No. 141/2000 and Directive 2001/83/EC are applicable.

U.S. situation 2024

The U.S. Food and Drug Administration (FDA) offers four different options for pursuing drug repurposing. (Federal Register 2024) The primary one is the submission of a new drug application filed under Section 505(b)(2) and approved under Section 505(c). This method uses a complete efficacy and safety data package, with some of the data sourced from studies not performed by the applicant.

These studies may be nonclinical, pharmacological, and clinical trials, as well as literature data. Similar to EMA, FDA also offers emergency use authorisation, accelerated authorisation, and orphan drug authorisation procedures. The former case's advantage is offered by demonstrating an effect in surrogate outcome measures for the purpose of covering unmet medical needs and/or impacting serious diseases. However, this does not eliminate the need to conduct post-authorisation confirmatory clinical studies. Repurposing for emergency use provides the opportunity to demonstrate the efficacy and safety profile by a variety of methods, even using only animal experiments if necessary. A potential limitation of this mechanism is the reliance on the Department of Health and Human Services for the definition of an emergency, which is not under the FDA's control. The addition of an orphan drug indication to the FDA also includes benefits such as different types of financial incentives and a reduced required data package, as well as the challenge of the relatively small number of indications and therapies to which the terms of the Orphan Drug Act are applicable.

The first and most critical observation is the absence of the term "drug repurposing" or its synonyms in the legislation of both agencies. To the greatest extent, this calls for regulation of the process and its detailed description in the regulatory framework, as initiatives to develop repurposing can only be effectively implemented if the terms are clearly defined. The study by Langedijk et al. (2015) also shows the absence of a clearly defined term, both in the review of scientific literature and in the initiatives of various drug regulators. The authors also recommend consistency in the use of the same term to refer to a specific phenomenon, as well as building the term by describing four main characteristics: concept, action, application, and product.

EU vs. US

The comparative analysis shows a higher absolute number of repurposing opportunities for the European drug regulator (5 in total) versus the US drug regulator (4 in total). This observation is due to the absence of a regulated mechanism for the addition of new indications during the initial marketing exclusivity period in the FDA, while the EMA offers a 1-year increase in marketing exclusivity. With this limited increase, the mechanism may not be effective enough to promote repurposing, which is also noted by Liddicoat et al. (2021), with the authors describing the reasons why companies consider the incentives behind this procedure to be redundant, unhelpful, inappropriate, and/or insufficient. Therefore, the study suggests that the advantages and disadvantages of this mechanism should be carefully analysed and retained before establishing its exact role for reuse.

A new text related to repurposing is included in the draft proposal for a new directive, which will repeal Directive 2001/83/EC and Directive 2009/35/EC. In order to provide an additional option for repurposing, a regulatory data protection period of four years is planned to be granted for a medicinal product in respect of a new therapeutic indication not previously authorised in the Union, subject to certain conditions. This proposed regulatory document provides significant data protection, but the European Federation of Pharmaceutical Industries and Associations (EFPIA) warns about the economic aspect of off-label use of competing/generic/biosimilar products, as well as difficulties in pricing and reimbursement for the new indication. It is important to highlight that drug repurposing is also included in the explanatory memorandum of the draft proposal for the new regulation. As a topic in the part "Stakeholder Consultations," this mechanism is mentioned as supported by key stakeholders such as healthcare providers, academia, and environmental organisations. On the other hand, the section "Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness," which proposes simplifying EMA's structure, also comments on repurposing. It is highlighted that additional resources, which are expected to become available after the aforementioned reorganisation, are to be focused on repurposing. Readiness to change the drug development paradigm is shown by Art. 48, which describes the scientific opinion on data submitted from non-profit entities for repurposing of authorised medicinal products. In this way, the new draft regulation would become the first regulatory document to include and regulate this mechanism.

Differences between the two agencies are also seen in the most typical mechanisms used for repurposing: the addition of a new indication for a drug with an established use (EMA) and authorisation through Section 505(b)(2) (FDA), respectively. One of the advantages of the U.S. legislation is the ability to demonstrate a satisfactory efficacy and safety profile through available data without the need of a proven established use. An important part of Section 505(b)(2) is the inclusion of the wording that some of the research "is not conducted by or for the applicant, and the applicant does not own the rights to it." This brings out an additional aspect of repurposing as a result of interaction between pharmaceutical companies, academia, and non-profit organisations. Such an alternative is not seen in EU regulation. In addition, the FDA provides a longer marketing exclusivity period for the added indication compared to the EMA (3 years vs. 1 year), which further offers a greater chance of return on investment. The other three procedures used by repurposing in both agencies show great similarities. The differences are mainly in different exclusivity periods and means of proving the drug is suitable for authorising using the specific procedure.

