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The changing focus of regulatory frameworks around the globe and the opportunities for harmonization

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The changing focus of regulatory frameworks around the globe and the opportunities for harmonization

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Editorial: The changing focus of regulatory frameworks around the globe and the opportunities for harmonization

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Editorial on the Research Topic
The changing focus of regulatory frameworks around the globe and the opportunities for harmonization

Regulatory framework

The regulatory environment is key for protecting public health and has become more complex and sophisticated in recent years, paralleling the advances in scientific discovery and 21st century technological opportunities. The pharmaceutical field and medicines and medical devices development is increasingly global, and multinational firms must make informed and often challenging decisions about where and when to locate their activity. It is vital that regulators provide the most effective approval systems that are proportionate and committed to patient safety and timely access, whilst supporting innovative research and efficient development programmes.

Increasingly, alongside bespoke regulatory initiatives found across different jurisdictions that reflect particular population or public health needs and life sciences ambitions, *reliance* (whereby the national regulatory authority in one jurisdiction may take into account and give significant weight to assessments performed by another national regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision), *harmonization* (process by which technical guidelines are developed to be uniform across participating authorities) and *convergence* (process whereby the regulatory requirements across countries or regions become more similar or "aligned" over time) are seen as growing themes. A number of "tools" exist to facilitate these more aligned approaches, including work at the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the International Coalition of Medicines Regulatory Authorities (ICMRA). It is also increasingly recognized that Regulatory Science plays an important role in adapting the global regulatory frameworks which exist to ensure that patients can access high quality medical technologies and public confidence in regulatory frameworks is maintained and improved.

Regulatory science and novel regulatory concepts

Regulatory Science can be defined as a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine, encompassing basic and applied medicinal science and social sciences, which contribute to the development of regulatory standards and tools. Regulatory Science is expected to be responsive to emerging changes in technology, clinical practice and societal and public health needs. Progress has been made in the application and evolution of regulatory (legislative) procedures for the benefit of patients and public health but also in driving and enabling innovation.

The current global landscape of medicines is changing rapidly with the increasing focus on gene editing techniques, specific modifications allowing for individualized medicines or targeted therapies for very small number of individuals. The conventional regulatory paths are mostly positioned for larger populations and may not be suitable for these type of approaches.

Regulatory sandboxes have emerged as an innovative mechanism to facilitate the development and approval of new technologies, including pharmaceuticals. A regulatory sandbox is an environment where firms can test new innovations under the supervision of a regulator. The aim is simple: to facilitate innovation in a safe and responsible manner. Innovations that can be tested include new products, services, solutions, technologies, business models and even policies. The application of regulatory sandboxes 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. The concept of regulatory sandboxes however is not limited to regulation of medicines for rare diseases and is being explored in a broader context in any situations where the established regulatory pathways might not be fit for purpose.

Research Topic—evolving regulatory processes

Our Research Topic covered elements of the' Changing Focus of Regulatory Frameworks Around the Globe and the Opportunities for Harmonization'. The Research Topic includes 10 papers from across the globe including Europe, Africa and Japan, exemplifying the diversity of the changing practice and emphasis of regulatory science, with the need to foster more harmonized and convergent approaches across the globe.

Scientific advice from competent authorities is a critical tool that helps innovators navigate the complexities of the regulatory requirements in medicines development. Gravanis et al. discuss the challenges and ongoing initiatives toward better integrated EU scientific advice, noting the increasing importance of parallel advice with other decision makers such as Health Technology Assessment (HTA bodies) and the need to forge closer links with medical device regulators. Despite the benefits of scientific advice to developer, patient, payer and regulator, there are challenges, and these include aspects such as the need to carefully manage the separation between individuals in prominent roles during early advice and later assessment, whilst being cognisant of capacity concerns and existing resource constraints in the EU medicines regulatory network.

Another important regulatory tool for innovators is qualification procedures of novel methodologies such as non-clinical and *in vitro* models, biomarkers and pharmacometric methods. Giannuzzi et al. analyse EMA qualification procedures and explore innovative research methodologies in the EU regulatory framework from a pediatric perspective. They found that only 6 out of 27 qualification procedures reported pediatric data, despite the fact that many more of these 27 procedures hold significant promise for application in the pediatric population. This study reiterates the call to strengthen the framework for pediatrics, which despite specific regulatory provisions, is often still a neglected area of research and development.

Capacity issues and immature regulatory systems can be detrimental for provision of timely access to medicines and other health technologies. Regulatory reliance provides one solution, described as the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision. Broojerdi et al. describe evidence-based approaches for promoting regulatory reliance, allowing for increased access to quality-assured medical products. A number of key recommendations are put forward to further improve and build the sustainability of the WHO-listed authorities framework, supporting the advancement of regulatory outputs and outcomes, and generating a positive impact on global public health.

Wens et al. tackle the challenging topic of defining unmet medical needs from a regulatory perspective, an increasingly important area of focus for the new EU pharmaceutical legislation and the linkage to bespoke pathways and incentives. In responses to a survey of stakeholders, areas of agreement and disagreement are elucidated with a clear recommendation for the need for further discussion on the proposed criteria for unmet medical need in order to avoid ambiguity and maximize the potential opportunities for patients.

Medicines regulatory harmonization provides several benefits including improving public health through faster availability of safe, high-quality, and effective medical products. It also enhances the standardization of technical guidelines and facilitates work-sharing among regulatory authorities. Ngum et al. compared the review models, target timelines and data requirements used in assessing applications by the East African Community Medicines Registration Harmonization (EAC-MRH) initiative. Their study led to several recommendations aimed at improving current registration processes, minimizing the duplication of limited resources, and reducing costs and burdens for the pharmaceutical industry.

In this Research Topic, Brown et al. highlight key advancements and ongoing challenges in regulatory and market access for rare disease medicines. Legislative initiatives such as the U.S. Orphan Drug Act and the EU Orphan Drug Regulation have significantly increased approvals of orphan drugs. Despite these regulatory successes, global patient access remains uneven due to fragmented pricing and reimbursement systems. Brown et al. emphasizes the need for collaborative efforts to bridge these gaps and translate innovation into tangible relevant outcomes for patients.

Similarly, Owusu-Asante et al. examine the status and improvement opportunities for Good Review Practices (GRevPs) in seven West African countries under the ECOWAS Medicines Regulatory Harmonization initiative. Their analysis identifies disparities in regulatory autonomy, transparency, and communication, highlighting Sierra Leone's notable dedication to continuous enhancement of regulatory review processes aligned with GRevP principles.

Building on these insights, Hassen et al. stress that ensuring pharmaceutical quality remains a significant public health issue in Africa, exacerbated by weak regulatory frameworks, limited resources, and corruption. They advocate adopting Quality by Design, embedding quality assurance throughout pharmaceutical production, to improve product reliability and safety. The study underscores the urgent need for African nations to harmonize regulations, enhance enforcement, and invest in regulatory infrastructure to protect public health.

Post marketing risk management measures hold an important place in managing uncertainties about the safety profile of medicines at the time of their marketing authorization. Different jurisdictions have introduced rules and actions with the scope to minimize risks, but also to follow up, identify and assess safety signals. Kameyama et al., have provided a review of the current situation and issues regarding termination of risk management plans in Japan. A retrospective analysis of a 10 year period (2013–2023) has shown that out of 72 drugs with RMPs completed re-examination, the RMP requirement was lifted for 69 drugs (95.8%) and remained for three drugs (4.2%) only. Since after removal of the RMP requirement there is limited information regarding risks that take time to manifest or insufficient information regarding safety during long-term administration, the authors call for reconsideration of the application of this rule. In addition, the authors emphasize the differences with EU and US legislations regarding pharmacovigilance and risk minimization activities, where such termination of RMP is not in place.

In conclusions the authors point to the potential source of confusion because medicines marketed in several parts of the world must comply with divergent regulatory requirements. With an increasing trend for globalization, aligning of regulatory RMP requirements across jurisdictions worldwide could help in global availability of medicines and it will guarantee better drug safety management.

Samukange et al. use the World Health Organization's Global Benchmarking Tool Plus Blood (GBT + Blood)—a recognized framework that provides detailed sub-indicators for evaluating specific regulatory functions related to blood, blood components, and plasma-derived products. This tool is widely used to assess the maturity of national regulatory systems and guide improvements in regulatory oversight. The authors have compared WHO-designated maturity level 3 (ML3) competent national regulatory authorities (NRAs) with non-designated NRAs. The results clearly indicate a disparity between the registration/marketing authorization function and the approval process for blood products. The authors concluded that there is an urgent need to prioritize and strengthen regulatory capacities, particularly in the approval process for blood products.

Summary and future perspectives

Medicines and medical technology development is a global endeavor and exchange of experience and knowledge between regulatory agencies working in different jurisdictions is not only necessary but seen increasingly as essential.

The publications included in this Research Topic provide an opportunity for focused discussion on specific aspects of the regulatory practices in certain parts of the world or the use of certain regulatory tools. While each individual publication tackles a specific aspect either in regulatory support in drug development, or in approval and post marketing safety monitoring, the common theme emerging are the gaps and divergences identified, and the proposal for re-thinking of the system to drive efficiencies, harmonization and reduce duplication. Although not comprehensive, this collection provides readers with a curated set of challenges and opportunities, highlighting the need for continued reflection and the exploration of alternative and innovative approaches in regulatory science and practice. The guest editors truly hope that this has opened the door for debate and future research in the domain of regulatory science, and it's positive growing impact on public health.

Author contributions

AM: Conceptualization, Writing – original draft, Writing – review & editing. DO: Conceptualization, Writing – original draft, Writing – review & editing. VS-B: Writing – review & editing, Writing – original draft, Conceptualization.

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Innovative research methodologies in the EU regulatory framework: an analysis of EMA qualification procedures from a pediatric perspective

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Introduction: The European Medicines Agency (EMA) offers scientific advice to support the qualification procedure of novel methodologies, such as preclinical and *in vitro* models, biomarkers, and pharmacometric methods, thereby endorsing their acceptability in medicine research and development (R&D). This aspect is particularly relevant to overcome the scarcity of data and the lack of validated endpoints and biomarkers in research fields characterized by small samples, such as pediatrics.

Aim: This study aimed to analyze the potential pediatric interest in methodologies qualified as "novel methodologies for medicine development" by the EMA.

Methods: The positive qualification opinions of novel methodologies for medicine development published on the EMA website between 2008 and 2023 were identified. Multi-level analyses were conducted to investigate data with a hierarchical structure and the effects of cluster-level variables and cluster-level variances and to evaluate their potential pediatric interest, defined as the possibility of using the novel methodology in pediatric R&D and the availability of pediatric data. The duration of the procedure, the type of methodology, the specific disease or disease area addressed, the type of applicant, and the availability of pediatric data at the time of the opinion release were also investigated.

Results: Most of the 27 qualifications for novel methodologies issued by the EMA (70%) were potentially of interest to pediatric patients, but only six of them reported pediatric data. The overall duration of qualification procedures with pediatric interest was longer than that of procedures without any pediatric interest (median time: 7 months vs. 3.5 months, respectively; $p = 0.082$). In parallel, qualification procedures that included pediatric data lasted for a longer period (median time: 8 months vs. 6 months, respectively; $p = 0.150$). Nephrology and neurology represented the main disease areas (21% and 16%, respectively), while endpoints, biomarkers, and registries represented the main types of innovative methodologies (32%, 26%, and 16%, respectively).

Discussion: Our results underscore the importance of implementing innovative methodologies in regulatory-compliant pediatric research activities. Pediatric-dedicated research infrastructures providing regulatory support and strategic advice during research activities could be crucial to the design of *ad hoc* pediatric methodologies or to extend and validate them for pediatrics.

KEYWORDS

innovative methodologies, pediatric research, regulatory, qualification procedure, European Medicines Agency

Introduction

Innovative methodologies, including pharmacometrics, innovative trial designs, personalized medicine, biomarkers, preclinical models, and *in vitro* models, provide effective and valuable avenues for generating robust research evidence in today's context. The leveraging real-world data and registries has also been recognized as an "innovative way" to an innovative approach to generate evidence for scientific health research, to complement or even replace the traditional clinical research setting (1).

Over the past decades, researchers and companies have increasingly proposed new research methodologies to gain evidence in the biomedical field. These methodologies have the potential to reduce the time and efforts required to identify the failure of successful drugs early (2–8).

For this reason, regulators encourage the implementation of new methods for conducting research and development (R&D) programs (9–15). To facilitate this, voluntary regulatory procedures have been established to endorse the acceptability of a novel methodology not yet integrated into medicines R&D and clinical management, including the Food and Drug Administration (FDA), qualification of Drug Development Tools (DDT), and the European Medicines Agency (EMA) qualification procedure of novel methodologies for medicine development (16–18). The EMA qualification procedure is in charge of changing under the remit of the EMA Committee for Medicinal Products for Human Use (CHMP) and/or the EMA Scientific Advice Working Party (SAWP). The procedure leads to a qualification opinion (QO) or a qualification advice (QA), based on the assessment of the submitted data. The former establishes the acceptability of a specific use of the method under evaluation (e.g., use of a novel methodology or a novel biomarker); the latter is adopted when the data submitted for qualification are still preliminary and not sufficiently supportive, but promising. In this case, further investigations and data sharing are encouraged by providing a letter of support. Notably, prior to the final QO decision, the procedure is opened to the public consultation of the scientific community, aiming to expand scientific scrutiny and discussion. All the steps of the qualification procedure take a maximum of 190 days (19). According to the EMA annual report, 21 qualification requests for novel technologies have been submitted in 2022, with a rising trend from 2018 (20). Since 2005, the EMA and FDA have accepted joint applications for qualifications for biomarkers and clinical outcome assessments, aiming to improve the harmonization of international guidelines.[1] Innovative research methodologies represent an opportunity to address the well-known challenges in the field of research and scientific progress characterized by small samples, especially in pediatrics and rare diseases. These challenges include the lack of science, scarcity of data, unavailability of proper preclinical models, age-related differences in pediatrics, lack of validated endpoints and biomarkers, geographic dispersion of experts, and specialized centers dealing with specific conditions (21).

For example, pharmacometrics methods, such as physiologically based pharmacokinetic (PBPK) modeling, are today increasingly utilized to help in defining doses for pediatric patients (22–26) and in first-in-human trials and to predict interactions between medicines (27–30). Moreover, pharmacometrics methods are expected to play a crucial role in other aspects of the medicine R&D, such as benefit–risk analysis (31, 32), to address the choice of a target molecule, optimize pre-clinical and clinical planning, and guide decision-making for future studies (3). This emphasizes the need for standardized approaches in pharmacometrics to enhance the quality and reproducibility of research in this field (11, 33), as well as the need for training to develop a skilled workforce in pharmacometrics (34).

Innovative trial designs are invented and tested as an alternative to the "golden standard" randomized controlled trial (RCT), aiming to identify responders with a small sample size while maintaining adequate statistical power. Starting from the EMA guidelines on clinical trials in small populations (35), master protocols (umbrella, platform, and basket trials) (8), cross-over and adaptive designs, sequential designs, n-of-1 trials, and randomized withdrawn designs can generate evidence to support the assessment of medicines (6, 36).

Personalized medicine approaches have the potential to effectively address the issue of diseases affecting small populations, so they can better find effective and reliable treatments and improve diagnostic outcomes in this field (37).

Other innovative tools and methods have been deemed useful to conduct pediatric studies (38).

In this work, we aimed to analyze the pediatric interest in methodologies qualified as "novel methodologies for medicine development" by the EMA since the introduction of this procedure. We also examined the duration of the procedure, the type of methodology, the disease or disease area addressed, and the type of

1 https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities

applicant of the qualification opinions, with and without pediatric interest. Finally, we assessed the availability of pediatric data at the time of the opinion release.

Materials and methods

Sample

For this study, all the positive qualification opinions of novel methodologies for medicine development released between 1 January 2008 (i.e., since the implementation of the regulatory procedure in the EU) and 31 December 2023 were sourced from the EMA website[2] and included in this study. Procedures with a draft QO and without the date of the final adoption by CHMP were not considered.

Data extraction

The opinion letters for all the procedures were consulted on the EMA website and analyzed to extract the following data:

- the type of applicant;
- the type of methodology;
- any specific medicinal product, disease, or disease area addressed;
- the availability of pediatric data at the time of the opinion release; and
- the duration of the procedure.

Data characterization and interpretation

The potential ***pediatric interest*** was defined according to a double-level analysis. First, we investigated whether the disease or the medicinal product, for which the methodology was qualified and where specified in the QO, was addressed in a Pediatric Investigation Plan (PIP); in contrast, diseases or products included in a product waiver or the list of class waivers were considered without pediatric interest. PIPs and waivers were retrieved from the EMA website. Second, we assessed whether each methodology was already applied and used in pediatric studies by consulting clinicaltrials.gov[3] and the literature. For QO concerning groups of methodologies, for example, groups of biomarkers qualified in a unique opinion for the same disease, we performed this check for each one.

The ***applicants*** were classified as either profit or non-profit. We also evaluated whether the development of the methodology was supported by any European public funding.

With regard to the ***type of methodology***, the classification was set based on the characteristics reported in the opinion letters, including the titles and keywords, given that the EMA does not provide any classification, conversely to the FDA.

The ***disease*** for which the methodology was referred was attributed to eight ***disease areas*** identified by EMA regulatory procedures, i.e., Pediatric Investigation Plans (PIPs), orphan designation, and European Public Assessment Report (EPAR), and then grouped according to the methodology detailed in our previous publications (21, 39). For methodologies applying to more than one area, we indicated "not applicable". Additionally, we identified the methodologies addressing a specific disease.

We examined the list of issues released by the SAWP to identify any requests for further data from the SAWP on the use of the methodology in the pediatric population and the corresponding answers provided by the applicants. We also evaluated whether such requests led to the inclusion of pediatric data supporting such use. Moreover, we analyzed the comments from stakeholders and related EMA feedback released during the public consultation. The main purpose was to assess any changes in the final qualification opinion compared to the initial submitted draft, focusing on considerations related to the pediatric population, and to determine whether these changes were the result of comments provided by the stakeholders or whether they were influenced by the list of issues provided by the EMA.

The ***duration of the procedure*** was defined as the number of months from the date of adoption by the CHMP for release for public consultation to the date of adoption of the final opinion by the CHMP. We did not consider the time between the date of submission and the adoption by CHMP, as well as the date of the draft agreed by the SAWP and the adoption by CHMP, because some dates were missing, as detailed in the Supplementary material.

Data were collected and analyzed by four researchers; the final check was conducted by two researchers, who also discussed any possible disagreements to reach a consensus. Advice was requested from an expert in the pediatric research field (AC) in the case of methodologies applicable to a wide spectrum of diseases and from an expert in statistics (GR) in the case of statistical methodologies.

Statistical analysis

We conducted a multi-level analysis to investigate data with a hierarchical structure and the effects of cluster-level variables and cluster-level variances. Generalized linear models (GLMs) were used for the analysis of time-series data. Differences were considered statistically significant when p-values were < 0.05, while a $p < 0.1$ indicates weak evidence or a trend. SPSS statistical package version 29.0 (IBM Corp., Armonk, NY, United States) was employed for all statistical analyses.

Results

Pediatric interest in qualification procedures from 2008 to 2023

From the implementation of the EMA Qualification Procedure for Novel Methodologies in 2008 to December 2023, 27 applications received a positive opinion; one of them was a joint procedure with the FDA (EMEA/679719/2008). Three opinions

2 https://www.ema.europa.eu/en

3 https://clinicaltrials.gov/

published on the EMA website resulted in a "draft" (and therefore not considered for the analysis).

As detailed in the methods section, we analyzed the potential *pediatric interest* of all the 27 methodologies included in EMA qualification opinions. Most of the methodologies (19/27; 70%) were potential of interest to pediatric patients (see Table 1 for detailed information):

- 14 addressed a disease or a medicine included in a PIP;
- 1 not specifically intended for a medicinal product or disease was found to be used in pediatrics from the literature and clinicaltrials.gov; and
- four were considered of pediatric interest by experts.

With regard to the eight methodologies without pediatric interest, seven of them referred to a disease included in a class or product waiver, and 1 was referred to a disease affecting children and included in PIPs, but the methodology was not applicable for children as it was not retrieved either in the literature or in clinicaltrials.gov.

Type of applicant

No significant differences were found in terms of the type of applicants: 11 procedures were submitted by profit organizations, whereas 16 procedures were submitted by non-profit ones, with a quite regular alternation during the years (Figure 1). Similarly, QO procedures with pediatric interest were applied to both profit (8) and non-profit (11) applicants.