Globalisation and widespread access and sharing of information nowadays further necessitate the need for harmonisation, as patients can easily explore the different options to treat their disease. Differences between countries can be a cause of undermining trust in evidence-based medicine, which, although less commented, can create a risk to public health. The importance of harmonisation is also highlighted by several forums of professionals in the field and through the work of various international organisations such as WHO, ICH, etc. (Workshop summary 2013; WHO 2024).

The need to regulate repurposing is clearly demonstrated by the functioning of various structures within the two agencies whose work addresses this topic. Within the structure of the EMA, repurposing is part of the focus of the STAMP expert group as well as the European Commission's Pharmaceutical Committee. The fact that repurposing has been a topic in 10 consecutive (83%) of the 12 total meetings and part of the action points and consideration in a total of 7 meetings (5 of them consecutive) definitively proves the relevance of the topic. The STAMP group also identified the most important challenges for repurposing (Fig. 1). Another important contribution of STAMP is the derivation of options for regulating repurposing, one of the most fundamental being the ability to review evidence generated by an organisation other than the MAH for the addition of a new indication. Some of the topics discussed include the recommendation and/or scientific advice to the pharmaceutical company, the involvement of organisations other than pharmaceutical companies through the application to hold or change a marketing authorisation, etc. The knowledge deficit in academia/non-profit organisations on regulatory pathways and the need for general accessibility of data collected on medicines were noted as well. Many of these elements are being implemented in the group's final proposal to build a regulatory framework for repurposing and the pilot project to support repurposing by academics and non-profits. A major contribution of these documents is the expansion of the functions of academic communities and non-profit organisations, which offers an opportunity to change the current paradigm in drug development. The proposed model of work is described in Fig. 2.

There are also initiatives to develop repurposing funded by the EU, the largest of these projects being the REMEDi4ALL and RePo4EU platforms launched in 2022. The platforms bring a wide range of expertise to address the difficulties of repurposing. The main objectives of REMEDi4ALL are to provide expertise, tools, and resources for all stages of repurposing, while RePo4EU places a particular focus on the repurposing methods and the integration of digitisation for increasing efficiency. Many other initiatives have been developed to improve repurposing in Europe, but these are independent from the EMA. Examples include the Value-Added Medicines group of the Medicines for Europe association, the Anticancer Fund, as well as many others.

Within the U.S., the field of drug repurposing is part of the work of the National Centre for Advancing Translational Sciences (NCATS) at the National Institutes of Health. NCATS activities include the identification of new therapeutic uses for approved drugs through its drug screening improvement programs, partnerships for effective preclinical and clinical data collection, and more. Similar to STAMP meetings, a workshop has been organised in December 2019 between the FDA, NCATS, and the Reagan-Woodall Foundation to discuss the development and regulatory challenges of repurposing drugs with expired patent protection. One of the recommendations highlighted making information available in an accessible location for those interested in the field of drug repurposing within a toolkit on which NCATS is already working. NCATS' primary product for repurposing purposes is the CURE ID, launched in 2019—a web-based tool for sharing real-world experiences with drugs used in a new way. Through an online case report form, users can directly