In addition, two opinion letters specifically mentioned that the methodology was fully or partly developed/studied in the context of European public funding, including the methodology "IMI PREFER" (EMADOC-1700519818-808373) in the context of the Innovative Medicine Initiative (IMI) project (grant agreement No. 115966) and the methodology "Proactive in COPD" (EMA/CHMP/SAWP/226829/2018) in the context of another IMI project (grant agreement No. IMI JU #115011).

Types of methodology

With regard to the types of methodologies, we classified them into the following categories: biomarker, endpoint, registry, statistical methodology, tool for data measurement/management, model (dose selection model, trial evaluation model), and research framework for patient preference study (Figure 2). Biomarkers, endpoints, and registries were the main types of innovative methodologies qualified by the EMA (37%, 30%, and 11%, respectively). The remaining qualified methodologies belonged to the other categories such as statistical methodology (7%), tool for data measurement/management (4%), research framework for patient preference studies (4%), dose selection (4%), and trial evaluation models (4%).

In line with the whole sample, endpoints, biomarkers, and registries were the main types of innovative methodologies with pediatric interest (32%, 26%, and 16%, respectively) (Figure 2).

Diseases and disease areas addressed

The qualified methodologies spanned eight different disease areas, namely, cardiology, endocrinology, gastroenterology, infectious and immune system disease, nephrology, neurology, oncology, and pulmonology, where neurology resulted in the most representation (33%), followed by nephrology (15%) and pulmonology (11%). Notably, 19% were not related to any specific area (Figure 3).

Out of 27 qualifications, 6 specifically addressed rare diseases: Duchenne Muscular Dystrophy, Huntington's disease, cystic fibrosis, and autosomal dominant polycystic kidney disease (ADPKD).

In line with the whole sample, in terms of disease areas, nephrology and neurology comprised the primary domains of methodologies with a pediatric focus, accounting for 21% and 16%, respectively (Figure 3). The five methodologies unrelated to a specific therapeutic area (26%) held potential pediatric interest (Figure 3, Table 1).

Availability of pediatric data at the time of the opinion release

Notably, only six of the total QOs reported pediatric data, as shown in Table 1. In particular, they are intended to assess both the safety and effectiveness of medicinal products and involve the use of patient registries ($n = 2$) or incorporate specific biomarkers ($n = 2$) and endpoints ($n = 2$) tailored to the pediatric population to reflect the disease's impact and progression (Figure 4, Table 1).

The examination of the list of issues released by the SAWP during the regulatory procedure, the applicants' corresponding answers, the stakeholders' comments, and the EMA's responses raised during the procedure highlighted that the only change between the draft and the final QO was related to the QO on an endpoint for Duchenne Muscular Dystrophy (DMD) studies (EMADOC-1700519818-1127132): in the list of issues, it was specifically required to provide updates from studies in the population below 5 years of age. During the consultation phase, the applicant submitted new data demonstrating that the performance of the tool was expected to be the same between 4- and 5-year-old children. Therefore, the age limit was lowered to 4 years of age in the adopted QO. This consultation phase and resulting modification did not result in a longer duration of the procedure (12 months overall, Figure 5).

For the other analyzed QOs, comments submitted by stakeholders or issues raised by the EMA related to pediatrics were duly acknowledged by the applicants; however, these comments did not lead to specific changes in the QOs (see Supplementary material for details).

Duration of the procedure

The overall duration of the procedures with pediatric interest was longer than the overall duration of procedures without any

TABLE 1 Qualification opinions with pediatric interest and their methodology type and disease area.

ID qualification opinion	Methodology	Type	Therapeutic area	Included in a PIP	Pediatric data in QO
EMADOC-1700519818-1127132	Stride velocity 95th centile as a primary endpoint in studies of ambulatory Duchenne muscular dystrophy studies	Endpoint	Neurology	Yes	Yes
EMADOC-1700519818-828910	Use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorization monitoring of medical products	Registry	Neurology	Yes	Yes
EMA/CHMP/SAWP/186420/2022	Islet autoantibodies (AAs) as enrichment biomarkers for type 1 diabetes (T1D) prevention clinical trials	Biomarker	Endocrinology	Yes	Yes
EMA/CHMP/SAWP/178058/2019	Stride velocity 95th centile as a secondary endpoint in Duchenne muscular dystrophy measured by a valid and suitable wearable device	Endpoint	Neurology	Yes	Yes
EMA/CHMP/SAWP/622564/2018	The European Cystic Fibrosis Society Patient Registry (ECFSPR) and CF pharmaco-epidemiology studies	Registry	Pulmonology	Yes	Yes
EMA/CHMP/SAWP/801872/2015	Pediatric ulcerative colitis activity index (PUCAI)	Endpoint	Gastroenterology	Yes	Yes
EMA/SA/00000104642	GFR slope as a validated surrogate endpoint for RCT in CKD	Endpoint	Nephrology	Yes	No
EMADOC-1700519818-946771	iBox Scoring System as a secondary efficacy endpoint in clinical trials investigating novel immunosuppressive medicines in kidney transplant patients	Endpoint	Infectious and immune system diseases	Yes	No
EMADOC-1700519818-907465	Prognostic Covariate Adjustment (PROCOVA^{TM})	Statistical methodology	N/A	No	No
EMADOC-1700519818-808373	IMI PREFER	Research framework for patient preference studies	N/A	No	No
EMA/CHMP/SAWP/483349/2019	eSource Direct Data Capture (DDC)	Tool for data measurement/management	N/A	No	No
EMA/CHMP/SAWP/792574/2018	Cellular therapy module of the European Society for Blood and Marrow Transplantation (EBMT) Registry	Registry	Oncology	Yes	No
EMA/CHMP/SAWP/513571/2015	Ingestible sensor system for medication adherence as a biomarker for measuring patient adherence to medication in clinical trials	Biomarker	N/A	No	No
EMA/CHMP/SAWP/473433/2015	Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluating patients with autosomal dominant polycystic kidney disease (ADPKD)	Biomarker	Nephrology	Yes	No
EMEA/H/SAB/049/1/QO/2014/SME	*In vitro* hollow fiber system model of tuberculosis (HFS-TB)	Model for dose selection	Infectious and immune system diseases	Yes	No

(Continued)

TABLE 1 (Continued)

ID qualification opinion	Methodology	Type	Therapeutic area	Included in a PIP	Pediatric data in QO
EMA/CHMP/SAWP/757052/2013	MCP-Mod as an efficient statistical methodology for model-based design and analysis of phase II dose-finding studies under model uncertainty	Statistical methodology	N/A	No	No
EMA/CHMP/SAWP/120610/2020	Treatment effect measures when using recurrent event endpoints	Endpoint	Cardiology	Yes	No
EMA/CHMP/SAWP/283298/2010	ILSI/HESI submission of novel renal biomarkers for toxicity	Biomarker	Nephrology	Yes	No
EMEA/679719/2008 Rev. 1	Final conclusions on the pilot joint European Medicines Agency/Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers	Biomarker	Nephrology	Yes	No

The table details if the methodology addresses a disease or a medicine included in a PIP and the availability of pediatric data in the QO. Methodologies spanning more than one therapeutic area were indicated as N/A.

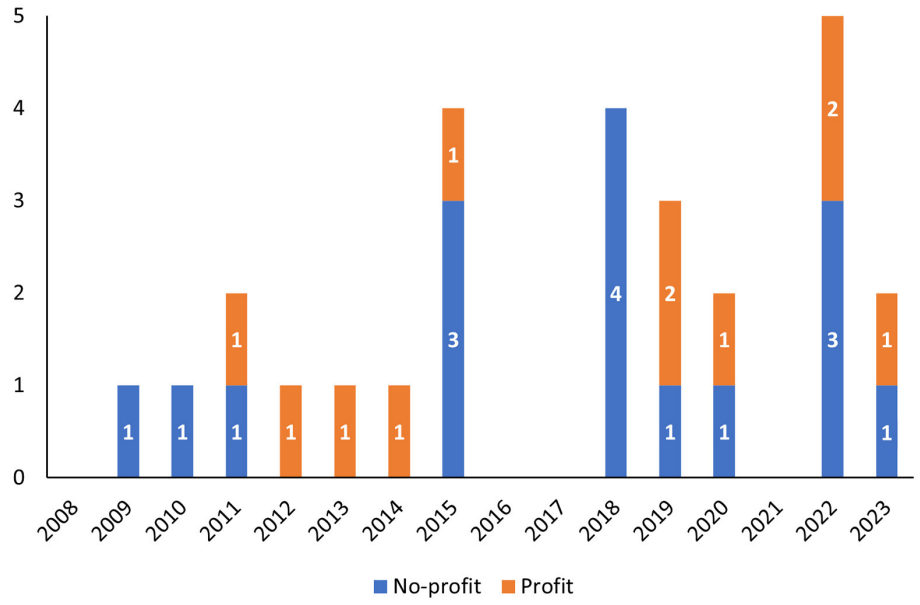

FIGURE 1
Qualification opinions from 2008 to 2023 grouped according to the year in which the opinion was adopted by CHMP and divided by the type of applicant (profit vs. non-profit).

pediatric interest (median time: 7.0 months vs. 3.5 months, respectively; $p = 0.082$; Figure 5A).

No significant differences were found in terms of the duration of the procedures between types of applicants, as detailed in the Supplementary material.

In parallel, the application procedures, including pediatric data, were adopted over a longer period (median time: 8.0 months vs. 6.0 months, respectively; $p = 0.150$; Figure 5B).

Discussion

Over the past years, there has been a growing interest in employing innovative methodologies in biomedical research to gather evidence, as demonstrated by the literature (3, 40–42) and institutional public documents at the EU level (43). In addition, there has been an increased awareness of the need to adapt these methodologies for drug discovery and development and subsequent regulatory acceptance (1, 40). The current

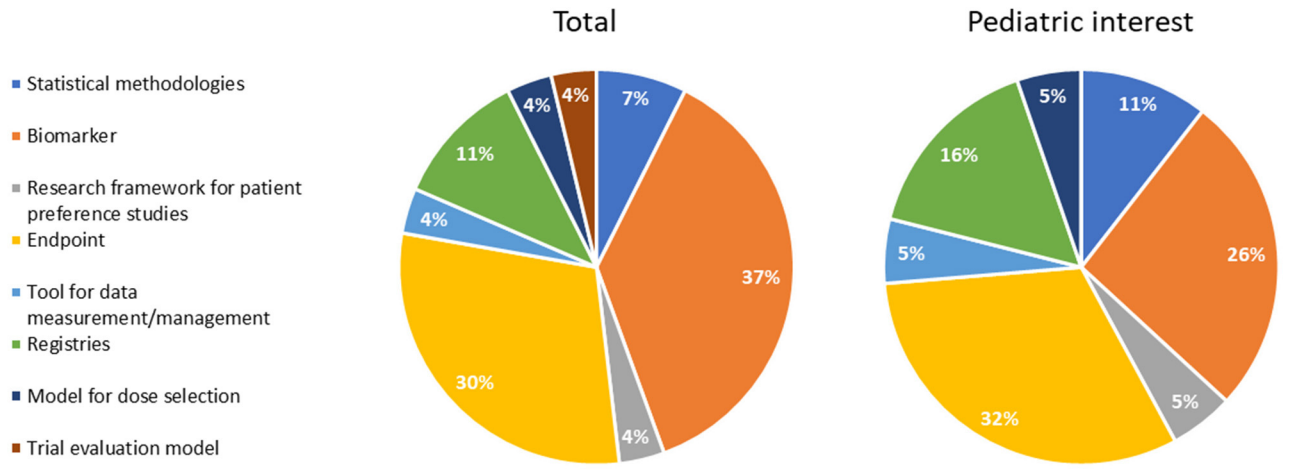

FIGURE 2
Qualification opinions grouped according to the type of methodology (total procedures and procedures of pediatric interest).

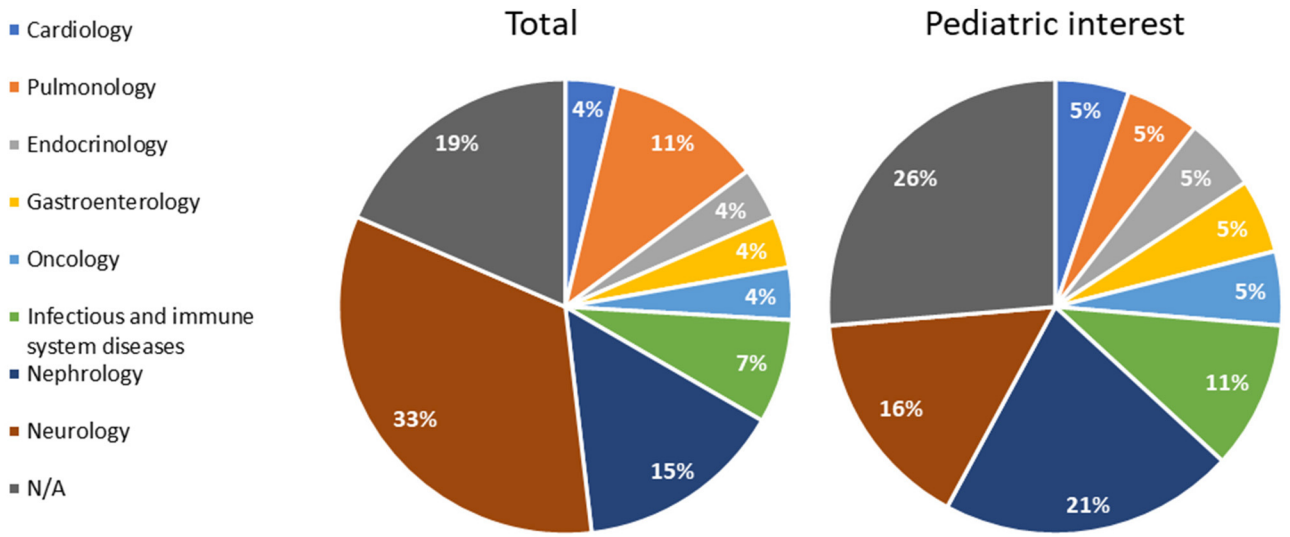

FIGURE 3
Qualification opinions grouped according to the disease area (total procedures and procedures of pediatric interest). N/A: methodologies applying to more than one area.

European Pharmaceutical Strategy recognizes the need for adapting scientific developments (genomics/personalized medicine) and technological transformation (data analytics and tools) to cutting-edge products, providing incentives for innovation, enhancing dialog among regulatory and other authorities, supporting collaborative projects on high-performance computing, artificial intelligence, and innovative trial designs, and a more patient-oriented medicine development (43).

In line with previous findings (40), our study shows that both profit and not-for-profit entities accessed the EMA qualification procedure. However, only a small percentage (about 10%) reached the full opinion. In fact, up to 2022, 209 requests for the qualification of novel methodologies were submitted to the EMA (20). In our analysis, only 27 applications received a positive opinion up to 2023.

Interestingly, biomarkers, endpoints, and registries emerged as the most represented methodologies qualified in the EU. Additionally, other types of methods were qualified as "regulatorily acceptable", including statistical methodologies, tools for data measurement/management, *in vitro* pharmacokinetics models, disease progression models, and research frameworks for patient preference studies. These methodologies spanned across different therapeutic areas, where neurology is the most represented, with some specifically developed for rare diseases. This aspect highlights the relevance and applicability of these methodologies in addressing challenges associated with small populations, for

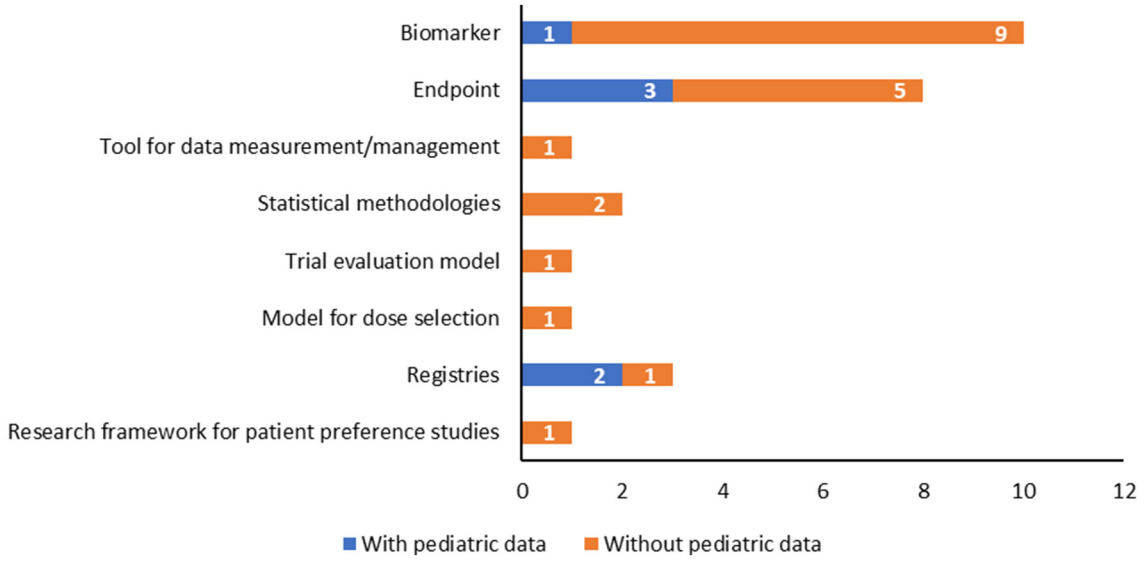

FIGURE 4
Qualification opinions with a pediatric interest grouped according to the type of methodology, highlighting those with pediatric data available.

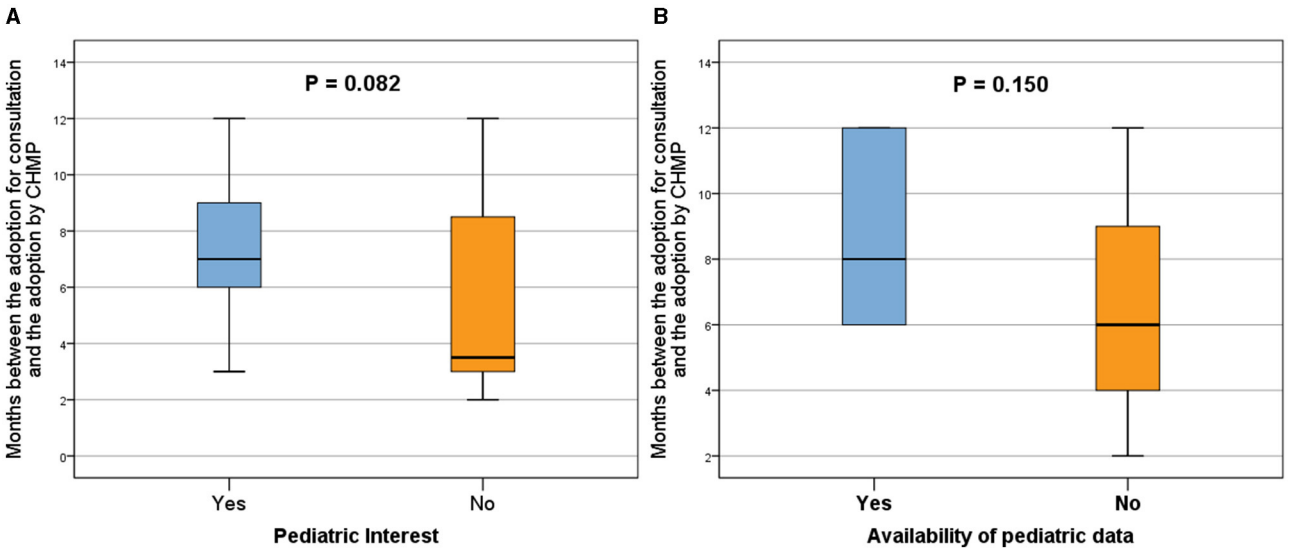

FIGURE 5
Analysis of the qualification procedure duration, defined as the months between adoption for consultation and adoption by CHMP, comparing the presence (Yes) or absence (No) of pediatric interest **(A)** and pediatric data in the QO **(B)**. Procedures with pediatric interest demonstrated an overall longer duration compared to those without pediatric interest **(A)**, and the inclusion of pediatric data extended the adoption period **(B)**. Box plots represent 25th, 50th, and 75th percentiles. Statistically significant differences were denoted by $p < 0.05$, while a $p < 0.1$ indicated a trend.

example, rare diseases, underscoring their potential impact on advancing therapeutic interventions in these specialized areas.

Of note, only one procedure was jointly released with the FDA. As mentioned, a methodology can be assessed by the EMA and FDA together to issue its regulatory acceptance. The two agencies put in place different types of common/parallel submissions regarding the R&D of medicines for human use (PIP, ATMP, scientific advice, orphan designations, qualification procedures for biomarkers, and clinical outcome assessments).[4] Interestingly, the FDA has a "qualification program" for drug development tools classified as animal models, biomarkers, clinical outcome assessments, and innovative science and technology approaches for new drugs. Conversely, the EMA does not provide any classification, making its procedure more "flexible" and allowing the inclusion of such research methodologies, such as registries. However, in line with previous findings (39), achieving harmonization between the two agencies still appears to be a lengthy process. The implementation of the ICH M15 guideline on model-informed drug development (44) would improve regulatory harmonization for model-based analyses

4 https://www.orpha.net/consor/cgi-bin/index.php

as part of dossier submissions related to the development of pharmaceutical products.

If we look at pediatrics, our results demonstrate that a substantial proportion of novel, qualified methodologies hold significant promise for application in the pediatric population. Notably, also in the pediatric field, biomarkers, endpoints, and registries were the predominant types of innovative methodologies, underscoring their importance in advancing pediatric clinical research.

Remarkably, stride velocity 95th centile (SV95C; EMA/CHMP/SAWP/178058/2019) became the first digital endpoint regulatorily qualified in 2019 (45), and it is still the only one included in an EU qualification opinion. Digital biomarkers may capture patient-generated data and provide more objective measurements than traditional approaches, as they allow continuous and longitudinal data collection and the use of automated analysis for data interpretation. This aspect is particularly important for pediatric patients living with rare diseases, where therapeutic options are limited and need to be developed using a patient-focused approach to achieve the biggest impact. While digital technologies, including digital endpoints, are increasingly developed to support diagnosis, monitoring, or therapeutic interventions in clinical care, challenges arise in clinical validation due to the lack of specific guidelines. FDA guidance on patient-reported outcomes (46) could be adapted to ensure clinical validation when using digital tools in medical product development, particularly for pediatric patients with rare diseases, where patient-focused approaches are crucial.

However, our study also raises a critical concern: specific studies aimed at obtaining pediatric data are generally poor/lacking in qualification opinions. The observed discrepancy is concerning, despite the incentives and efforts implemented by the regulatory authorities in the EU to support pediatric R&D, such as the EU Pediatric Regulation (47). Only six of the examined methodologies were submitted for qualification with pediatric data. Moreover, our analyses showed that the inclusion of pediatric data in the procedure is associated with a longer duration of the overall process. However, the sample size was too small to detect a statistically significant difference.

The poor availability of data specifically generated from pediatric studies underscores the critical need for concerted efforts for the incorporation of pediatric data in research, emphasizing the importance of ensuring that innovative approaches are effectively translated into tangible benefits for pediatric patients.

Another missed opportunity for the inclusion of children in clinical research is represented by the IMI PREFER case (EMADOC-1700519818-808373). The PREFER (Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle) framework primarily focuses on incorporating patient preferences in benefit-risk assessments for medical treatments. While the framework highlights the importance of patient involvement, including preferences from various patient populations, based on our latest knowledge, it does not specifically focus on children. Furthermore, it is worth noting that the MSCOA (Multiple Sclerosis Clinical Outcome Assessment), as referenced in QO EMA/CHMP/SAWP/74371/2020, has been designed to capture clinical outcome assessments in patients with multiple sclerosis. However, it was not expressly tailored for children, despite its potential relevance for the pediatric population. Obtaining pediatric data would allow for an understanding of the efficacy and safety of treatments for children affected by multiple sclerosis.

Further interest in the pediatric field might come from the fact that some chronic diseases affecting adults have rare genetic forms with a pediatric onset, as in the case of chronic heart failure in children affected by congenital heart defects or cardiomyopathies (48). In these circumstances, even if the disease does not have a pediatric interest *per se*, early identification and intervention in pediatric patients can significantly impact their long-term outcomes. This emphasizes, on the one hand, the interconnected nature of pediatric and adult medicine in addressing complex chronic diseases and, on the other hand, the importance of a comprehensive approach to medical research and practice that considers the entire spectrum of human life, from infancy to adulthood.

The raised concern is pervasive across various domains of pediatric research, highlighting the imperative to allow the implementation of the continuous advancement of science and innovation in pediatric research. This objective could be achieved, as mentioned above, through the adoption of optimization of clinical study designs, innovative statistical approaches, extrapolation, and other pharmacometric approaches across pediatric ages to support their use in pediatrics (23, 25, 31, 49). Currently, it is well known that the use of pharmacometric approaches can streamline R&D while maintaining the reliability of data. This aspect would also be applicable to the need to include pediatric data without relying solely on the generation of new data. For example, extrapolation methodologies could be used to infer pharmacokinetics, pharmacodynamics, and efficacy from a reference patient population or from animals, another compound or disease (50). The application of these strategies would maximize the usefulness of existing knowledge with the minimum number of subjects enrolled, thus making it more comprehensive and worthwhile to include pediatric data in the qualification procedure.

Additionally, innovative methods for obtaining informed consent and assent or their updates (e.g., digital consent and assent) could be adopted to improve pediatric research. Similarly, approaches for collecting blood samples or other types of biological material could be updated, potentially minimizing pain, discomfort, and distress in pediatric studies (38).

Further exploration of ways to strengthen the research framework in the pediatric field is essential to ensure the highest standards of care and safety for pediatric participants.

At the EMA level, several initiatives are in place to support the application of new and innovative methods in the research of medicines, especially in areas concerning small populations, such as rare diseases and pediatric subjects. EMA working parties collaborate with scientific committees to assist companies and researchers in this effort. For example, the EMA has established the Innovation Task Force (ITF) (51) to ensure coordination across the agency and to serve as a platform for early dialog with applicants regarding innovative aspects in the development of medicines. Crucial insights and guidance may derive from the actions and initiatives led by this task force and the above-mentioned

pharmaceutical strategy for Europe (43), which actively support the integration of innovative methods in clinical trials and, more broadly, in the overall development of medicines. Further expectations come from the Accelerating Clinical Trials in the EU (ACT EU)[5] initiative. It has been set up in the EU to develop a competitive center for innovative clinical research. Therefore, ACT EU does represent an opportunity to bring innovation to clinical research, particularly in multi-center trials. Pediatric networks, such as c4c (conect4children, a large collaborative European network aimed at facilitating the development of new drugs and other therapies for the entire pediatric population),[6] TEDDY (the European Network of Excellence for Pediatric Research),[7] specialistic pediatric networks, and the other members of the European Network of Pediatric Research at the European Medicines Agency (Enpr-EMA),[8] as well as EPTRI,[9] the European Pediatric Translational Research Infrastructure, and the other pan-European Research Infrastructures, ECRIN,[10] BBMRI,[11] and EATRIS,[12] could contribute providing and updating specific tools and services to conduct pediatric studies (38).

Even more recently, the European Commission has funded two new projects under the call "Modeling and simulation to address regulatory needs in the development of orphan and pediatric medicines" (HORIZON-HLTH-2023-IND-06-04). These projects fully addressed the regulatory acceptance of innovative research methodologies in pediatric research. Their outputs could then provide meaningful insights into the relevant field.

Another way to move forward could be to strengthen the awareness and coordination between EU regulatory procedures, for example, orphan designation, PIP, and clinical trial applications. In all these regulatory submissions, specific references could be made if a "qualified" innovative methodology has been used. Such a regulatory provision could improve awareness of the regulatory acceptance of a "research method" not only among researchers, medicine developers, and other applicants but also among regulators. In addition, to ensure that pediatrics is not left behind when innovative methodologies are developed, an explicit statement on the presence or absence of pediatric data could be included in the application form when defining the context of the use of the methodology. This suggested approach would better delineate the usefulness and applicability of the methodology in the pediatric field. Very recently, a checklist to guide the structure and content of qualification applications and a periodical re-evaluation of the qualified elements to ensure the standards that are maintained over time has been proposed.[13] If applied, such modifications would represent an occasion to implement pediatric-specific information in the procedure.

Overall, our results support the importance of implementing innovative methodologies into regulatory-compliant pediatric research activities. In this context, dedicated pediatric research infrastructures could assist in addressing the data gaps in pediatric research, offering regulatory support and strategic advice throughout the research process. These infrastructures play a crucial role in designing *ad hoc* pediatric methodologies or extending and validating existing ones for pediatrics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

VG: Data curation, Methodology, Writing – original draft. AB: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. ST: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. GR: Formal analysis, Writing – review & editing. ET: Data curation, Investigation, Writing – review & editing. DB: Supervision, Writing – review & editing. AC: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

AB, GR, ET, and DB were employed by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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5 https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/clinical-trials-human-medicines/accelerating-clinical-trials-eu-act-eu

6 https://conect4children.org/

7 https://www.teddynetwork.net/

8 https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema

9 https://eptri.eu/

10 https://ecrin.org/

11 https://www.bbmri.it/

12 https://eatris.eu/

13 https://www.ema.europa.eu/en/events/joint-heads-medicines-agencies-hma-european-medicines-agency-ema-multistakeholder-workshop-patient-registries

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1369547/full#supplementary-material

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Current situation and issues regarding termination of risk management plans in Japan

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Introduction: In Japan, drugs approved after the 2013 implementation of the risk management plan (RMP) have the opportunity to be evaluated for RMP termination. However, the guidelines for risk management following the termination of an RMP remain unclear. Drugs are evaluated for RMP termination at the timing of reexamination. Reexamination system is unique to Japan and initiated in 1979, verifies the approved efficacy and safety of a newly marketed drug based on the data from its actual use over a certain period. This study investigated drugs in Japan for which the RMP requirement was lifted upon reexamination and those for which it was not. We organized their characteristics and considered future issues.

Methods: We identified drugs with RMPs and obtained information on RMP termination from the public website of the Pharmaceuticals and Medical Devices Agency (PMDA). The survey period spanned 10 years, from April 2013, when the RMP was implemented, to March 2023.

Results: During the survey period, 72 drugs with RMPs completed reexamination in Japan. The RMP requirement was lifted for 69 drugs (95.8%) and remained for three drugs (4.2%). Upon RMP termination, 16 out of 69 drugs (23.2%) had important potential risks not listed in the package insert, with malignant neoplasm being the most common. Eleven drugs (15.9%) had important missing information not listed in the package insert, with the most common being the impact on cardiovascular risk. Two drugs (2.9%) had ongoing additional pharmacovigilance activities, and 43 drugs (62.3%) had additional risk minimization activities.

Conclusion: Upon reexamination completion, the RMP requirement was lifted for many drugs and remained for a few. Should safety concerns require continued attention following reexamination, we advocate for the continuation of the RMP, guided by more explicit rules. In light of the harmonization of RMP rules with those of other countries, there is a desire for enhanced drug safety management.

KEYWORDS

RMP termination, risk management plan, drug safety, pharmacovigilance, reexamination system, safety concerns, Japanese drug regulatory system

1 Introduction

A risk management plan (RMP) is a document that outlines the systematic approach to managing drug safety from the development phase through the post-marketing phase. It is designed to ensure the safety of drugs and is mandated to be established at the time of approval (1–3). Since 2013, the formulation and implementation of an RMP have been prerequisites for drug approval in Japan. The requirement for an RMP is lifted when it is confirmed that there are no issues. These issues include whether: (1) The risks and risk minimization materials listed in the RMP have been adequately disseminated in the medical setting. (2) There are no new safety concerns. (3) There has been no significant change in the occurrence of existing risks. (4) Missing information has been collected. Even after the requirement for an RMP is lifted, standard safety measures such as issuing necessary warnings and collecting safety information continue (4).

Drugs are evaluated for RMP termination at the timing of reexamination. The reexamination system is unique to Japan and initiated in 1979, verifies the approved efficacy and safety of a newly marketed drug based on the data from its actual use over a certain period. The outcome of the reexamination can lead to continuation of the drug's current approval, modification or deletion of the indication, or cancellation of the approval (5–7). Drugs approved post-2013, when the RMP was implemented, are also being reexamined sequentially after a designated reexamination period. Concurrently, these drugs are evaluated for potential RMP termination. Despite the possibility of RMP termination, clear guidelines for risk management post-RMP termination are lacking (8). According to a survey conducted among companies, responses varied after the requirement for an RMP was lifted. These variations included whether to continue the RMP as an internal document, whether to continue risk minimization activities, and whether to change signal evaluation criteria (9). To our knowledge, no other studies have investigated the termination of RMP.

In this study, we investigated drugs for which the requirement for an RMP was lifted (RMP-terminated drugs) and drugs for which it was not lifted (RMP-continuing drugs). We organized their characteristics and considered future issues.

2 Materials and methods

In this study, we identified drugs with RMPs from the public information provided by the Pharmaceuticals and Medical Devices Agency (PMDA). We designated drugs as "RMP-continuing drugs" if the requirement for an RMP had not been lifted and the reexamination for all indications had been completed. We also checked the PMDA website's "List of drugs for which the formulation and implementation of RMP as a condition for approval has been lifted" (4) and designated all listed items as "RMP-terminated drugs." The survey period spanned 10 years, from April 2013, when the RMP was implemented, to March 2023. We investigated "RMP-terminated drugs" and "RMP-continuing drugs" to determine whether the safety concerns (important identified/potential risks, important missing information) listed in the RMP submitted at the time of reexamination are included in the current package inserts, whether additional pharmacovigilance activities are ongoing, and whether there are additional risk minimization activities. We also investigated the characteristics of "RMP-continuing drugs."

The RMPs submitted at the time of reexamination and the current package inserts were obtained from the PMDA website's "Information Search for Prescription Drugs" (10). For "RMP-continuing drugs," we created a unique database from publicly available information, identified drugs with RMPs approved after April 2013, for which the requirement for an RMP had not been lifted, and for which reexamination for all indications had been completed. This study was prepared in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) reporting guidelines for cross-sectional studies (11). All statistical analyses were performed using JMP Pro 15, with two-sided p-values less than 0.05 considered statistically significant. The Fisher's exact test was used for comparisons between categorical data.

3 Results

From April 2013 to March 2023, a total of 72 drugs with RMP underwent reexamination for all indications. The background information is detailed in **Table 1**. When classified by therapeutic indications, the most common were neuropsychiatric and diabetes drugs, each comprising 8 drugs, or 11.1% of the total. Other hormonal drugs (including antihormonal drugs), accounted for 7 drugs, or 9.7%. There were 17 drugs (23.6%) indicated for pediatric use and 1 drug (1.4%) for orphan diseases.

Out of the drugs studied, 69 (95.8%) had terminated their RMPs, while 3 (4.2%) were still continuing with their RMPs. Among the RMP-terminated drugs, none had important identified risks not listed in the package insert after the termination of the RMP. However, 16 drugs (23.2%) had important potential risks, and 11 drugs (15.9%) had important missing information not listed. At the time of RMP termination, 2 drugs (2.9%) had ongoing additional pharmacovigilance activities, and 43 drugs (62.3%) had additional risk minimization activities. For the RMP-continuing drugs, all safety concerns were included in the current package insert. At the time of the survey, none of these drugs had ongoing additional pharmacovigilance activities, but all 3 drugs (100%) had additional risk minimization activities (**Table 2**).

In this study, we examined the safety concerns not listed in the package inserts of 69 drugs that had terminated their RMPs. At the time of reexamination application of these drugs, we identified 164 important potential risks in the last RMPs, of which 24 risks (14.6%) were not included in the package inserts. The most common risks not listed were related to malignant neoplasms (9 risks), accounting for 31.0% of the total number of important potential risks related to malignant neoplasms (29 risks). This was significantly higher than that for other important potential risks ($p = 0.0165$). Seven out of nine of these risks were for drugs indicated for diabetes. Other important potential risks not listed in the package insert were related to infection, the cerebral cardiovascular system (3 risks each), antibody production, the urinary system, administration error (2 risks each), disseminated intravascular coagulation, and suicide-related events (1 risk each) (**Table 3**). We also found

TABLE 1 Overview of background information.

		N	%
Drugs with RMP that have undergone reexamination for all indications		72	
Therapeutic indication classification*	Other hormonal drugs (including antihormonal drugs)	7	9.7
	Antihypertensive drugs	3	4.2
	Antiepileptic drugs	3	4.2
	Neuropsychiatric drugs	8	11.1
	Diabetic drugs	8	11.1
	Follicular/Progestin hormone agents	4	5.6
	Others	41	
Pediatric indication		17	23.6
Orphan drugs		1	1.4

*If there were multiple therapeutic indication classification categories for one drug, each was counted as multiple.

92 items of important missing information, of which 16 items (17.4%) were not included in the package inserts. The most common missing information not listed was the impact on cardiovascular risk, accounting for 100% of the total number of missing information regarding this issue (seven items). This was significantly higher than other missing information ($p < 0.0001$). All seven items pertained to the drugs indicated for diabetes. They were marked as missing information owing to the lack of information specific to Japanese individuals or regarding long-term administration. Other important missing information not included in the package insert was related to safety when administered to patients with liver dysfunction (5 items), safety when administered to patients with cardiovascular disease, drug interactions, safety during long-term administration, and safety during administration under actual usage conditions (1 item each) (Table 4).

In our study of the 69 drugs that had terminated their RMPs, we investigated the additional pharmacovigilance activities and risk minimization activities that were ongoing at the time of reexamination application. There were two ongoing additional pharmacovigilance activities: one postmarketing clinical trial (50.0%) and one special drug use-results survey regarding long-term use (50.0%). We investigated details in the respective reexamination reports (12, 13). The post-marketing clinical trial was conducted with the aim of enabling continued administration of the drug to subjects who had obtained a therapeutic effect in the clinical trial, with only one Japanese patient receiving the drug. The special drug use-results survey collected 1,461 cases, surpassing the target number of 1,000 cases. Ongoing additional risk minimization activities included creating and distributing materials for patients (33 activities, 47.8%), creating and distributing materials for healthcare professionals (29 activities, 42.0%), and reporting the occurrence of side effects on company websites (3 activities, 4.3%). Other activities included measures to prevent administration errors, the creation and provision of patient cards, ensuring distinguishability from existing formulations with different concentrations, and safety measures related to pain associated with chronic low back pain and osteoarthritis (one activity each, 1.4%) (Table 5).

The drugs that were still continuing with their RMPs were Concerta tablets (methylphenidate hydrochloride), Lamictal tablets (lamotrigine), and Botox Vista Injection (botulinum toxin type A) (14–16). The details were investigated in the respective reexamination reports (17–19). Two of these three drugs were neuropsychiatric drugs. Concerta tablets had drug dependence noted in the reexamination report, and the approval conditions were altered after the reexamination, mandating stricter distribution management. Lamictal tablets, an antiepileptic drug, had previously had a drug safety alert (blue letter) (20) issued regarding serious skin disorders. For Botox Vista Injection, distribution management was mentioned as an additional risk minimization activity. Upon checking Botox Injection (21, 22), which has a different RMP from Botox Vista Injection but contains the same ingredients, it was found that reexamination had not yet been completed for all indications.

4 Discussion

Upon completion of the reexamination, it was demonstrated that the formulation and implementation of the RMP as a condition for approval were lifted for a significant majority of drugs (95.8%). The three RMP-continuing drugs (4.2%) might share characteristics such as being neuropsychiatric drugs, antiepileptic drugs, having drug dependence, distribution control, and past blue letter issuance. However, RMP-terminated drugs also exhibited these same characteristics (six for neuropsychiatric drugs, two for antiepileptic drugs, four for drug dependence, none for distribution control, and one for past blue letter issues). This suggests that there were no discernible characteristic differences between the RMP-continuing drugs and the RMP-terminated drugs. According to a questionnaire survey, a company voluntarily stated in its reexamination application materials that the RMP of a certain drug, for which a blue letter had been issued, would be continued, and the regulatory authority agreed as proposed (9). However, even for Yaz combination tablets (drospirenone/ethinyl estradiol betadex), for which the RMP was terminated, a blue letter had been issued in the past for thrombosis (23). For one drug, the approval condition was changed at the time of reexamination, and for another drug, reexamination for a drug with the same ingredient had not been completed, suggesting that the continuation of the RMP might

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depend on timing. However, given the small number of RMP-continuing drugs, it was challenging to identify the characteristics that led to the continuation of the RMP.