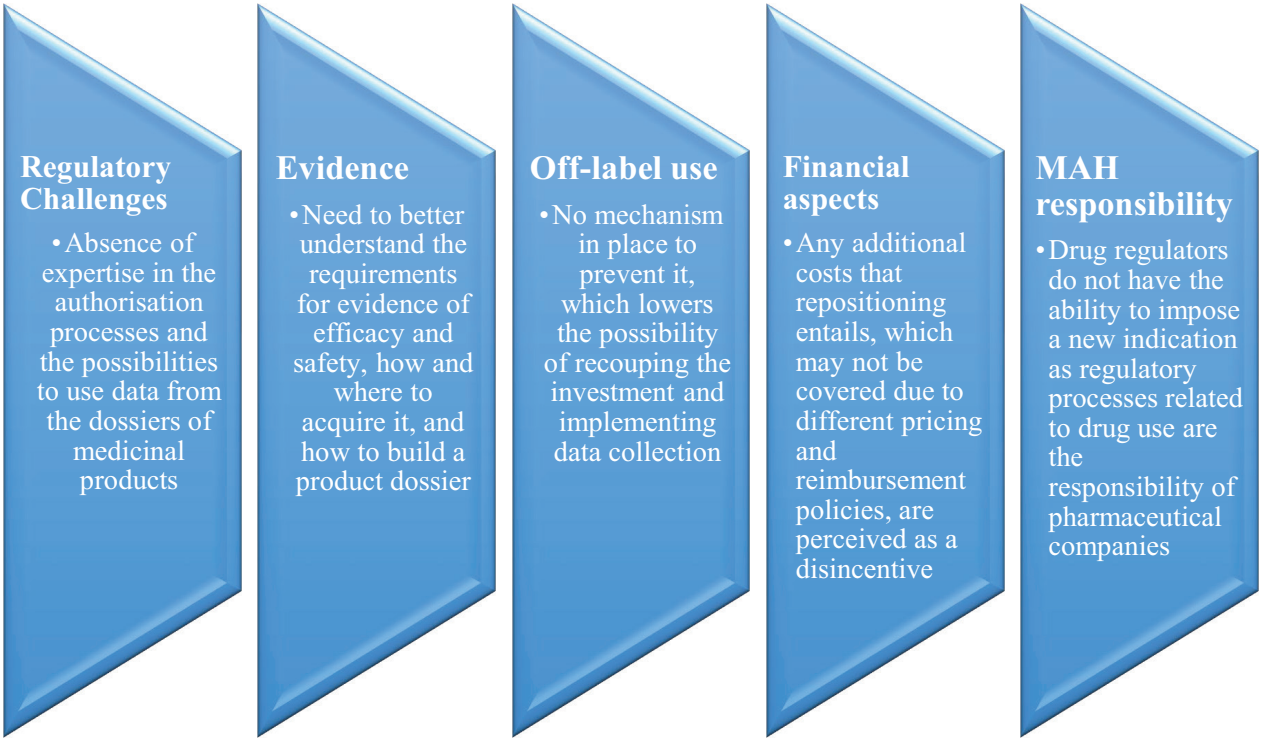

Figure 1. Most important challenges for repurposing commented in STAMP group meetings.