Upon the completion of the reexamination process, a significant number of RMPs were terminated. However, we posit that there may be a larger number of RMPs that are worth continuing. Our study revealed that there were safety concerns that were not included in the package insert for drugs that had terminated their RMPs. As for important potential risks, 14.6% of the potential risks were not listed in the package insert at the time of RMP termination. If these potential risks persist after the reexamination, a challenge arises as there will be no mechanism to confirm them conveniently in the clinical setting post-RMP termination. A study conducted by Saito et al. demonstrated that safety concerns could potentially trigger severe adverse reactions (24). Although the study examined safety concerns in the J-RMP at the time of approval, not reexamination, we believe it is fair to say that at least caution is necessary if safety concerns persist at the time of reexamination. We suggest that potential risks should be included in the package insert if the RMP is terminated, similar to how some drugs mention non-clinical results or risks associated with similar drugs. Otherwise, it would be preferable to continue RMP until every potential risk is either removed or elevated to an identified risk. The purpose of the RMP in Japan is to consolidate all risk management into a single document and ensure through evaluation. We believe that this purpose should remain consistent pre- and post-reexamination. Moreover, among the important potential risks not listed in the package insert upon RMP termination, risks related to malignant neoplasms were the most prevalent. The proportion of important potential risks not listed in the package insert was significantly higher than other potential risks. The reexamination reports for these drugs did not mention the removal of important potential risks. Instead, they stated "No new safety concerns were observed" or "The information is insufficient and the causal relationship with this drug is unclear. Therefore, we will not add any additional information to the package insert and will continue to collect similar information in the future." However, given that malignant neoplasms require time to develop pathologically, it is often challenging to identify risks during the reexamination period. For instance, six out of nine risks related to malignant neoplasms not listed in the package insert were associated with incretin-related drugs. It took approximately 10 years from initial approval to the completion of reexamination, a period deemed insufficient to assess the risks of the occurrence of malignant neoplasms pathologically. Therefore, in such instances, it is preferable to continue the RMP, rather than terminating it leading only to routine pharmacovigilance activity. Regarding important missing information, 17.4% of the items were not included in the package insert. Among the missing information not listed in the package insert upon RMP termination, missing information regarding the impact on cardiovascular risk was the most common. The proportion of important missing information not listed in the package insert was significantly higher than other missing information. Of the seven items, two specified the deletion of missing information in the reexamination reports, while the remaining five did not include such instructions. Instead, they included statements such as "No new safety concerns were observed" or "We will continue our routine pharmacovigilance activity and will consider whether to issue a warning in the package

TABLE 2 Status of risk management plan (RMP) termination/continuation and details of safety concerns /additional activities for drugs post-reexamination.

Reexamination completed drugs (N = 72)	Number of drugs (%)	Drugs with important identified risks not listed in package inserts	Drugs with important potential risks not listed in package inserts	Drugs with important missing information not listed in package inserts	Drugs with ongoing additional pharmacovigilance activities	Drugs with additional risk minimization activities
RMP-terminated drugs	69(95.8)	0	16(23.2)	11(15.9)	2(2.9)	43(62.3)
RMP-continuing drugs	3(4.2)	0	0	0	0	3(100)

insert depending on the situation of the event occurrence." In these cases, the period from initial approval to completion of reexamination was less than 10 years, which is considered to be a pathologically insufficient period to evaluate cardiovascular risk. Consequently, if there is insufficient information regarding risks that take time to manifest or insufficient information regarding safety during long-term administration, it is preferable to continue the RMP. Based on these findings, it is better to decide whether to continue the RMP based on specific criteria, such as continuing the RMP if there are safety concerns that necessitate ongoing attention or terminating the RMP if there are no safety considerations. Among the conditions currently specified for lifting the RMP formulation and implementation as a condition for approval, there are "no new safety concerns" and "no significant changes in the manifestation of existing risks." However, there are no standards regarding potential risks that require continued attention, which would be beneficial to add to the rules. Additionally, although it is clearly stated that "information about missing information has been sufficiently collected," the reality is that RMPs were terminated even if the information was insufficiently collected, necessitating a reconsideration of whether the rules are being appropriately applied.

From a risk assessment and management perspective, periodic safety reports (7, 25, 26) are required during the reexamination period, with report documents being prepared in line with the contents of the RMPs. However, once the reexamination is completed, there ceases to be a regular opportunity for risk assessment, leaving this responsibility to individual companies. According to a previous survey, companies varied in their approach to changing the signal evaluation criteria post-reexamination and in their decision to continue the RMP as an internal document even after the requirement for an RMP as a condition for approval was lifted (9). Furthermore, when the RMPs were terminated, 62.3% of drugs had additional risk minimization activities listed in the RMP, many of which were related to the preparation and distribution of materials to patients and healthcare professionals. The same survey revealed differences among companies in their decision to cease additional risk minimization activities when the RMP was terminated, with three companies stopping and six continuing. There was a general consensus that it was challenging to determine whether to continue these activities, as the government had not provided clear guidance (9). Therefore, it would be beneficial for the government to provide guidelines to replace the RMP regarding risk management after the RMP is terminated. The same survey also highlighted the inconvenience of not being able to view risk minimization materials on the PMDA website after the RMP was removed from the approval conditions at the end of the reexamination period. From this perspective as well, guidance may be needed on effective ways to continue risk minimization activities even after the RMP has been terminated.

In the context of overseas RMPs, there is no mention of termination in the guidelines regarding the RMP of the EU (EU-RMP) (27, 28). The EU-RMP primarily focuses on safety concerns that require special attention and establishes individual pharmacovigilance activity or risk minimization activity for each safety concern. Safety concerns are removed from the EU-RMP if they are determined to be unnecessary (28, 29). As for risk evaluation and mitigation strategies (REMS) in the United States, it is not created for all drugs, but only when it is necessary to implement additional measures beyond the "Precautions for Use," and when it is not necessary, it will be excluded (30). What they have in common is that they focus only on safety concerns or drugs that require specific action. Conversely, the Japanese RMP (J-RMP) is different because its purpose is to consolidate risk management into one document and ensure that evaluations are surely performed (1). In the J-RMPs, all safety concerns are broadly described. This includes not only those that necessitate special attention but also those for which routine pharmacovigilance activities and risk minimization activities are required (31). However, post-reexamination, the RMP continues only for drugs that require special attention, leading to a discrepancy in the policies pre- and post-reexamination in Japan. The RMP is a dynamic document that undergoes periodic reviews. Actions such as adding important identified risks, reclassifying potential risks to identified risks, incorporating additional risk minimization activities, and deleting missing information are undertaken. Yet, the removal of potential risks or additional risk minimization activities often does not occur until reexamination (9, 32). While utilizing reexamination as an opportunity to review safety concerns is beneficial, a more proactive review of the RMP, such as removing potential risks or additional risk minimization activities before reexamination, is advisable. It would also be beneficial to establish certain rules, like monitoring potential risks and missing information that would take time to evaluate, by continuing the RMP even post-reexamination. Furthermore, despite many pharmaceutical products being sold overseas, regulatory requirements differ between Japan and other countries. This could potentially lead to confusion, given that there are many safety concerns described in the J-RMP but not in the EU-RMP. In the future, there will likely be an increase in cases where the J-RMP is terminated and the EU-RMP continues. Despite the trend of globalization, regulatory RMP requirements vary across jurisdictions worldwide (33, 34). However, aligning them to the same standards would help eliminate confusion. On the other hand, the REMS in the United States differs significantly from J-RMP or EU-RMP, making harmonization difficult and likely to remain an issue in the future.

Our study does have certain limitations. First, the J-RMP system is relatively new, and as a result, there are currently not many subjects available for investigation. In this study, we conducted our research based on the information available 10 years after the implementation of the RMP, but it is crucial to closely monitor future trends as the number of drugs that have an RMP and will undergo reexamination is expected to increase. Second, as there is a time lag until the completion of the reexamination is reflected on the PMDA website, there may be some drugs that are not included in the list of RMP-terminated products, even though the formulation and implementation of the RMP as a condition for approval have been lifted. However, this number is very small and is not considered to significantly impact the results of this study.

In conclusion, upon completion of the reexamination, it was demonstrated that the formulation and implementation of the RMP, as a condition for approval had been lifted for many drugs, with a few exceptions. As risk management becomes more thorough, the importance of safety concerns will change over time. Therefore, we support the termination of the RMP when the conditions are met, utilizing the existing reexamination system as an opportunity to evaluate RMP terminations. However, there may

TABLE 3 Detailed analysis of important potential risks for the 69 drugs with terminated risk management plans (RMPs).

	Total *N* (risks)	Not listed in package inserts (risks)	%	*p*-value
Important potential risks	164	24	14.6	
Malignant neoplasm	29	9	31.0	0.0165
Infectious disease	13	3	23.1	0.4083
Cerebral cardiovascular risks	10	3	30.0	0.1648
Antibody production	5	2	40.0	0.1557
Urinary system risks	7	2	28.6	0.2721
Medication error	6	2	33.3	0.2130
Disseminated intravascular coagulation	1	1	100.0	0.1463
Suicide-related events	6	1	16.7	1.0000

TABLE 4 Comprehensive details of important missing information for the 69 drugs with terminated risk management plans (RMPs).

	Total *N* (items)	Not included in the package insert (items)	%	*p*-value
Important missing information	92	16	17.4	
Impact on cardiovascular risk	7	7	100.0	< 0.0001
Safety when administered to patients with liver dysfunction	19	5	26.3	0.3083
Safety when administered to patients with cardiovascular disease	1	1	100.0	0.0284
Drug interactions	3	1	33.3	0.4402
Safety during long-term administration	5	1	20.0	1.0000
Safety during administration under actual use conditions	3	1	33.3	0.4402

TABLE 5 In-depth details of ongoing additional activities for the 69 drugs with terminated risk management plans (RMPs).

	Ongoing	Details	Number	%
Additional pharmacovigilance activities	2	Post-marketing clinical trials	1	50.0
		Special drug use-results survey (survey regarding long-term use)	1	50.0
Additional risk minimization activities	69	Creation and distribution of materials for patients	33	47.8
		Creation and distribution of materials for healthcare professionals	29	42.0
		Reporting the occurrence of side effects on company websites	3	4.3
		Measures to prevent administration errors	1	1.4
		Creation and provision of patient cards	1	1.4
		Ensuring distinguishability from existing formulations with different concentrations	1	1.4
		Safety measures for pain associated with chronic low back pain and osteoarthritis	1	1.4

be more RMPs that are better to continue with, and we propose clarifying the criteria for deciding whether to terminate RMPs and provide flexibility for continuing them. It would be beneficial to establish rules and take measures, such as continuing the RMP if there are safety concerns that require ongoing attention. As many pharmaceutical products are expected to undergo reexamination and have their RMPs terminated in the future, we believe that addressing the issues that will arise when the RMP is terminated will lead to recommendations for an appropriate J-RMP system. Better drug safety management is desired considering the unification of RMP rules with other countries.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study did not require institutional review board approval or patient informed consent because it was based on publicly available information and involved no patient records.

Authors contribution

NK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing–original draft, Writing–review and editing. AH: Data curation, Formal analysis, Writing–review and editing. HM: Conceptualization, Funding acquisition, Supervision, Writing–review and editing.

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Conflict of interest

NK is an employee of CMIC Holdings Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Evaluation of the review models and approval timelines of authorities participating in the East African Medicine Regulatory Harmonisation initiative: alignment and strategies for moving forward

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Introduction: Medicines regulatory harmonisation has been embraced by many national regulatory authorities (NRAs) to improve public health through faster availability of safe, high-quality, and effective medical products to patients and enhanced standardisation of technical guidelines and work sharing, leading to reduced cost to pharmaceutical companies. After ten years of implementing regulatory harmonisation by the East African Community Medicines Registration Harmonization (EAC-MRH) initiative, it is now imperative for participating NRAs to rely on each other to minimise duplication of use of limited resources. Major challenges in implementing reliance are the lack of clear registration processes and delays in the approval. The aim of this study was to compare review models, target timelines and data requirements used in assessing applications by EAC-MRH NRAs so as to align and propose strategies for improvement.

Methods: A validated questionnaire that standardises and captures review processes was completed by the head of the medicine's registration division in each of the seven EAC-MRH NRAs. A country report based on the completed questionnaire was developed for each NRA and validated by the heads of the respective authorities.

Results: Most applications received by all countries were for generics except Kenya, which received a significant number of new active substance applications (55 and 53 in 2020 and 2021). Mean approval times for generics using full review varied, with Tanzania's time declining for the three years. Target timelines for full review for the five countries ranged between 180 calendar days (Tanzania) to the

highest 330 days (Zanzibar). The three countries (Kenya, Rwanda and Uganda) utilising the verification review model had a target timeline of 90 days. All six authorities conducted abridged reviews and fast-track assessments through a priority review track. The common technical document format was mandatory for applications in all authorities. The target timeline for key milestones in the review process varied for each country with a few similarities.

Discussion: The study has provided a baseline for review models, target timelines and data requirements utilised in assessing applications for registration by EAC-MRH NRAs. Implementing the recommendations from this study will enable the NRAs to align and improve their registration processes.

KEYWORDS

East African Medicines Regulatory Harmonisation (EAC-MRH), joint assessment procedure, regulatory review models, regulatory reliance, African Medicines Agency (AMA)

1 Introduction

One of the key functions of national medicines regulatory authorities (NRAs) is the review of applications and registration of medical products submitted by pharmaceutical manufacturing companies. NRAs are expected to have effective and efficient regulatory systems to ensure that timely marketing authorisation is granted for safe, effective and good-quality medical products. One of the objectives of establishing the East African Community Medicines Registration Harmonization (EAC-MRH) project was to build the capacity of NRAs in the region through work sharing, training, and twinning. Currently there is a strong advocacy for reliance, especially as most of these authorities delay issuing marketing authorisation for medical products, leading to a significant backlog.

Over several years, the process of medicines regulatory harmonisation has been embraced by many NRAs to improve public health through faster availability of safe, high-quality, and effective medical products to patients. This has enhanced the harmonisation of technical guidelines and work sharing, leading to reduced costs to pharmaceutical companies as they prepare one single set of applications to submit to several countries. After ten years of implementing regulatory harmonisation by the EAC NRAs, it is now imperative for these NRAs to rely on each other so as to minimise duplication of their use of limited resources. One of the major challenges in implementing reliance; however, is the lack of clear registration processes in the NRAs and the delay in the approval of medical products.

1.1 Reliance

With the complexities that come with the granting of marketing authorisation for medical products, most regulatory authorities are now embracing the concept of reliance as a way of improving performance. It is now clear that no one authority can do it all, especially with new advanced health technologies and emerging diseases plaguing the world. The main objectives of harmonisation initiatives are to build trust amongst NRAs so that they can rely on each other's decisions. According to the World Health Organisation (WHO) guidelines on good reliance practices, NRAs are encouraged to implement reliance to minimise duplication of effort especially given their limited resources. Countries with weak regulatory systems are called upon to rely on WHO-listed authorities (WLAs). According to the (1) R&D Briefing 93, in the past five years there has been an increase in the use of facilitated regulatory pathways for approval of new medicines, even by well-resourced NRAs but regulatory reliance and work sharing will especially help low- and middle-income countries to have access to innovative medicines in a timely manner (2).

1.2 Registering medical products in low-to-middle income countries

The main function of NRAs is to register medical products in their countries. This is also known as granting marketing authorisation or product licensing (3). Countries have different regulatory requirements for the registration of pharmaceutical products. Understanding the review models and approval timelines for the East African Community as an emerging market for pharmaceutical companies is critical (4) in fast tracking the registration process to provide the much-needed medical products to patients in a timely manner. There has been a general indication that for applicants interested in these markets, NRAs should ensure that the application procedures are clear, that communication and transparency is enhanced, with timelines for approval of products clearly outlined, and with registration guidelines for countries in the same region being harmonised and registration processes being effective and efficient (5, 6).

However, reviewers have also raised the challenge that long review timelines experienced in the registration of medical products are sometimes caused by the delay in manufacturers' or applicants' response to queries. It is therefore important to understand that regulatory authority requirements for review

models should inform the industry and other stakeholders what to expect from the authorities.

The first paper of this series focused on comparing the key milestones in the review process using a general model with a process map and milestones. It also examined how these authorities build quality into the review by analysing their good review practices and how quality is built into the decision-making practices of the EAC NRAs and whether there are measures in place to guide good decisions.

The aim of this paper, which is the second of this series is to compare the review models, target timelines and data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative so as to align and propose strategies for improvement.

2 Materials and methods

2.1 Study participants

The study participants included Senior Programme Officers from the Medicines registration divisions in the seven NRAs; Pharmacy and Poisons Board-PPB, Kenya; National Drug Authority-NDA, Uganda; The Tanzania Medical Devices Authority (TMDA); Zanzibar Food and Drugs Authority (ZFDA) Tanzania; Drug and Food Control Authority DFCA South Sudan; Burundi Food and Medicines Regulatory Authority (ABREMA) and Rwanda Food and Drugs Authority.

According to rules of the Ethics Committee of the University of Hertfordshire, as the study participants were not patients or healthcare professionals working in healthcare facilities, the researcher was permitted to use informed implied consent; that is, by agreeing to participate in the study and complete the questionnaire, the participants had implicitly provided their consent.

2.2 Data collection

A validated questionnaire (Optimising Efficiencies in Regulatory Authorities: OpERA) describing the organisation structures, regulatory review systems for market authorisation of new active substances (NASs) and generics, including their overall timelines from the date of submission of the application to when it is approved, good review practices (GrevP) and quality decision-making practices, was completed by each of the authorities in 2022 and 2023. The questionnaire is composed of six different parts: Part 1 documents the organisation of the authority with the focus on its structure and resources; Part 2 covers the types of review models used by the authority for the scientific assessment of medicines; Part 3 is based on key milestones in the review process with the focus on the process map and milestones; Part 4 relates to good review practices (GrevP) and how an authority builds quality into their regulatory processes; Part 5 focuses on the quality of the decision-making processes based on whether the authority have good measures in place to guide decision making; and Part 6 describes the challenges and opportunities available to the national regulatory authorities.

2.3 Models of regulatory review

A risk-based approach to review involves different review models that describe the ways in which authorities assess the scientific data received from applicants during the assessment process. This can vary depending on whether the data are assessed in detail by the authority, or the authority relies on results of the assessment conducted elsewhere. The decision to choose a type of review model will also depend on the type of product and its status with other authorities.

The different steps in the review process do have a significant effect on the review timelines and subsequent market authorisation. There are three types of review models that NRAs can use:

The verification review (type 1) is used to minimise duplication by allowing a product that has been registered in a recognised authority to be marketed in the receiving country. The main responsibility of the receiving country is to verify that the product has indeed been registered elsewhere and is exactly the same product.

The abridged review (type 2) model also minimises the use of resources by not reviewing scientific data that have been assessed elsewhere but focusing on reviewing the product based on its local conditions, which could be climate, infrastructure for distribution, benefit-risk assessment, and medical practice culture.

The full review (type 3) is employed when the authority assesses the complete application including all the scientific data. This is carried out with applications that have not been reviewed elsewhere and requires more human resources and an improved infrastructure.

3 Results

For the purpose of clarity, the results of this study will be presented in three parts: Part 1: Metrics of applications received and registered; Part 2: Review models, extent of scientific assessment and data requirements and Part 3: Targets of key milestones in the review process.

3.1 Part 1: Metrics on NASs, generics, and WHO prequalified generics

All seven countries completed the OpERA Questionnaire. However, South Sudan did not report any data since they had not received any applications for the specified study period. Kenya received 55 applications for NASs in 2020 and approved 18 and received 53 applications in 2021 out of which 47 were approved. In 2022 Rwanda received 409 applications for NASs and approved 160 and in 2023 received 398 applications and approved 60 (Table 1).

All the six NRAs received applications for generics, with Tanzania approving the highest number of applications (499) for 2020 and (503) 2021. It is interesting to note that the number of generics approved by Tanzania dropped in 2022 to 359. Kenya received more applications (692) in the same year (2020), but only granted marketing authorisation for 81 products. Burundi in 2020 received 157 applications and approved 110 but in 2023 approved 57 with 342 applications received. In 2021, Kenya received 909

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TABLE 1 Comparison of metrics for NASs, generics, and WHO-prequalified generics (2020–2023).

Country	Burundi				Kenya				Rwanda				Tanzania				Uganda				Zanzibar			
Year	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
NASs																								
Received	0	0	0	0	55	53	N/S	N/S	0	0	409	398	0	0	0	0	NS	NS	0	0	0	0	0	0
Approved	0	0	0	0	18	47	N/S	N/S	0	0	160	60	0	0	0	0	NS	NS	0	0	0	0	0	0
Generics																								
Received	157	68	80	342	692	909	N/S	N/S	533	615	390	379	631	975	1,079	764	508	849	804	905	8	10	14	22
Approved	110	0	36	57	81	368	N/S	N/S	46	55	147	51	499	383	359	51	389	405	430	571	1	2	0	0
WHO pre-qualification																								
Received	0	2	0	1	10	35	N/S	N/S	16	18	7	3	7	22	16	14	10	12	7	6	1	0	0	0
Approved	0	0	4	1	10	20	N/S	N/S	0	11	7	0	7	14	13	12	10	12	7	3	1	0	0	0

NASs, new active substances; WHO, World Health Organization; N/S, not specified.

applications and only approved 368 while Uganda received 849 and approved 405. Burundi on the other hand did not approve any product in 2021 even though they received 68 applications. Uganda received the highest number (849) of applications in the region in 2021 and was able to register 405 generic products during the year. Tanzania in 2021 received 704 applications and registered 503 while Zanzibar received 10 applications in the same year but only approved two in 2022 (Figure 1).

Kenya and Rwanda saw a slight increase in WHO pre-qualified generics approved in 2021 while Burundi and Zanzibar did not receive WHO pre-qualified applications. Tanzania in 2021 received 15 WHO pre-qualified applications and approved 13. For Uganda there has been a decline in the number of WHO pre-qualified applications from 2021 to 2023 (Table 1).

3.2 Mean approval times

While Kenya received a number of applications for NASs, they approved 18 applications in 2020 and 47 applications in 2021 (Table 1), but they did not indicate the mean approval times for a full review of NAS applications (Table 2). Tanzania saw a decline in the mean approval times for the full review of generics in three consecutive years (202 days in 2020, 93 days in 2021 and 61 days in 2022). Rwanda took 1,035 days for the full review of generics in 2022, which declined to 735 days in 2023, while full review of generics in Kenya increased from 575 days in 2020 to 739 days in 2021. The mean approval timelines for generics in Uganda saw a slight decrease in 2022 (238 days) from 261 days in 2021; however, there was an increase in 2023 to 284 days (Figure 2).

For WHO pre-qualified applications, Rwanda (484 days) and Kenya (341 days) took a longer mean approval times using full review while the other countries took less than 100 days for the approval of generics (Table 2).

Using verification review, authorities in Burundi and Zanzibar took an average of 90 days in 2022 to review WHO pre-qualification applications. Zanzibar also reported taking a mean approval time of 78 days to review EAC-MRH-recommended applications. From 2020 to 2023, Uganda reported mean approval times of less than 65 days for generics and WHO pre-qualified products. Kenya and Rwanda did not report the mean approval times for verification review type for NASs, Generics and WHO pre-qualified applications (Table 2).

For the abridged review type, Zanzibar spent 180 days in 2020 as mean approval times for generics. Burundi took 90 days in 2022 for WHO pre-qualification while Tanzania took 14 days in 2021 and 13 days in 2022. In 2021, Rwanda took 484 days for approval of WHO pre-qualification application. Kenya and Rwanda did not submit information on mean approval times when using the abridged review and verification types (Table 2).

3.3 Part II: Review models used for scientific assessment

All of the six authorities carry out full and abridged reviews for scientific assessment.

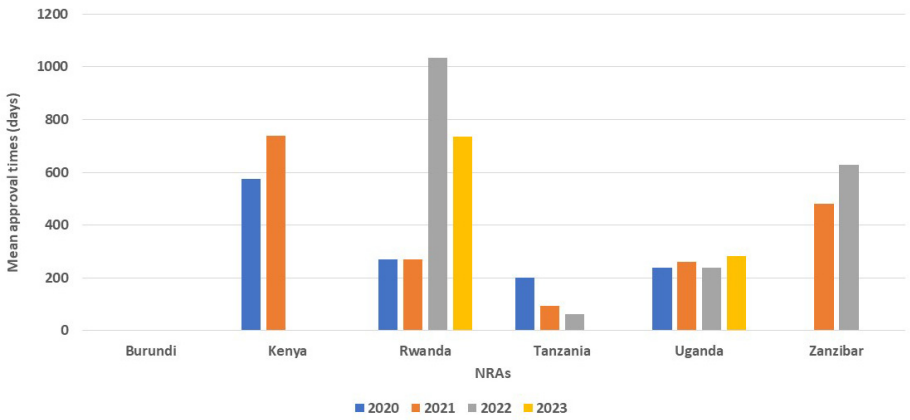

FIGURE 1
Comparison of number of generics approved from 2020 to 2023.

3.3.1 Verification review (type 1)

Burundi, Tanzania and Zanzibar do not conduct verification reviews for generics. However, Burundi and Zanzibar do use verification review for WHO-prequalified and EAC-MRH-recommended applications. The reason for not implementing type 1 assessment by TMDA is that they do not employ mutual recognition policies yet. The authority offers special import permits based on its regulations. Kenya and Rwanda conduct verification reviews for selected applications like WHO pre-qualified and WLA-approved products, and authorities who have valid agreements to share reports. For Uganda, verification reviews are used for WHO collaborative registration procedures (CRP) and EAC-recommended products (Table 3).

Reference authorities used by the NRAs include WHO-prequalification programme authorities, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) founding members and WLAs such as Swissmedic, European Medicines agency (EMA), United States Food and Drug Authority (US FDA), South Korea, Singapore and EU Medicines Network. In addition to WLAs listed above, East African Community work sharing Initiative (EAC-MRH), Intergovernmental Authority on Development (IGAD), TMDA and Ghana FDA were also reference authorities for PPB. All three countries had a 90-day target time for the verification review.

3.3.2 Abridged review (type 2)

All six authorities conducted abridged reviews. Type 2 assessment is used by Burundi-ABREMA for selected applications such as products that have been registered by WHO, WLAs, PPB, NDA, TMDA and EAC-recommended products. While Kenya, Rwanda, Tanzania, and Zanzibar use abridged reviews for selected applications that were previously approved by WHO-prequalified and WLA-approved products. For Tanzania, these selected applications must be approved in at least two reference countries, and not rejected in any other reference country. Uganda utilises the abridged review pathway for over-the-counter (OTC) products. Products category reviewed by Zanzibar are NAS, major line extensions, generics and biosimilars. Kenya and Uganda have a target time of 105 calendar days, Rwanda 90 calendar days, and Tanzania 126 days (Table 3).

3.3.3 Full review (type 3)

All six authorities conduct type 3 assessment for all applications that do not qualify for type 1 or type 2 data assessments. Only Kenya and Tanzania conduct Type 3B [a full, independent review of pre-clinical (safety) and clinical (efficacy) is carried out] for all major applications. The other authorities conduct type 3A in which data on quality, pre-clinical (safety) and clinical (efficacy) are assessed in detail but there are requirements for pre-registration elsewhere before the authorisation can be finalised (Table 3).

Only Burundi did not have a target time for full review of applications. Tanzania had the lowest target time for full review of 180 calendar days, followed by Uganda, 261 days, Kenya, 262 days, Rwanda, 270 days, and Zanzibar, 365 days (Table 3). Table 6 provides additional data for these targets with respect to major milestones.

3.3.4 Fast-track/priority review

All six authorities conduct fast-track assessments through a priority review system. Only Tanzania and Zanzibar indicated a target timeline of 90 and 126 calendar days, respectively, for review of fast-tracked applications in 2022 (Table 3). The authorities conduct a rapid assessment of the application to obtain pharmacological, marketing/commercialisation, pharmacovigilance, and additional clinical trials information. Applicants were charged a higher fee for priority review that achieve a shorter timeline.

3.3.5 Data requirements

In all six authorities a Certificate of a Pharmaceutical Product (CPP) is required to be submitted with an application or before authorisation is issued. A common technical document (CTD) format is mandatory for applications in all authorities and all review types, require submission of full data for Modules 1–5 and summary data for modules 2.3, 2.4 and 2.5 (Table 4).

The authorities then conduct a detailed assessment, and prepare an evaluation report. Factors considered in assessing product risks and benefits include differences in medical culture/practice, ethnic factors, and national disease patterns. The authorities also endeavour to obtain internal assessment reports from other authorities such as the referenced authorities,

TABLE 2 Comparison of mean approval times NASs, generics and WHO prequalified generics 2020–2023 (calendar days).

Country	Burundi				Kenya				Rwanda				Tanzania				Uganda				Zanzibar			
Year	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023	2020	2021	2022	2023
Full review																								
NASs	N/A	N/A	N/A	N/A	N/V	N/V	N/V	N/V	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0	N/A	N/A	0	0	0	
Generics	N/A	N/A	N/A	N/A	575	739	N/V	N/V	270	270	1,035	735	202	93	61	85	237	261	238	284	0	480	630	
WHO Pre-qualification	N/A	N/A	90	90	N/A	341	N/V	N/V	90	90	484	90	83	N/A	N/A	79	54	60	56	65	0	0	0	
Verification																								
NASs	N/A	N/A	N/A	N/A	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Generics	N/A	N/A	N/A	N/A	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/A	N/A	N/A	N/A	N/V	N/V	54	43	0	0	78	0
WHO Pre-qualification	N/A	N/A	90	90	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/A	N/A	N/A	N/A	54	60	56	65	90	90	90	
Abridged																								
NASs	N/A	N/A	N/A	N/A	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	0	0	
Generics	N/A	N/A	N/A	N/A	N/V	N/V	N/V	N/V	N/V	N/V	N/V	N/V	241	153	93	N/A	N/V	N/V	N/V	N/V	180	0	0	
WHO Pre-qualification	N/A	N/A	90	90	N/V	N/V	N/V	N/V	N/V	N/V	484	90	N/A	14	13	N/A	N/V	N/V	N/V	N/V	0	0	0	

N/A, not applicable; N/V, not available.

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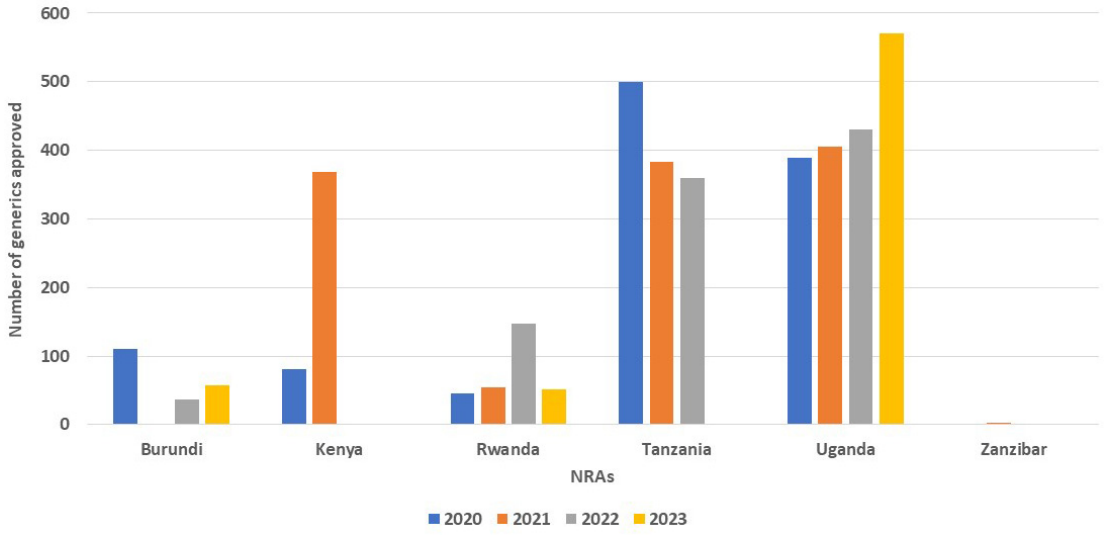

FIGURE 2
Comparison of mean approval times for generics using full review from 2020 to 2023.

TABLE 3 Review models employed and target timelines (calendar days—2022–2023).

Type of review model	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Verifications review (type 1)	x	✓c	✓c	x	✓a	x
Target	N/A	90	90	N/A	90	N/A
Abridged review (type 2)	✓b	✓c	✓c	✓c	✓e	✓c
Target	N/A	105	90	126	105	126
Full review (type 3)	✓3A	✓3B	✓3A	✓3B	✓3A	✓3A
Target	N/A	262	270	180	261	365
Fast track/priority review	✓	✓	✓	✓	✓	✓
Target	N/A	N/A	N/A	90	N/A	126

a: For World Health Organization (WHO) collaborative registration procedure (CRP) and East African Community (EAC)-recommended products. b: For WHO CRP, WHO-listed authority (WLA)-approved and EAC-recommended products. c: For WHO-prequalified and WLA-approved products. e: For OTC products.

public assessment reports available through the internet such as the European Public Assessment Reports (EPARs) or through participation in the WHO collaborative registration procedure where access is given to reports of prequalified products. All six authorities also have access to reports assessed through the EAC-MRH initiative, as part of participation in the EAC-MRH programme. A primary scientific review is conducted by the authority staff, although Tanzania also includes external reviewers.

Apart from Kenya and Zanzibar, the other four authorities set targets for review times spent on the scientific assessments. Only Uganda does not have a recording procedure that allows the company response time to be measured. All the authorities recognise medical urgencies and thus implement priority reviews for qualifying products. Only Tanzania conducts sequential processing of technical data. For all six authorities, physicians comprise less than 25% of the authority medical review staff. All the authorities have an approval times target for the overall time for the review and approval of an application (Table 5).

3.4 Part III: Targets for key milestones in the review process

In line with good review practices, each regulatory authority should set a target timeline for each milestone and the overall process. In the first article of this series, the review process, and key milestones for the six authorities were reported. This article reviews the target timelines for these key milestones. A standardised process map for review and approval of medical products demonstrates key milestones that are usually recorded and monitored by mature regulatory authorities in the review of applications.

3.4.1 Receipt and validation

Uganda had no target time for receipt and validation of applications. Kenya has the shortest target time of 3 days, followed by Tanzania with 5 calendar days, and Rwanda with 30 days. Both Burundi and Zanzibar have 90 calendar days as their target (Table 6).

TABLE 4 Summary comparison of key features of the regulatory systems for medicines.

Marketing authorisations	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Certificate of Pharmaceutical Product (CPP) is required with the application or before authorisation is issued	✓	✓	✓	✓	✓	✓
Common technical document (CTD) format is mandatory for applications	✓	✓	✓	✓	✓	✓
Medical staff: More than 25% within the authority review staff are physicians	x	x	x	x	x	x
Review times: The authority sets targets for the time it spends on the scientific assessment of NASs and generic applications	✓	x	✓	✓	✓	x
Approval times: The has a target for the overall time for the review and approval of an application	✓	✓	✓	✓	x	✓
Questions to sponsors are batched at fixed points in the review procedure	✓	✓	✓	✓	✓	✓
Company response time: Recording procedures allow the company response time to be measured and differentiated in the overall processing time	✓	✓	✓	✓	x	✓
Priority reviews: The authority recognises medical urgency as a criterion for accelerating the review and approval process for qualifying products	✓	✓	✓	✓	✓	✓
Sequential processing: Different sections of technical data reviewed sequentially rather than in parallel	x	x	x	✓	x	x
Price negotiation: Discussion of pricing is separate from the technical review and does not delay the approval of products	x	✓	x	x	✓	✓
Sample analysis: The focus is on checking quality in the marketplace and requirements for analytical work do not delay the marketing authorization	✓	x	x	✓	✓	✓

TABLE 5 Extent of scientific assessment for full review.

	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Chemistry, manufacturing and control (CMC) data extensive assessment				✓		✓
Non-clinical data extensive assessment	✓	✓	✓	✓	✓	✓
Clinical data extensive assessment	✓	✓	✓	✓	✓	✓
Bioequivalence data extensive assessment				✓		
Additional information obtained (where appropriate)	✓	✓	✓	✓	✓	✓
Other agencies internal review reports	✓	✓	✓	✓	✓	✓
Medical and scientific literature	✓			✓		

TABLE 6 Comparison of targets for key milestones in the full (type 3) review process -(calendar days).

Target	Burundi	Kenya	Rwanda	Tanzania	Uganda	Zanzibar
Receipt and validation (A–B)	90	3	30	5	No target time	90
Queuing (B–C)	60–180	< 365	60–150	35	365	60–180
Primary scientific Assessment (C–D)	90	No target time	No target time	100	180	180
Questions to applicant (Clock stop) (D–E)	90	180	90	180	180	180
Review by Expert Committee (G–H)	90	No target time	60	1	30	1
Approval procedure (Admin)	30–90	< 30	< 30	< 30	30–90	< 30
Overall approval time (A–I)	90	730	365	180 (exc. Applicant time)	547	365

A for biosimilar products not approved by a reference authority only.

3.4.2 Queue time

Queue time is that time taken to start the scientific assessment after the application has been validated or accepted for review. Uganda and Kenya have the longest queue time of 365 days, followed by Burundi, Rwanda and Zanzibar with queue times ranging from 60 to 180 calendar days. Tanzania had the shortest queueing time of 35 calendar days (Table 6).

3.4.3 Primary scientific assessment

Burundi had the shortest target for primary scientific assessment of 90 calendar days followed by Tanzania with 100 days, including peer review. Uganda and Zanzibar have primary scientific assessment target times of 180 days. Kenya and Rwanda did not have target times (Table 6)

3.4.4 Questions to applicants

Here the clock stops as the assessment is paused and time given to the sponsor to respond to any queries. The target for clock stops is 90 days for Burundi and Rwanda, and 180 days for Kenya, Tanzania, Uganda, and Zanzibar (Table 6).

3.4.5 Review by expert committee

Four of the authorities use expert committees to make decisions on approval or refusal of marketing authorisation of medical products. Zanzibar does not use expert committees; Tanzania takes one day to make the expert committee decision while Uganda takes 30 days followed by Burundi with 90 days. Kenya does not have a target time (Table 6).

3.4.6 Authorisation procedure

This is the time it takes to issue the overall approval after the scientific opinion has been made. Four of the authorities (Kenya, Rwanda, Tanzania, and Zanzibar) take less than 30 days. Uganda takes 30 to 90 days; however, the sponsor is informed of a positive scientific opinion before the authorisation is issued, whereas Burundi does not give a target (Table 6).

4 Discussion

The aim of this study was to compare the review models, target and review timelines as well as data requirements utilised in assessing applications for registration by countries participating in the EAC-MRH initiative to align and propose strategies for improvement. Countries with higher populations received higher numbers of applications and are also autonomous authorities. Ozawa et al. (7) demonstrate how improving the autonomy of health facilities improves access to essential medicines.

It is interesting to note that only one country in the region received applications for NASs in 2020 and 2021. This is not surprising, as several studies have highlighted that that the number of NASs launched in low- and middle-income countries are very few as compared to high-income countries (5, 8). Most innovative medicines or new medicines are usually first approved by well-resourced regulatory authorities (3). The study by Centre for Innovation in Regulatory Science [CIRS] (1) reported how six major regulatory authorities (Europe, USA, Japan, Canada, Switzerland and Australia) have used facilitated regulatory pathways and internationalisation for approvals of new medicines. It is hoped that many new and complex molecule applications will be submitted through the operationalisation of the African Medicines Authority (AMA).

It would be important to understand the reason for a decline in the number of applications received and approved by Burundi in 2021 as compared to 2020 and the decrease in mean approval times for generics in Tanzania from 202 days in 2020 to 61 days in 2022.

All six authorities in the region are implementing reliance, as the majority employ the verification and abridged review models (9, 10). It is important to note that countries in this region are already relying on each other, which is the major success of the EAC work-sharing initiative. To enhance collaboration, it will be critical for these countries to have mutual recognition or cooperation agreements especially for Tanzania, which is unable to implement the verification review due to the absence of mutual recognition agreements. It is also going to be beneficial for inter-regional economic community (REC) reliance to be instituted for the REC-MRH initiatives so that the different regions can also rely on the decisions of each other. This study provided a clear understanding of the review processes and regulatory requirements for registration of medical products in the authorities in East Africa. This will act as a baseline for future studies especially when there will be need to evaluate progress and identify any improvements as the AMA becomes operationalised. Other authorities have also been given the opportunity to better understand these review processes and can learn from each other as they share experiences.

4.1 Recommendations

As a result of this study, the following recommendation should be considered by the six authorities taking part.

1. EAC-MRH as a reference authority: All authorities participating in the EAC-MRH initiative should consider formally recognising EAC-MRH as a reference authority for a reliance pathway.
2. Timelines and targets: Authorities should consider documenting all key milestones and relevant timelines in order to monitor and measure their regulatory performance.
3. Information system: NRAs should develop information systems that can track registration timelines from the date the application is received to the date the registration is granted.
4. Mutual recognition: Develop and implement mutual recognition agreements to enhance reliance practices amongst NRAs in the region as well as inter-REC reliance.
5. Communication to applicants: All authorities should communicate their regulatory requirements to applicants on their website in order to facilitate a seamless review process as well as improve timelines.

6. Capacity building: Authorities should consider the following:

- Exchange of staff between authorities
- Secondments
- In-house education and training and continuous professional development

4.2 Study limitations

This study focuses on East Africa region and the respective national regulatory authorities; while it provides detailed insights into the EAC-MRH initiative, the findings may not be generalisable to other regions or global regulatory practices.