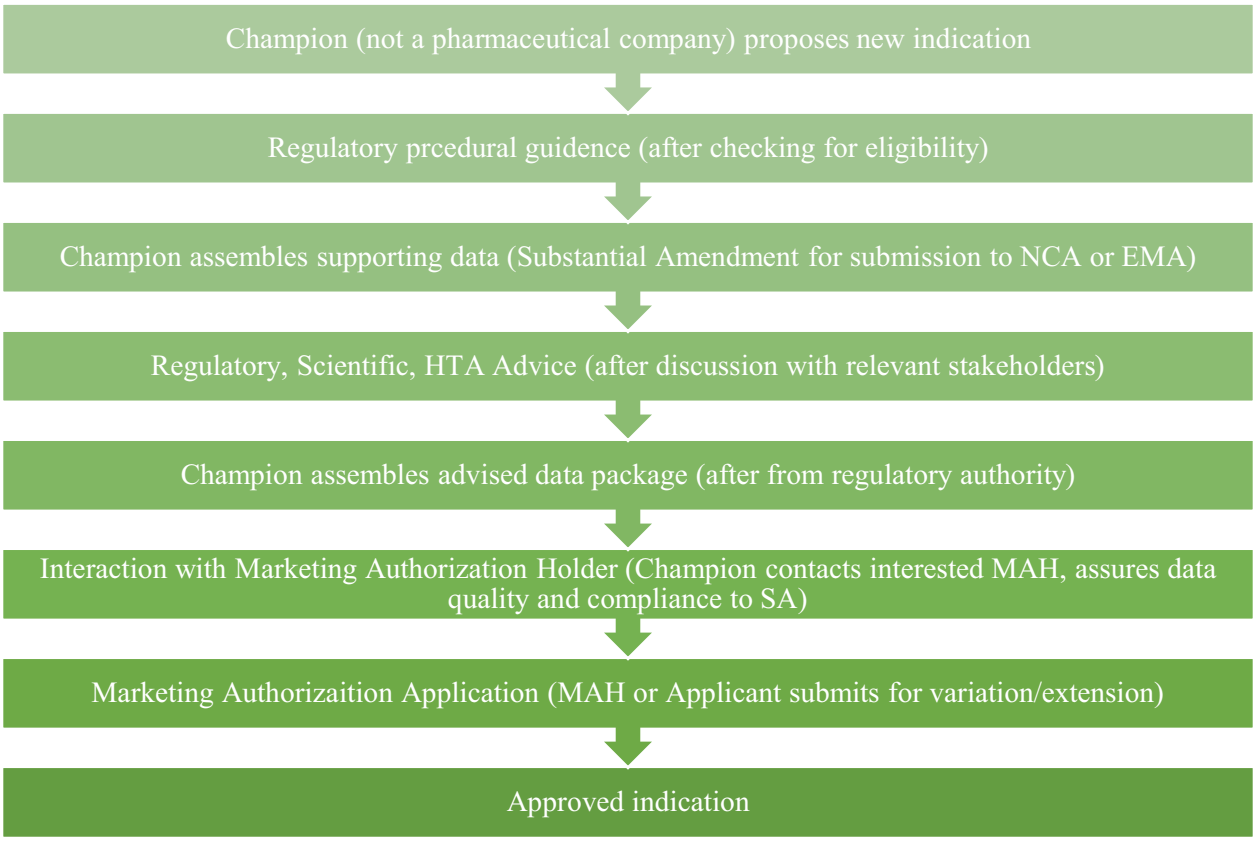

Figure 2. Proposed steps for repurposing of medicinal products out of data and patent protection by not-profit organisations (Safe and Timely Access to Medicines for Patients expert group 2019).

report treatment outcomes. Thanks to the platform's ability to receive and organise this information, promising new therapeutic uses can be identified for formal testing and potentially avoid worthless or harmful uses. Additionally, piloted during the COVID-19 pandemic, the project is being extended to manual and automated collection of data from EHR and registries with the same case report form. A similar repurposing support tool, also a product of NCATS's work, is the OpenData COVID-19 portal. It was developed to share data rapidly and freely on potential activity against SARS-CoV-2 of drug molecules or authorised drug products. Activity is tested using screening and analysis methods previously developed by the centre's scientists.

The only large, multi-functional, and state-funded collaboration in the U.S. is the Cure Drug Repurposing Collaboratory (CDRC), founded in 2020 with funding support from the FDA and NCATS and led by the Critical Path Institute. This project provides a venue for sharing clinical practice data to track different uses of authorised drug products in therapeutic areas with unmet medical needs. All this is intended to accelerate and optimise research efforts in various areas through analyses to identify candidates for repurposing, provide a roadmap for repurposing regulation, generate real-world evidence (RWE) for adding new indications of authorised drug products, and more. As a multi-step process, drug repurposing requires identification and overcoming major challenges throughout different stages. Fig. 3 shows the planned CDRC stages.

An examination of the structure of the FDA reveals that the Division of Bioinformatics and Biostatistics of the National Centre for Toxicological Research is the only structure in whose focus repurposing is partially found. The mission of this division includes developing an integrated capacity to meet the growing needs in areas such as biomarker development, drug safety, repurposing, precision medicine, artificial intelligence, rare diseases, endocrine disruptors, and risk assessment through the capabilities of bioinformatics and biostatistics.

A comparison of repurposing structures and initiatives in the EU and U.S. shows significant differences. Firstly, there is a large difference between the time of the first meeting discussing repurposing—2015 for STAMP and 2019 for FDA. The topic is addressed in a total of 10 of the Expert Group meetings, whereas for the U.S. governmental structures, it is addressed in their only workshop on the topic. This represents a prerequisite for the different development and regulation of repurposing due to the highly uneven discussion of the topic. Critical analysis reveals another difference in the source of the initiatives aimed at improving repurposing. Within the EU, the generator of these initiatives is EMA itself, whereas in the U.S. this is carried out by an entity external to the medicine's regulator—NCATS. The source-regulator discrepancy of initiatives in the U.S. system can lead, on one hand, to reduced effectiveness and a shift in focus of these initiatives. On the other hand, external generation of proposals may