In addition, South Sudan did not report any data since they had not received any applications for the specified study period. Furthermore, Kenya and Rwanda did not record information on mean approval times for different review models.

Whilst this study provides a broad overview of the quantitative data obtained from the questionnaire, it lacks in-depth qualitative insight from the stakeholders that would have added more context to the findings.

Given the extent of the quantitative data collected by the Questionnaire, it would have been desirable to also collect qualitative data through interviews and focus groups involving regulatory officials, pharmaceutical companies, and healthcare professionals in order to provide richer context for the quantitative findings.

Although the limitations of the study have the potential of introducing biases to the findings, this is believed to be minimal since the design of the study was "hypothesis generating" as opposed to "hypothesis testing." This means that factual aspects of the findings were reported without extensive extrapolation of the results.

5 Conclusion

This study serves as the first comparative evaluation of review models for the NRAs of the EAC countries. It has provided a baseline for review models, and target and review timelines as well as data requirements utilised in assessing applications of medical products for registration by countries participating in the EAC-MRH initiative. It is important for NRAs to have open-minded discussions, document best practices and share experiences so as to learn from each other or from reference authorities. Reliance mechanisms should be developed and implemented by the countries in the region. Implementing the recommendations from this study will enable the NRAs to align and improve their registration processes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

NN: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. MN-S: Writing – review & editing. RH: Data curation, Writing – review & editing. FS: Data curation, Writing – review & editing. CI: Data curation, Writing – review & editing. JO: Data curation, Writing – review & editing. FA: Data curation, Writing – review & editing. AO: Data curation, Writing – review & editing. SA: Data curation, Writing – review & editing. SW: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. SS: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

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WHO-listed authorities (WLA) framework: transparent evidence-based approach for promoting regulatory reliance towards increased access to quality-assured medical products

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Background: Increased global access to safe, effective and quality-assured medical products remains a primary goal for the full realization of the World Health Assembly Resolution WHA 67.20 on regulatory systems strengthening for medical products as well as target 3.8 of the Sustainable Development Goals (SDG). To promote the development of efficient regulatory systems, the WHO introduced the Global Benchmarking Tool (GBT) in 2016, upon which the WHO–Listed Authority (WLA) framework was later established. This study aimed to appraise the development of the WLA framework across various phases while highlighting its achievements, challenges, and areas for improvement.

Methods: An exploratory study design using a qualitative approach was used to gather information from relevant documents as well as views and experiences from purposefully selected participants from diverse backgrounds. Data was collected using a combination of desk reviews and In-depth one-to-one or small group interviews employing semi-structured interview guides with open-ended questions. Data was analysed using an inductive thematic analysis approach.

Results: The leading role of the WHO was noted in developing and implementing essential documents and mediating consultative processes among stakeholders. The framework was revealed to bring an evidence-based, inclusive, and transparent approach to recognizing regulatory authorities (RAs) operating at the highest standards of performance. The framework was anticipated to promote regulatory reliance among all RAs, the WHO's prequalification programme, and procurement agencies. Furthermore, remarkable progress towards WLA listing was noted among transitional WLAs including the Stringent Regulatory Authorities (SRAs). Challenges related to the availability of resources, resistance to change, and complexity were associated with the framework.

Conclusion: The study provides a well-rounded view with regard to the roles of the WHO, Member States and other stakeholders in establishing and operationalizing the WLA framework. Furthermore, evaluating the performance

and possible WLA designation of RAs operating at international regulatory standards underscores its high relevance in contributing to public health globally. Maintenance along with timely addressing of highlighted next steps to improve the framework particularly in creating better understanding, more communication, and coordination are highly encouraged.

KEYWORDS

WHO listed authority, WLA, medicines regulation, stringent regulatory authorities, global benchmarking tool, reliance, regulatory systems strengthening, national regulatory authority

1 Introduction

Regulatory Authorities (RAs) are increasingly challenged by the need to adapt to emerging technologies that bring forth innovative products for which very limited regulatory expertise exists (1, 2). Moreover, the rising trends of Substandard and Falsified (SF) medical products pose an imminent threat to global public health security (3).

Suboptimal and inadequately harmonized regulatory systems substantially limit the effective sharing of regulatory information, transparent approaches, and reliance on regulatory decision-making. In that, the European Union (EU), among other regions, has exemplified a successful transformation of originally divergent national regulatory systems into a well harmonized regional regulatory network which has promoted the establishment of similar undertakings in other regions. In the absence of harmonized and coordinated regulatory efforts, RAs are forced to rely on their limited capacities to discharge a broad array of regulatory functions (4–6). Further, the impacts of globalization and the expansion of global trade necessitate collective interventions to promote the advancement of regulatory systems. Such challenges, among others, have substantiated the efforts by the World Health Organization (WHO) and other stakeholders in devising more effective approaches to build regulatory capacity, harmonization, and collaboration in different forms (7–9).

The establishment of the WHO Global Benchmarking Tool (WHO-GBT) in 2016 marked a significant milestone in the WHO's efforts to advance transparency and capacity building in regulatory practices (8, 10–12). The step came as a means of implementing the recommendations of the World Health Assembly (WHA) Resolution 67.2 in 2014. Through the GBT, WHO has managed to use independent experts in generating evidence and evaluating the RAs' overarching regulatory framework and eight key regulatory functions (10–12). Further, the GBT has introduced the concept of categorizing RAs into Maturity Levels (MLs) as adopted from ISO 9004 (11, 12).

Since its introduction, the GBT has demonstrated extensive benefits in terms of providing a structured approach for evaluating regulatory systems, promoting Good Regulatory Practices (GRPs) principles, and enablers, as well as regulatory collaboration and reliance (13). Additionally, the tool has enabled RAs to identify their strengths and weaknesses, formulate Institutional Development Plans (IDPs), and implement suggested improvements (10, 11, 14).

Over time, with the increased use of the GBT, the achievement of Maturity Level 3 (ML3) was recognized as an essential target for a regulatory authority to be considered as applying an acceptable level of regulatory oversight (WHA 67.20). ML3 refers to the third out of four Maturity Levels on the WHO-GBT which indicates that the respective RA has a stable, well-functioning and integrated regulatory system. While working with Member States towards this objective, and to leverage the capacity of already advanced authorities to increase access to quality-assured medicines and vaccines, as well as to guide procurement decisions, WHO together with the Global Fund adopted the concept of Stringent Regulatory Authority (SRA) (11). As per the current definition, SRAs are either members and observers of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) or are RAs with legally binding agreements on mutual recognition with ICH members as before the 23rd of October 2015 (15, 16).

SRAs are stated to possess adequate regulatory resources, robust and transparent procedures, and high levels of industrialization to enable optimal discharging of all regulatory functions (Mace 2021). Since their inception, SRAs have played a big role in guiding regulatory reliance by the WHO Prequalification (PQ) programme and RAs from across many countries and regions. Moreover, procurement bodies at national, regional and international levels have been guided by Marketing Authorization (MA) granted by SRAs in procuring medical products (11, 15).

Despite notable achievements, the SRA concept faces criticism in aspects of not admitting additional members, implying the lack of harmonized stringency among other RAs, and having a skewed distribution of SRAs to the industrialized global north. Furthermore, the generalized SRA designation of all regulatory functions and product categories, the absence of a comprehensive and transparent evaluation process, and the lack of a mandate to assess regulatory capacity by the ICH are perceived to affect the credibility of the SRA concept (11, 15).

Building upon the strong foundation of the GBT, designating RAs as WHO Listed Authorities (WLA) was prompted by the requests of Member States and as it was discussed during the 17th International Conference of Drug Regulatory Authorities (ICDRA) in 2016 in South Africa. The request was further endorsed by WHO's Expert Committee on Specifications for Pharmaceutical Products (ECSPP) (11, 17, 18). Following these events, transitional arrangements were necessary before embarking on the full operationalization of the WLA framework. Such

arrangements included replacing the WHO interim list of NRAs with the transitional WLA (tWLA) list which was assigned the validity of five years starting from the publication date of the Interim WLA operational guidance. Briefly, the tWLAs comprise of RAs operating at ML3 or ML4, SRAs, NRAs of regional reference in the region of the Americas, as well as Functional or Highly performing NRAs for vaccines. These arrangements aimed at i) recognizing achievements and work of all RAs in the interim list, ii) protecting the global supply chain of quality-assured medical products, iii) offering a clear and transparent path for RAs on the list to becoming WLAs, and iv) ensuring that the processes are feasible and efficient (14, 18).

A WLA is formally defined as "A regulatory authority (RA) or a regional regulatory system (RRS) which has been documented to comply with all the relevant indicators and requirements specified by WHO for the requested scope of listing based on an established benchmarking and performance evaluation process" (13, 16, 18, 19). The framework is purposed to provide a transparent process for global recognition for RAs and RRSs operating in conformity to internationally recognized standards, guidelines, and GRPs (11, 14, 16, 20). The introduction of such values was aimed at building trust among RAs, improving regulatory systems, expanding the pool of reliable RAs, and ultimately promoting access to safe, effective and quality-assured medical products (11, 13, 16). This study focused at appraising the development of the WLA framework across various phases while highlighting its achievements, challenges, and areas for improvement.

2 Methodology

We employed an exploratory qualitative study design to investigate various aspects of the WLA framework by reviewing selected documents and interviewing key participants from across the WHO, WLAs, transitional WLAs, donors, pharmaceutical industries and international procurement agencies. A total of 17 documents including peer-reviewed articles from recognized scientific journals, policies, concept notes, manuals, operational guides, technical reports, and assessment tools were appraised through desk reviews (Supplementary material).

Purposeful sampling was used to obtain 14 organizations from different categories established to be important players across different phases of conceiving, developing and operationalizing the WLA framework (Table 1). Following the same sampling technique, a total of 27 participants were selected including at least one participant from each organization. Selection of the individual participants was made by either the WHO or their respective organizations based on their involvement with the WLA framework, experience, and nature of their roles.

A combination of one-to-one and small-group in-depth interviews was carried out (between September 2023 and April 2024) based on the available number of participants from the respective organization. We used a semi-structured interview guide with open-ended questions to gather the views and experiences of the study participants regarding the historical background, objectives, benefits, challenges, and suggestions regarding the WLA framework, among other aspects (Supplementary material). A unique interview guide was used for each of the six categories of participants' organization (Table 1). The interview guides were tested for their suitability via a combination of peer debriefing and pilot testing involving the first two participants from each category. Subsequent alterations to the tools were undertaken to enhance the clarity, flexibility, and adequacy of allocated time.

The same interviewer conducted all interviews through video calls on an online platform (Zoom Video Communications, California, US). Interviews were conducted in English language and lasted for 45 – 60 minutes. We established the saturation of obtained information upon observing the recurrence of similar themes from participants among each target group. Upon reaching this point, no further participants were recruited.

Inductive thematic analysis was employed to evaluate the obtained data as per the guidance provided by Braun and Clarke (21). The approach was selected due to having an extensive dataset, a shortage of literature on the subject matter, and the intention to ensure greater flexibility in identifying, analysing, and reporting the available themes and patterns (9, 21, 22). Following the transcription process, we performed further analyses of the data and generated the respective narratives as per the procedures outlined in our previous work (9). The selection of individual highlighted quotes from the participants was based on the virtue of providing the best representation of the respective theme, offering unique insights, special emphasis, diversity of perspectives, as well as effective communication of the points.

Each study participant was provided with detailed informed consent and voluntarily took part in the study. To avoid bias and ensure confidentiality, the organizations' and participants' identities were concealed during the first transcription and replaced by codified identifications.

3 Results

3.1 Role of the WHO towards operationalization of the WLA framework

The role of the WHO through its different units and teams was recognized across the major areas of providing leadership as well as coordinating collaborative efforts and communication. The study has found crucial roles of the WHO in the development and implementation of policies, guidance documents, and the Performance Evaluation (PE) framework (Table 2). The WHO was also acknowledged in the initiation and overseeing of consultative processes through engaging with the public, experts from Member States, relevant WHO teams, regional offices, and all key stakeholders such as funders and global procurement agencies.

3.2 Benefits of the WLA framework

In the context of regulatory systems, the WLA framework was regarded by many participants as bringing forth an evidence-based, objective, and transparent approach to recognizing RAs operating at high standards. Compared to the SRA concept, the framework was anticipated to offer greater flexibility by allowing the listing of one or more of the WHO-recommended regulatory functions,

TABLE 1 Summary description of recruited organizations, their categories and respective number of interviewed participants.

Category/target group	Organization—Country/Office	Number of participants
WHO Headquarters and Regional Offices	The World Health Organization (WHO)—Headquarters	4
	The World Health Organization (WHO) —South-East Asia Regional Office (SEARO)	1
	Pan American Health Organization (PAHO/AMRO) —Latin America	1
WHO Listed Authority (WLA)	Ministry of Food and Drug Safety (MFDS) —South Korea	2
	Swiss Agency for Therapeutic Products (Swiss Medic) —Switzerland	2
Transitional WHO Listed Authorities (tWLAs)	European Medicines Agency (EMA) —Europe	2
	Agency for Medicinal Products and Medical Devices (HALMED) —Croatia	1
	United States Food and Drug Administration (US-FDA) —United States	3
NRAs practicing reliance on SRAs	South African Health Products Regulatory Authority (SAHPRA) —South Africa	1
	Ghana Food and Drug Authority (Ghana FDA) —Ghana	1
Agencies involved in international procurements of health products	United Nations Development Agency (UNDP) —Headquarters	1
	United Nations Children's Emergency Fund (UNICEF) —Headquarters	5
Donors, stakeholders and partner organizations to the WHO	Bill and Melinda Gates Foundation (BMGF) —Headquarters	1
	Council for International Organizations of Medical Sciences (CIOMS) —Headquarters	1
	International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)—Headquarters	1

and product categories, as well as facilitating a more equitable geographical distribution of WLAs.

> *"I must say that, if there is one transformative concept that WHO has introduced over time that will have an impact on regulatory oversight over products, it is this WLA framework." (Participant 2, WHO Headquarters).*

> *"The difference here is this (WLA) is evidence-based, that an assessment is done and there is a minimum set of standards that all the WLAs meet, and I think that's highly beneficial..., another huge benefit is that countries may feel much more confident, relying on the work of a regulatory authority within their region." (Participant 15, tWLA 2-SRA).*

Furthermore, the framework was commended for promoting investment in regulatory systems, along with fostering regulatory collaboration, convergence, good reliance practices and good regulatory practices by yielding higher trust in agencies with proven levels of good performance beyond the assessment of the configuration of the regulatory system. These values were viewed to optimize resources and highly support the WHO-PQ programme in expanding the pool of reliable experts, regulatory authorities, and product types. Additionally, the established transitional arrangements were regarded as giving adequate time to RAs and other stakeholders who rely on SRAs to update their respective policies, laws, and guidelines. This is in line with the creation of three possible pathways (standard, abridged, and streamlined) for RAs of different backgrounds to undergo PE based on the level of pre-existing evidence. These efforts were geared towards optimizing the use of available resources while providing robust frameworks for relying on the current and future WLAs.

> *"We are expanding the pool of authorities that others can rely upon, including our own Pre-qualification program which will also rely on authorities beyond the current SRAs." (Participant 5, WHO-Headquarters).*

> *"...if you have this WLA, it is very clear, you can even put it in the law, that if we use reliance, we use it based on what the WHO has done, these are authorities you can rely on, they are trustworthy partners." (Participant 26, Partner Organization 1).*

Moreover, the framework was anticipated to increase global access to safe, effective and quality-assured medical products, hence the promotion of public health. There was a common agreement among participants from procurement agencies regarding the potential of the framework to increase the number of reliable suppliers (due to effective regulatory oversight), streamline procurement processes, and ensure effective responses to public health emergencies. Designation of WLAs was also expected to yield economic rewards to manufacturers and governments, by facilitating equitable and timely access to global markets for products regulated by WLAs.

TABLE 2 Overview of aspects covered in different documents issued by the WHO with respect to the WLA framework.

Covered Domains/Aspects	WHO Global Benchmarking Tool (12)	WLA Concept note (11)	WLA Policy Document (16)	PE Manual (23)	WLA Operational guidance (14)	TAG-WLA Terms of Reference (20)	WHO TRS No. 1033 (13)
Historical background on the WLA framework		•	•		•	•	
SRA concept and/or WHO-Prequalification programme		•	•		•	•	
GBT based WHO maturity levels	•	•	•	•			
Roles of the WHO and stakeholders		•	•		•	•	
Objectives and description of the WLA framework		•	•		•	•	•
Criteria and progress for WLA listing		•	•	•	•		
WLA and objectives of the Resolution WHA 67.2	•	•	•		•		
Status achieved by RAs towards WLA listing					•		
Impact of WLAs on regulatory outputs, outcomes, and impact		•	•		•	•	
Impact of WLA in regulatory collaboration, convergence, harmonization, and reliance		•			•	•	

PE, Performance Evaluation; TAG, Technical Advisory Group; TRS, Technical Report Series; WLA, WHO Listed Authority; full details of the documents are provided

> *"I think as industrial stakeholders we are very supportive of the WLA framework; we understand it is a good process for recognition and to have a better or a more comprehensive program for assessment." (Participant 27, Stakeholder Organization-Manufacturing and Supply of Pharmaceuticals).*

3.3 Necessary resources and support for operationalization of the framework

The study has identified the allocation of adequate personnel, time, and financial resources to be essential requirements for operationalizing the framework. The current WLAs and tWLAs undergoing PE reported putting in place task forces comprised of dedicated staff with required expertise, including those from outside the RAs. Other participants pointed out the essence of effective mechanisms for planning, prioritization, quality assurance, as well as the involvement of NRA's top management and the government throughout the PE process.

> *"The main challenge was to find out who is the best possible expert or where is the best possible expertise in our agency to answer those questions and to bring the documentary evidence." (Participant 10, WLA 2).*

Furthermore, the WLAs reported being supported by the WHO in the form of overall guidance, clarification of complex aspects, and access to information. Concerning other resources, the studied WLAs and tWLAs under PE were notably self-sufficient in facilitating the listing process.

3.4 Clarity regarding the WLA framework

The lack of detailed understanding of the WLA framework was a commonly inferred challenge among participants of diverse backgrounds. This was mostly revealed by information gaps regarding the objectives of the framework and its difference from the GBT-based maturity levels with respect to reliance and guiding procurement activities (Figure 1).

> *"...but if we were to ask the difference between Maturity Level 3 and 4, and WLA, I don't think it is so clear and, beyond that, I think in terms of reliance they are also not very clear... I'm not yet convinced that there is sufficient clarity on how WLAs can contribute to establishing reliance mechanisms and how this*

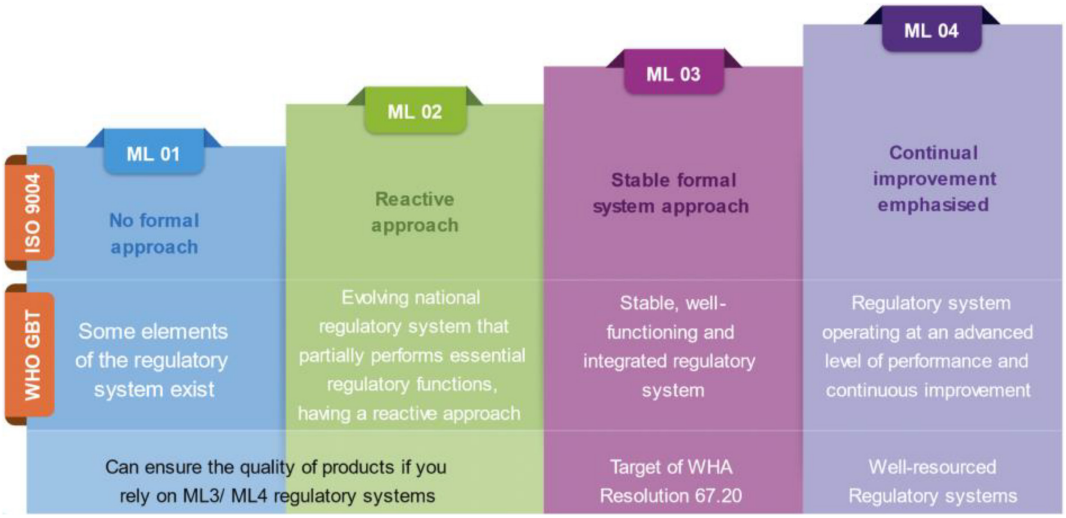

FIGURE 1
Description of the meaning and expectations of the four Maturity Levels (ML) as per the original ISO 9004 categorization and its subsequent adoption under the WHO-Global Benchmarking Tool (GBT).

> *can impact the procurement dimension." (Participant 4, WHO Regional Office).*

Furthermore, participants from the WHO and partners underlined the need for the GBT to be understood as a capacity-building instrument, whereas the performance evaluation for the WLAs was designed to measure the performance of regulatory systems, and the WLA framework was thus conceptualized to promote regulatory reliance at different levels.

> *"GBT was never designed to be used for performance assessment or for establishing reliance mechanisms to be used in a procurement setting. That was never the case. We need to be very clear on this aspect and to distinguish between the two approaches: GBT is for capacity building, it is not for the procurement, it is not for the performance assessment, that is WLA" (Participant 1, WHO Headquarters).*

> *"I believe there is a difference between possessing a specific regulatory capacity at a given point in time and achieving the necessary level of performance." (Participant 25, Donor and stakeholder organization in the supply chain of medical products).*

3.5 Acceptability and progress towards WLA listing

The WLA framework was found to be highly acceptable among participants from diverse backgrounds. The expression of interest by multiple SRAs to become WLAs was regarded as an essential factor in ensuring a smooth transition between the two concepts. High levels of confidence, determination, and commitment were noted among participants from the tWLAs regarding the attainability of the WLA listing in the given timeframe of five years. Apart from the good progress among tWLAs to undergo PE, some participants from the WHO expressed uncertainties about the timely completion of the transition by some tWLAs. The delay was perceived to originate from differences in priorities, levels of commitment and availability of resources.

3.6 Complexity of the performance evaluation process

Resistance to change due to the strong desire to maintain the status quo, fear of the unknown, and concerns about potential disruption of the global medicines supply chain were experienced from within and outside of the WHO. Further, participants from tWLAs and WLAs pointed out difficulties in striking a balance between transparency and confidentiality along the listing process. This is because the WLA framework strongly promotes transparency in all regulatory activities, a configuration that has created problems in some jurisdictions where legal constraints on confidentiality issues are extremely challenging. Nonetheless, such requirements are cross-cutting, hence necessitating all candidate WLAs to be ready to abide by them.

Hurdles in managing priorities between undergoing PE and discharging routine regulatory functions, as well as complexities in securing inputs from multiple centers or departments within the NRAs, were also stated. Securing input from all players within the organization was notably necessitated by the nature of PE to request in-depth details of all regulatory functions.

> *"I think it is a very heavy process and I understand why it is heavy and complicated." (Participant 11, tWLA 1).*

In addition to the newness and complexity of involved processes, which were perceived to be comprehensive, difficulties in interpreting and understanding the language and requirements of different PE indicators were shared among participants. Furthermore, participants from the WHO reported facing challenges in aligning diversity related to regional differences, legal and policy issues, and avoiding the negative influence of political imperatives on technical aspects of the framework.

> *"On the political side, especially with the impetus for local production, both politicians and manufacturers are seeing that their national regulatory authorities should become WLAs now, for them to be able to participate in global trade, and they are often applying a lot of pressure to the WHO, and those pressures are a big challenge." (Participant 2, WHO-Headquarters).*

3.7 Modular approach and scope of WLA listing

The modular approach of the WLA framework allows for the stepwise listing of specific regulatory functions or product categories. This approach was requested by Member States to ensure more flexibility in attaining the WLA designation. Nevertheless, this was perceived to bring complexity and confusion to some participants from international procurement agencies. The participants anticipated laborious and lengthy screening of the listed WLAs before arriving on procurement or other reliance decisions.

> *"...but for me, the biggest challenge is that they are listed for specific functions, that makes it challenging for the end user (e.g. procurement agencies) to keep track of what functions the WLAs are listed for." (Participant 22, UN Agency involved in global procurements-1).*

However, other participants expressed opposing views in favor of functions and product category-based listing of WLAs.

> *"...this complexity is a challenge, but I think there is no easy way around it, because this way (listing of specific functions and product categories) of approaching the framework was demanded by Member States." (Participant 2, WHO-Headquarters).*

> *"WLAs should be linked to certain product categories because it is impossible to say that any small agency can power equally well everything, it is just not realistic, this is not happening." (Participant 26, Partner Organization 1).*

Moreover, the need for the inclusion of medical devices within the scope of the WLA framework was commonly shared among participants from global procurement agencies, being perceived as an urgent and necessary future development of the framework to guarantee patients' access to a broader range of medical products.

4 Discussion

4.1 Roles of the WHO and Stakeholders

The WHO has played vital roles across different phases of developing and implementing the WLA framework. This is demonstrated by a widespread recognition and appraisal of its roles among participants of diverse backgrounds as well as a set of documents that form strong pillars of the entire WLA framework (12, 14, 16, 23). Nevertheless, that success would not have been possible without the notable support from Member States, stakeholders, partner organizations, donors, and the public at large. Furthermore, the respective interdependencies between the WHO, ICDRA and ICH in the creation of overarching health policies, facilitation of dialogues and cooperation, and development of technical guidelines for the regulation of medical products and harmonization are extremely valuable in ensuring a unified approach to enhancing the quality, safety, and efficacy of pharmaceutical products globally. These findings underscore the essence of effective leadership, coordination, and documented guidance in executing complex and multifaceted programmes involving diverse players (23–25).

4.2 Realized benefits of the WLA framework

The concrete outcomes of the WLA framework include bringing forth a significant transformation in advancing regulatory outputs, outcomes and impact, ultimately contributing to the promotion of public health globally. Based on the demonstrated higher level of transparency and evidence-based listing of WLAs, the framework is on the right course to the full realization of its objectives including offering an outstanding contribution to the development of good reliance practices. Contrary to the SRA concept, the expected increase in the number of WLAs over time guarantees their broader global distribution, hence providing a closer collaborating hand to an increasing number of NRAs (11, 16). However, for effective realization of such benefits, countries, regional and global entities must put in place enabling environments for smooth collaboration and reliance on WLAs. To this end, changes in the global regulatory landscape due to the introduction of the WLA framework necessitate parallel efforts among all Member States and stakeholders to align with its objectives, processes, and implications (26, 27).

4.3 Resource allocation and technical support

Resources of varying nature constitute a critical aspect for the operationalization of the framework on the side of

the WHO as well as the RAs. This study has highlighted the need for careful evaluation, planning, and allocation of needed assets before undergoing the PE process for WLA listing. Considering inequalities among countries, there is a strong need for support mechanisms to ensure that the prospect for WLA listing is open for all RAs desiring to be listed based on self-evaluation (4). Such measures should include encouraging countries to prioritize budgeting for strengthening regulatory capacity, increased investment in staff training, and seeking financial and technical support from governments and external stakeholders (4, 9).

4.4 Clarity, acceptability and progress towards WLA listing

Regardless of broad acceptability, and aspirations for achieving the status, information gaps still exist, and some stakeholders are still confusing the purposes of the WLA framework to that of the GBT. Furthermore, there are concerns about the timely achievement of the transition to fully listed WLA status among tWLAs as well as the limited level of clarity and understanding of the WLA framework due to its newness or being newer compared to the GBT modality. The ascending nature of levels in the GBT framework has led to the general perception of ML4 as the highest and hence most competent NRAs even in terms of performance. However, this is not the case as the GBT is not designed for thoroughly measuring the performance of RAs (12, 23). To facilitate smooth transitioning and draw maximum benefits from the framework, the WHO, Member States, and relevant stakeholders should ensure sustainable advocacy for the framework particularly among RAs.

4.5 Complexity of the framework and resistance to change

Based on the perspective and routine operations of the involved party, resistance to change, process complexity, and optional listing of regulatory functions and product categories, are among the core hurdles associated with the WLA framework. Other studies have reported on resistance at individual and organizational levels following the introduction of substantial changes to the existing structures and/or operations (7, 9). However, due to the increasing number and extent of challenges related to regulatory oversight, constant improvement of the existing systems is imperative. Although there should be room for addressing difficulties related to process complexity, those undertakings should not be at the expense of the achieved framework's robustness, transparency, and meticulous nature of the framework.

As pointed out by participants from the WHO, the current design of the WLA framework is an outcome of extensive consultative processes involving Member States and a wide array of stakeholders (14, 16). Thus, the challenges still existing in the WLA framework are mostly associated to the introduction of a new process which involves multiple and diversified stakeholders, as well as to the intrinsic comprehensiveness of the WLA framework.

Taken together, the framework's complexity is in tandem with ensuring that it is highly trustable and credible hence contributing to the overall acceptability of the WLA concept across a wide range of stakeholders. This is confirmed by the positive attestations from the RAs which have achieved the WLA status on the extent to which the PE process has contributed to improving their regulatory outputs and outcomes. Furthermore, the current performance evaluation was reported to be lesser complex as compared to the initially proposed version. The adopted simplifications were made following public consultations and piloting in three countries and were meant to make the framework more accessible, affordable, reasonable and realistically applicable.

TABLE 3 Summary of recommended actions towards improving and sustaining the WLA framework.

Recommendation	Details
Continued WHO's engagement and support	• Continue to engage with and provide customized support to RAs interested in WLA listing • WHO should use existing WLAs to promote regulatory excellence through experience and expertise sharing.
Improve clarity and awareness of the WLA framework	• Enhance communication of the BGT as a capacity-building instrument. • Communicate the WLA framework as a path to evaluate and recognize regulatory performance over time
Smooth Management of the transition process	• Ensure that the transition process is as smooth as possible to avoid disruption in global supply chain of medical products • Prioritize assessments based on factors such as the applicant's regulatory capacity, geographical distribution, and manufacturing capacity.
Develop a searchable database for WLAs	• Allow easier navigation and tracking of WLA-listed functions, product categories and geographical locations by creating a searchable and openly accessible database
Expand scope of the WLA framework	• Ensure the frameworks relevance in the changing regulatory environment by including other product groups such as medical devices, in vitro diagnostics, blood products and vector control products.
Ensure continuous improvement and monitoring	• Implement continuous improvement measures. • Establish constant monitoring of the framework's performance through feedback mechanisms, stakeholder involvement, and dedicated impact studies after three years of operationalization
Enhance transparency, information sharing and a balance with confidentiality	• Make PE outcomes and assessment reports publicly available so as to promote trust, accountability, and knowledge sharing in regulatory decision making. • Ensure a balance between transparency/information sharing and confidentiality aspects

In recognition of the merits of the WLA initiative, collective efforts are needed to address the existing hurdles while preserving its core values (7, 15). Impressively, the WHO indicated to be taking necessary measures to provide targeted training, clarifications, and answers to specific requests, to help the stakeholders in understanding and navigating the stated complexities.

4.6 Recommended future steps in operationalizing the WLA framework

A number of key recommendations were discussed by the participants for further improvement and sustainability of the WLA framework. The suggested actions cut across the need for continued engagement, improved communication, and expanding the scope of products categories, among others. Table 3 provides an overview of the recommended measures.

To this end, it is crucial that all stakeholders fully understand the intended applications of the framework and their specific roles within it. This includes regarding the WLA designation as not as a once-off event, but rather as a dynamic process involving continuous monitoring and transparent interactions, self-evaluations and collaborative efforts towards the common goal of protecting public health.

5 Conclusion

The study has highlighted key aspects of the WLA framework. Significant roles played by the WHO and its stakeholders, including the commitment and investment from Member States were crucial across different phases of developing the framework towards its operationalization. Moreover, through designating RAs operating at international regulatory standards, the framework will largely contribute to the advancement of regulatory outputs and outcomes, and ultimately achieve a greater and more widespread impact on global public health. Besides common acceptability, the framework is faced with several challenges including being resource-intensive, resistance to change, and lack of clarity among stakeholders. The study has put forward recommended steps to address the existing challenges to ensure smoother operationalization and full realization of the framework's potential.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Author contributions

AB: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. AS: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing. MA: Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing. RD: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review and editing. HS: Formal analysis, Investigation, Methodology, Validation, Writing – review and editing. RG: Formal analysis, Investigation, Validation, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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A narrative review on problems in product quality, regulatory system constraints, and the concept of quality by design as a solution for quality assurance of African medicines

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Background: The provision of medicines with confirmed quality and efficacy is critical for maintaining the public health and building confidence in the healthcare systems. However, the presence of poor-quality medicines still presents a significant challenge in the pharmaceutical landscape across the African regions. This is further exacerbated by the lack of consistency or discrepancy in the current regulatory framework. As a consequence, given the current constraints, a robust regulatory structure that can guarantee the supply chains attainment of the intended medicinal product requirements are required.

Objective: The review aimed to provide a detailed analysis of the quality issues in the pharmaceutical supply in Africa, highlighting the challenges and proposing potential solutions for its mitigation.

Methods: The review was conducted from May 2023 to April 2024. This narrative review examined poor-quality medicines, regulatory challenges, and mitigation strategies in the African pharmaceutical industry. The review utilized databases such as Google Scholar, PubMed, and Web of Science. The search strategy was customized to include open-access articles published in peer-reviewed scientific journals in English and focused exclusively on studies conducted in African countries.

Results: The review portrays the prevalence of poor-quality medicinal products in various regions of Africa. Among various categories of findings, 42% of the reports on poor-quality medicinal products come from the African region, as per the WHO report. Furthermore, separate findings on substandard medicinal products from many African countries were encountered. The presence of problems in the regulatory system, such as the absence of any pharmacopeia belonging to any African country and variation/inconsistency in each country's regulatory set-up, was indicated. Other factors for the inability to enforce regulatory law, such as insufficient skilled and committed human resources, the presence of corruption, as well as financial resource scarcity, were revealed in the review. From the situational analysis, the possibility of building a robust

quality assurance system in the near future through a quality by design approach under existing resource limitations was discussed.

Conclusion: The pharmaceutical sector in Africa faces significant challenges, including the prevalence of poor-quality medicines and weak regulatory enforcement. Tackling these challenges are vital for enhancing health outcomes throughout the continent through the provision of high-quality medicines. Trending toward quality by design in the quality assurance system under prevailing financial scarcity can be very beneficial.

KEYWORDS

narrative review, poor quality medicine, challenges, quality by design, regulatory system, Africa

1 Introduction

Medicines require special attention, without which, many people around the world are denied proper healthcare (1). Unlike typical consumer products, even small deviations from the recommended dosage or formulation of medicines can have serious health impacts (2). This is because any excess or deficiency can lead to adverse effects or ineffective treatment (3). On the contrary, deviation from the theoretical recommendations of drug monograph can also bring either a lack of desired clinical outcome or the worst scenario of development of drug resistance in the case of antimicrobials (4). Guaranteeing fair access to safe and affordable medications is essential for attaining the highest possible standard of health, which aligns with one of the Sustainable Development Goals. To enhance the utilization of medicines and their beneficial effects on public health, it is imperative to develop a strong regulatory framework for pharmaceuticals (5). In Africa, the National Medicines Regulatory Authorities encounter multiple challenges. These include prolonged product registration timelines, underdeveloped regulatory structures, redundancy in regulatory procedures, shortages in organizational capacity, and inefficiencies in certain cases (6).

The need for special precautions in regulating the quality of medicinal products has been recognized for centuries. This is exemplified by the establishment of various institutions and regulations dedicated to ensuring the quality of medicine. One of the earliest examples is the creation of the United States Pharmacopeia by a group of volunteers in 1820 (7). The establishment aimed to compile a comprehensive collection of standardized recipes for drug preparation, ensuring consistency and dependability throughout the United States. Furthermore, the United States Drug Importation Act of 1848 formally acknowledged the United States Pharmacopeia as a credible authority on drug quality standards and inspection services. This legislation required the inspection of imported pharmaceuticals at customs to verify compliance with the defined quality criteria. It represented the inaugural law in the United States focused on regulating drug quality. By emphasizing the need to determine medications that meet requirements beyond pharmaceutical or biological quality, as well as demonstrating preclinical, and clinical safety as well as efficacy in medicinal products, this act laid the groundwork for modern drug regulation (8).

Despite the historical events with the establishment of medicines quality affiliated centers as early as the beginning of the 19th century, few documented evidences from Africa indicated the emergence of medicines quality regulation-related guidelines even until the end of the first half of the 20th century documented in Ethiopia (6). Unfortunately, none of the African countries, except Egypt, currently have their national pharmacopeia (9, 10). Though there is institutional awareness of worldwide regulatory frameworks, quality control has been based on stringent sampling and laboratory testing procedures, which are not financially or temporally practical. The modern regulatory landscape has moved beyond just "quality by testing" or "quality by chance" methodologies and has instead placed a singular emphasis on the principles of quality by design (11, 12). It was first coined in the USA since in 1992 and becomes an institutionalized regulatory concept in FDA at year 2004 GC (13, 14). Nowadays quality by design paradigm is advocated for its efficiency in terms of time and cost.

The study revealed that, due to poorly implemented regulatory frameworks for medicines in Africa, there has been evidence of the influx of substandard and falsified medicinal products into the continents (15). For instance, the study conducted in 2024 indicated that 22.6% of poor-quality drugs were found in Africa (16). Additionally, about 34.6% medicine found in the market were unregistered (17). This report emphasizes how critical it is to solve the problems caused by counterfeit and substandard medications in Africa. To ensure the availability of safe, effective, and high-quality medications, strengthening regulatory mechanisms, building capacity, encouraging collaboration, and raising public knowledge are essential initiatives that will preserve public health and rebuild public confidence in healthcare systems (18).

The prevalence of substandard medicines in Africa can be attributed to the inadequate and flexible regulatory frameworks governing the pharmaceutical industry. To mitigate this issue, it is essential to establish stringent quality standards and design principles. Addressing the historical oversight of

quality in African nations is vital, necessitating continuous efforts to enhance regulatory measures. Consequently, the pharmaceutical sector in Africa should focus on integrating quality into the product development process from the beginning, rather than relying exclusively on end-stage testing (19). Without adherence to these principles, it becomes challenging to address problems effectively and implement corrective and preventive actions. Accordingly, developing the concept of quality by design (11) in a pharmaceutical environment is critical as a solution of quality assurance of pharmaceutical products. This will enable more flexible regulatory relief, while still guaranteeing product quality and patient safety.

According to a report by the World Health Organization, substandard and falsified medicinal products represent a significant global issue that endangers public health and patient safety, while also contributing to a concerning rise in antimicrobial resistance. This issue is particularly widespread in low- and middle-income countries, where it is estimated that one in ten medical products may be substandard or falsified (20). Evidence suggests that the presence of substandard antimicrobials in Africa was unavoidable; nevertheless, there is often a failure to recognize the fundamental reasons for quality deficiencies in the manufacturing area (16, 21). The principle of quality by design is not yet widely implemented in contemporary pharmaceutical manufacturing facilities in Africa. In the current scenario, the target product quality profile is one of the critical elements of quality by design in regulatory environments. The TPP will help identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties (22).

This review has been undertaken to identify current problems in medicinal product regulation in Africa and forward solutions for efficiency improvement options through a comparative quality by design approach. The review focuses on documenting defective products within the categories of agricultural pesticides, veterinary drugs, and human medicinal products. Moreover, it aimed to identify factors contributing to the presence of defective products in the market and propose QBD-based alternatives as remedies for existing problems.

2 Materials and methods

2.1 Search strategy

The narrative review, conducted from May 2023 to April 2024, focused on examining the issue of substandard pharmaceuticals, challenges, and potential mitigation strategies within Africa's pharmaceutical environment. The review utilized databases such as Google Scholar, PubMed, and the Web of Sciences. Key steps and methodologies involved in the review were language and time frame, which were restricted to English-language publications, drug advocacy websites, and data collected from African published literature that specifically addressed issues related to poor-quality medications, existing problems with regulatory standards, and potential solutions within the pharmaceutical industry on the continent.

2.2 Quality data evaluation method

The Medicine Quality Assessment Reporting Guidelines checklist was utilized to ensure the quality and rigor of the selected articles in the review. This checklist provides a structured framework for assessing the methodology of studies on medicine quality, encompassing 12 specific criteria (23) (Supplementary File 1). The included quality medicine articles had the following information: study objective, study design, sampling method, data collection, quality control tests, statistical analysis, ethical considerations, limitations of results reporting, interpretation of results, funding and conflicts of interest, and conclusion.

A comprehensive approach to revising the regulatory system information conducted by utilizing an online database and incorporating previously published findings ensures that the review was grounded in credible sources and up-to-date data (6, 24–27).