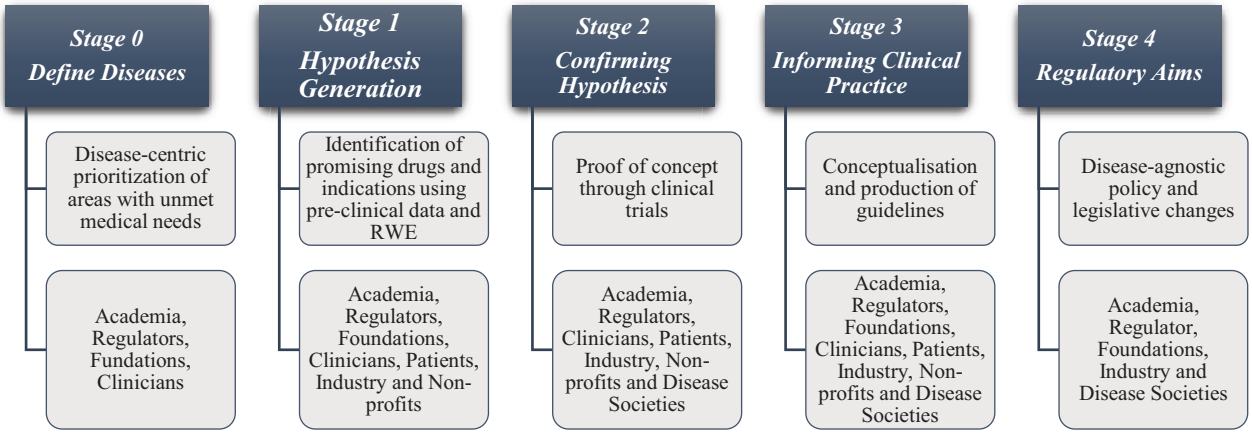

Figure 3. Representation of CURE Drug Repurposing Collaboratory Roadmap (Critical Path Institute 2024).

also lead to delays in their implementation for a variety of reasons, including different structures, ineffective communication, and other barriers to interaction shown in the Li et al. (2018) study.

A major difference is also found in the focus of the approaches and projects for repurposing purposes funded by the two entities: while for EMA it is the regulation of the mechanism, for FDA it is the way to generate evidence for the implementation of repurposing. A possible reason for the EMA to adopt this focus of work is the need for legislative changes in order to allow the possibility that some of the research in a drug dossier is not conducted by or for the applicant and the applicant does not own the rights to it, similar to U.S. Section 505(b)(2). Another important reason is the influence of academia and non-profits in generating hypotheses and evidence for repurposing, but this needs further stimulation. The work of Polamreddy and Gattu (2019) explores the topic by analysing collaborations for repurposing between 2012 and 2017. Their results show only a 20% and 9% share of projects between industry, NGO, and academia, respectively, representing a very limited share of collaborations. These results are obtained against a background of significant migration of professionals from industry to academia, as well as increasing funding opportunities from non-profit organisations.

A historical example of the need to harmonise repurposing is the approval for use of Bevacizumab (Avastin®) in indication metastatic breast cancer in combination with paclitaxel, also shown in the study by Montero et al. (2012). This indication was added in 2007 in the EU and in 2008 in the U.S., both via repurposing mechanisms. Published data from the FDA-mandated confirmatory trials failed to demonstrate positive effects on overall survival, and this caused the withdrawal of approval for the indication. On the other hand, the EMA did not discontinue use in the indication as the benefits continued to outweigh the risks. The lack of harmonisation shown by this example can lead to divergent effects, such as allowing the use of a medicinal product that lacks sufficient quality, efficacy, and safety or depriving patients of timely access to treatment. Another example of the need to regulate repurposing is shown by Gozzo et al. (2020) in their analysis of the Italian healthcare system and the widespread use of the repurposing mechanism during the Covid-19 pandemic. As one of the most severely affected EU countries, Italy used repurposing to reduce the time to access new therapies. However, the subsequent analysis of health crisis management shows the implementation of a large number of additional measures and the critical review of various regulations in the field, which demonstrates weaknesses in the regulatory framework of repurposing.

Conclusion

The conducted comparative analysis shows a clear need for regulation of drug repurposing, with the inclusion and detailed description of the term in the legislative framework emerging as a key point. The differences found in the procedures for granting authorisation for use also point out an opportunity to harmonise regulation between the two leading agencies, which would bring benefits such as timely access to innovative interventions, more effective management of health crises, and, in general, saving humans' lives. Additionally, harmonisation of drug regulation plays a key role in raising public awareness and trust in evidence-based medicine. Regulating the involvement of organisations other than the MAH in the repurposing process is one of the main means of increasing its efficiency. NCATS' work demonstrates the impact of digital and automated tools to detect potential for repurposing. The first international conference on repurposing, held in 2024, testifies that this mechanism is a modern and promising one, but also recognises the imperative of regulating the process in a harmonised way across drug agencies.

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Authors' contribution statement

Conceptualisation: IG, VG-K; Writing—original draft preparation AI, VG-K; Writing—review and editing VG-K, IG; Visualisation: AI; Supervision: IG. Funding acquisition: IG, VG-K; Methodology: AI, VG-K.

All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

The authors confirm that the data supporting the findings of this study is available within the article.

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