3 Literature search results

3.1 Historical evolution of medicines regulation

Since medicine has been a part of human history for centuries, methods for ensuring its quality have developed steadily throughout a time (28). Historically, the evolution of medicines regulation has been driven by the need to protect public health and ensure the safety and efficacy of pharmaceuticals (29). Unfortunate events, rather than the growth of medical knowledge, have been the main force behind the regulation of medicine. Risks are inherent in pharmaceutical a procedure, which emphasizes how important strong control is. Good regulation guarantees that pharmaceuticals, especially veterinary medications, fulfill quality, safety, and efficacy requirements (30). This is essential to preserving market integrity, safeguarding public health, and avoiding problems like inferior or fake goods from reaching consumers. Enforcing conformity with established recommendations and standards is a major responsibility of regulatory organizations. This entails carrying out routine inspections, keeping an eye on unfavorable incidents, and taking appropriate corrective action as needed. Regulators can contribute to the safe and efficient operation of the pharmaceutical business by upholding strict oversight and regularly updating standards in light of new information and developing dangers (31).

The evolution of medicine regulation has been complex, with significant milestones like the Apothecary Wares, Drugs, and Stuffs Act of 1540 and the Food and Drugs Act of 1875, and the National Medicines Regulatory Authority in the UK (32). Similarly, although different institutional naming, enactments for establishment NMRA's in Turkey (33), Switzerland (1900), USA (1906), Norway (1928), and Sweden (1934) mainly for patent protection and trade promotion, though the laws in Norway and Sweden focused on product safety as well (34). Profession known to act starting from 1911 with further improvement to the Scientific Expert Committee of the German Medical Association (1958-61), and later on with official enactment passed in 1963 to establish the First German Medicines Act initiated in response to the thalidomide birth defect tragedy in 1961 (35).

In the USA, the official regulatory structure traces back since to the development of the pure foodPure Food and drugs act Drugs Act of 1904 by the US congress Congress. This is followed by the issuance of the Food, Drugs and cosmetic Cosmetic Act, of 1938 issued after the death of over 100 people in 1937 due to sulphanilamide elixir prompting assessment of safety before any product is marketed (36). In the early 1960s, the thousands of pregnancies were affected by thalidomide-induced phocomelia. It has also and other defects causing caused to transform and institutionalize institutionalized throughput drug safety and efficacy screening procedure establishments in NMRAs globally for investigational new drugs and monitoring of clinical trials has also received attention (32). The current European Medicines Agency was established in 1995 to ensure the safety and efficacy of medicine and medical devices within the modern-day 25-state member community (37). Pharmaceutical companies in today's competitive environment employ diverse strategies to gain regulatory relief, whether through traditional methods like quality testing or systematic approaches. The traditional regulatory evaluation system assesses product quality and performance through constraints on manufacturing processes and final product testing. In contrast, modern regulations prioritize the incorporation of quality through design. Consequently, the present emphasis on quality implementation in pharmaceutical industries can be attributed to the principle of quality by design. The quality by design (11) concept concerning pharmaceutical quality assurance becomes an issue with its efficiency and effectiveness in terms of both time and money over routine quality assurance through rigorous sample analysis. In this regard quality by design is defined as building quality in design instead of testing from final product (38).

3.2 Current trends in medicinal product quality in African countries

Global sustainable development goals: The third priority goal of the global sustainable development program is to ensure healthy lives and promote well-being for all at all ages. This includes a focus on access to quality, safe, effective, and affordable essential medicines and vaccines (39). Among sub-targets considered, access "to quality, safe, effective and affordable essential medicines and vaccines for all is emphasized" (40).

Challenges driving poor-quality medicines in Africa: Ensuring quality, safety, and effectiveness in the global medicine supply chain is fraught with challenges. In the African context, these challenges are compounded by limited financial resources, which impact the ability to access quality medicines. Apart from that, difficult and complex regulatory frameworks can impede the efficient distribution of quality medicines (41). Additionally, there is a higher prevalence of defective medicines due to gaps in regulatory implementation and poorly designed disincentives for non-compliance (42). This situation contributes to adverse health outcomes due to gaps in regulatory implementation as well as poorly designed disincentives for noncompliance, creating undesired health outcomes (43). A regional summary from the WHO revealed 42% of reports on defective quality medicines coming from the African continent (44) (Figure 1). Addressing the issue of falsified and substandard medicines in Africa also necessitates strengthening the local regulatory system for controlling pharmaceutical manufacturing practices. This local manufacturing can serve as a means to increase the availability and accessibility of quality essential medicines across the African continent.

3.3 Consequences of defective medicinal product quality

Health impact: Unexpectedly High Active Pharmaceutical Levels: Medicines with unexpectedly high levels of the active pharmaceutical ingredient (45) can lead to toxic reactions, severe side effects, or even death (45, 46). Apart, contamination with harmful substances can cause serious health issues, including infections, organ damage, or cancer.

Long-term illness: Defects in medicinal product quality are attributed to life-threatening illnesses and other indirect socioeconomic outcomes. Either unexpectedly high levels of the expected API or else product contamination with other dangerous substances can result in death or long-term illness for individuals taking these defective quality medicines. Long-term illness may also be due to the continuation of the treatable disease that remained due to the absence or reduced level of API; perhaps a preventable disease can also rise in a community, especially in the case of defective vaccines. Defective-quality products with subtherapeutic API levels also pose a risk of antimicrobial resistance, resulting in the nullification of the role of antimicrobials for human survival (47, 48).

Indirect socioeconomic outcomes: The socioeconomic impact of defective product quality in the supply chain has been estimated. Globally Falsified medicinal products constitute a market share estimated to be US$ 200 billion making it the most profitable business among illegally copied items (49). In Africa, compared to other global perspectives, the rise of poor quality medicines was indicated attributable to the absence of strict supply chain regulation, track and trace technology as well as enforcement regimens that are in place in Europe and united states (40). Furthermore, the socioeconomic impact of defective quality medicines in Africa has also been estimated. Antimalarial drugs in sub-Saharan Africa resulting socioeconomic impact specifically deaths due to poor quality (47) of drugs estimated at 7,500–150,800 from malaria and pneumonia (50).

3.4 Prevalence of poor-quality medicine in African countries

The quality defects in the pharmaceutical market, particularly in Africa, are categorized into substandard, unregistered, falsified, and counterfeited products. Each category has distinct implications for regulatory management and public health (40). For reasons of avoiding disparity the World Health Organization has adopted a working definition of substandard medicinal products to refer to apparently authorized medicinal products that fail to meet quality standards for manufacturing and distribution, while unregistered or unlicensed products are products that have not passed through approval procedures by regulatory bodies before marketing. The last category, falsified or counterfeited products, is agreed to

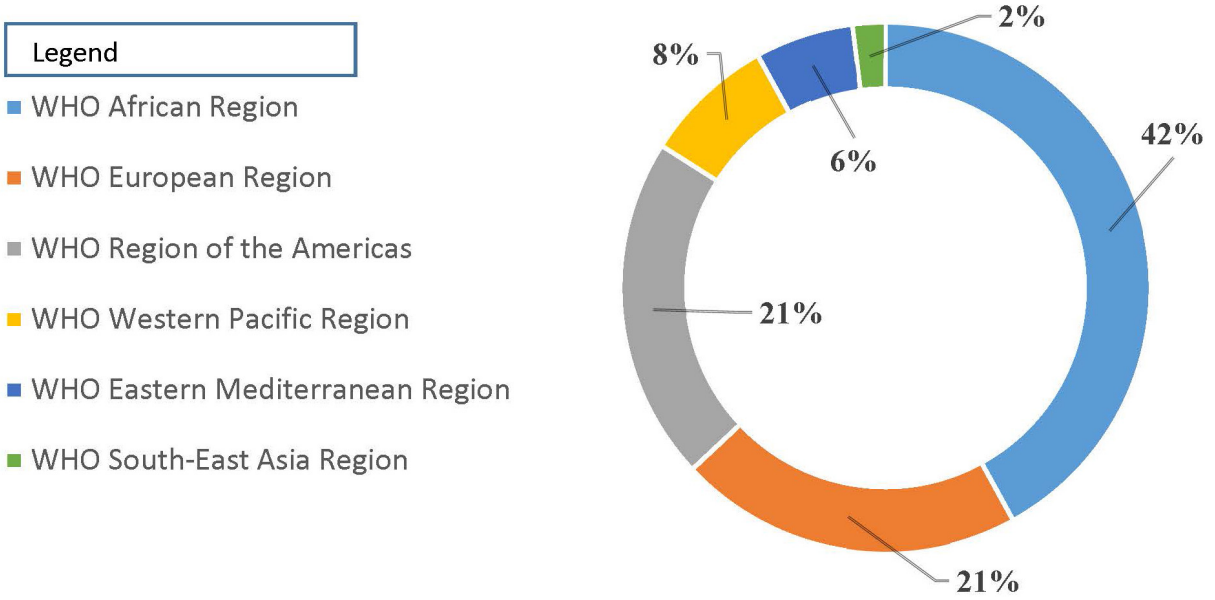

FIGURE 1
Reports of medicine counterfeited/substandard [Source: WHO (44)].

refer to products deliberately concealed or lied about in terms of product identity, composition, or source (51). The later classification was the most unreliable and unethical pharmaceutical trade, constituting a criminal act. Quality defects encountered in African pharmaceutical supply are thus discussed using the WHO working definition.

Under ideal circumstances, is it in Africa or elsewhere in other parts of the world that products in the pharmaceutical supply system should pass through national regulatory checkups for their quality, safety, and efficacy? However, the circulation of unregistered medicinal products has been reported in many African countries. Surveys highlighted the circulation of unregistered drugs in the supply chain in Ethiopia, mainly in border regions, due to weak border control and regulatory implementation (6). In Kenya, a survey on first-line antiretroviral drugs revealed that 27.47% of the products encountered were unregistered after being manufactured by known and licensed manufacturers. However, it was found with proper API content (52).

The common quality defect documented in African countries is the prevalence of substandard drugs failing to fulfill defined manufacturing standards such as assay, uniformity of packaging, labeling consistency, and product active matter release performance (23, 53–55). The most common defects in quality reported from the African drug supply chain consist of antimalarials, anti-infectives, and, to a lesser extent, antihelmentics (53, 56).

Estimating the proportion of counterfeit drugs in the pharmaceutical supply in African countries is challenging due to the limitations of convenience sampling, which often does not provide a comprehensive or representative picture. Despite these challenges, several studies have highlighted the prevalence of substandard and counterfeit drugs, particularly antimalarials, across various countries (57). In African countries, studies have been undertaken on the circulation of substandard and counterfeited drugs. In Ethiopia, quality analysis on ten veterinary product batches from six trademarks of Albendazole demonstrated two products failing to meet the minimum content as claimed (58). In Nigeria, studies on antibiotic drug products 48% (59); of samples of Amoxicillin, Amoxicillin-Cloxacillin combination-trimoxazole and Tetracycline and 36.5% (55) of samples of chloroquine and selected antibacterial drug were substandard compared to set pharmacopeias limits.

A counterfeit antimalarial drug product, Coartem®, was discovered in Cameroon in 2013 and distributed in West and Central Africa. The counterfeited product, known to contain little or no active pharmaceutical ingredient, was distributed in hospitals and street vendors, with the same logos as the Global Fund Affordable Medicines Facility—Malaria Programme in Cameroon and Nigeria (60). Recent reports on other counterfeited antimalarial drugs were also found documented from sub-Saharan African countries Uganda and Central African Republic (61), Cameroon, Chad, Democratic republic of Congo, Niger, Nigeria (62). Six batches of quinine sulfate 300 mg were found counterfeited from Chad (three), Cameroon (63), and Nigeria (63), with the manufacturer's claim being Remedica Ltd., with no active ingredient detected in them.

The review highlighted illustrates significant challenges in the fight against counterfeit pharmaceuticals and diagnostic products:

Outdated WHO essential drugs program logo: The use of outdated or fraudulent logos on falsified products can mislead healthcare professionals and patients about the authenticity and quality of the medications. This underscores the need for vigilance and verification of the legitimacy of pharmaceutical products (64).

Falsified chloroquine phosphate tablets: The documentation by the World Health Organization (65) of falsified chloroquine phosphate tablets from Cameroon, the Democratic Republic of

Congo, and Niger highlights the global nature of the counterfeit drug problem. Counterfeit chloroquine can undermine treatment efforts and pose serious health risks (66).

Counterfeit HIV diagnostic tests: The case of falsified Uni-Gold™ HIV tests from Kenya, with altered expiry dates, reveals the risks associated with counterfeit diagnostic tests. The discrepancy in expiry dates can lead to false results and inadequate treatment, further complicating the management of HIV (62). These instances emphasize the importance of robust regulatory frameworks, stringent quality control measures, and effective surveillance systems to combat counterfeit medicines and diagnostic products. Collaboration between regulatory authorities, manufacturers, and international organizations like WHO is crucial to address these challenges and protect public health (67).

A study from ten West African countries on cardiovascular drugs Amlodipine and Captopril from both licensed and illegal outlets has indicated a 50% prevalence of poor quality products among products from Asia in illegal outlets (68, 69). Drug quality differences for products with the same origin but different marketing region was also reported from product quality analysis in south Africa compared to other European country (70). The Substandard and Falsified products reported from African countries through Global Surveillance and Monitoring System were summarized in Table 1, and Substandard Medicinal Product Survey Undertaken and Published from Different African Countries were also summarized in Table 2.

3.5 Challenges in product regulation

3.5.1 Human resource in medicines regulation

Both the shortage of well-trained health professionals and the level of motivation among available staff have been repeatedly attributed to the scarce status of the current health service to alleviate existing health problems in Africa. A severe shortage of health professionals in sub-Saharan Africa has been indicated as a major problem for scaling up the quality of service delivered to communities in these localities (71). Improving the human resource situation as a tool for health development goals is equally important to bring about change in health service quality, including service supply regulation.

The quality by design reality in the regulatory sector needs long-term vision for improvement in the government or public institutions, which will rely on the way human resources are managed in the sector. Regulatory enforcement in the health sector is inherently affected by the level of motivation among the available staff working in these public institutions. Motivations can be either financial in terms of supporting livelihoods or non-financial motivations related to the establishment of transparent institutional management that is palatable to health workers (72). Institutional transparency can be the basis for required task ownership and responsibility. In this regard sub-Saharan African countries are known for lower budgetary allocations compared to other resource rich countries (73) which can be reflected in lower financial incentives allocated to the sector.

3.5.2 Law enforcement and corruption

Despite the fact that many African states have regulatory establishments and legal frameworks, they are not only less implemented but also not powerful compared to the economic benefits illegal dealers achieve from illegal trade. This has been substantiated by reports in east African economic community member states (Tanzania, Brundi, Kenya, Rwanda, and Uganda) (74).

Law enforcement in product quality regulation involves an integrated joint task including different stakeholders, such as inspectors from medicines regulation, usually of technical skills, community police units, and judicial bodies, to interpret and implement corrective actions of wrongdoers against codified legislation. However, gaps in law enforcement have been found and published in African countries, demanding attention for quality by design reality to come into effect on the ground. Among the observations (75).

Besides defective rule of law implementation, corruption is a common phenomenon. Corruption happens when an agent in service at any one of the public or private institutions can influence the expected outcome of service, enabled to give decisions on an exclusive basis, the corrupted exercise of role with an intended consequence to bring a private benefit for an agent or another affiliated person, company, organization, etc. The corrupt act usually takes place in conditions where there is a lack of transparency in the rules or concealed information. In the presence of corruption, resources are used inefficiently, with higher costs and prices resulting in distortions in output with reduced quality (76).

The impact of corruption affecting decision decisions on any one of the components in the pharmaceutical system is detrimental to health gains expected from access to quality medicines (77). In drug discovery, corruption whether with its actual or perceived impact is considered as one of the number of issues precluding pharmaceutical companies from undertaking clinical trials in Africa (78), and affecting the continent in its share of global drug development efforts. Corruption in the pharmaceutical sector (79).

In sub-Saharan Africa, studies related to corruption in the overall health sector in South Africa have indicated affecting that it negatively both patient care and healthcare worker morale (80). Regulatory costs and irregularity in budget allocation has have been indicated as an impediment to African product quality regulation (43).

3.5.3 Inconsistencies in regulatory infrastructure

Africa has 54 regulatory authorities with 10 keys (81) with regulatory functions of registration licensing post-market surveillance (5). The legal framework established in product regulation differs among countries in Africa, lacking uniformity and creating problems during transboundary drug trade and import-export procedures (11). In many African countries, veterinary and medical products are regulated by sections under the health ministry, while others establish veterinary product regulation under the ministry of agriculture, as is the is the case in Ethiopia (41). Furthermore, agricultural pesticides are managed under separate sections, either from medical devices or even from veterinary pesticide regulatory units (Table 3). Living aside the pros and cons behind specialized structures to handle regulatory units under fragmented sections, harmonization of quality control schemes cannot be managed equally at the same pace. Resource redundancy in building the same facility in different sections is also not economically sound. In some countries, ownership claims have also been raised by veterinarians when veterinary

TABLE 1 Substandard and falsified products reported from African countries through GSMS.

Drug entity	Country of product encounter	Physical form	Information labeled on the product			Quality analysis findings	Stated manufacturer	References
			Batch	Manuf. date	Expiry date			
Chloroquine phosphate	Cameroon	Tablets 100 mg	660	05/2017	05/2021	Falsified label and or contain below expected API	Jiangsu Pharm.	(62)
		Tablet 250 mg	660	09/2022	09/2022		Jiangsu Pharm.	
		Tablet 250 mg	660	05/2019	04/2023		Jiangsu Pharm.	
		Tablet 100 mg	660	08/2018	08/2022		Jiangsu Pharm.	
		Tablet 100 mg	EBT 2542	01/2019	10/2022		Astral pharm.	
Chloroquine phosphate	Democratic Republic of Congo	Tablet 250 g	N°:1605059	05/2019	04/2023		Dawa Limited Brown & Burk Pharm	
			N°: 065622	11/2018	11/2022			
Chloroquine phosphate	Niger	Tablet 100 mg	HV1116	06/2019	05/2023		None	
		Tablet 100 mg	NBJT02	11/2019	10/2022		None	
		Tablet 100 mg	NBJT01	11/2019	10/2022		None	
Uni-Gold HIV 1/2 rapid diagnostic kit	Kenya	KIT	HIV7120026		5/12/2020	Falsified labeling, delayed result	Trinity Biotech plc.	
			HIV6120030		29/07/20			
Quinine sulfate	Nigeria	Tablet 300 mg	44680	04/2017	04/2021	No quinine identified	REMEDICA LTD–Cyprus	
			44680	09/2017	10/2020			
Quinine sulfate	Chad	Tablet 300 mg	44680	10/2018	10/2023	No quinine identified; Traces of chloroquine	Remedica Ltd–Cyprus	
			44680	04/2017	04/2021			
			44680	03/2015	03/2018			
Quinine sulfate	Cameroon	Tablet 300 mg	44680	09/2017	10/2020	No quinine identified	Remedica Ltd–Cyprus	
Quinine sulfate	CAR	Tablet 300 mg	7711006	8/2018	7/2021	Falsified Label	Phamachim Bulgaria* and Enitop Pharmaceutical Nig. Ltd.# Phamachim, Bulgaria*	(61)
		Tablet 800 mg	00952005	06/2015	12/2020			

(Continued)

10.3389/fmed.2024.1472495

TABLE 1 (Continued)

Drug entity	Country of product encounter	Physical form	Information labeled on the product			Quality analysis findings	Stated manufacturer	References
			Batch	Manuf. date	Expiry date			
Quinine sulfate	Chad	Tablet 300 mg	7711004	5/2018	4/2021	Falsified Label	Phamachim Bulgaria and Enitop Pharmaceutical Nig. Ltd.	
Quinine bisulphate	Uganda	Tablet 300 mg	7422	03/2017	04/2021	Falsified label and no expected API	Laboratory & Allied Ltd.	
Augmentin (Amoxicillin trihydrate—Potassium clavulanate)	Uganda and Kenya	Tablet (500 mg/125 mg)	786627	Aug 2016	Aug 2019	Falsified Labeling and none of the API	SmithKline Beecham Limited	
Hydrochlorothiazide	Cameroon	Tablet 50 mg	16G04	06/2017	30/5/2021	Falsified labeling, No expected API@	Laboratoires Sterop	
Artemeter 20 mg + lumefantrine 120 mg combination	Cameroon	Tablet	NOF 2153	01.2013	11. 2015	Assay with very little or no API	100%	(60)
			F2929	01.2012	01.2016		100%	
			F1901	01.2012	01.2014		100%	
			F2261	01.2012	01.2014		100%	

@5gm glibenclamide trace obtained instead of expected hydrochlorothiazide, GSMS, Global Surveillance and Monitoring System. # Manufacturer name is indicated on the product label of declared counterfeited product. * Country of origin is indicated on the product label of declared counterfeited product (not necessarily).

10.3389/fmed.2024.1472495

TABLE 2 Substandard medicinal product survey undertaken and published from different African countries.

Drug entity	Place of encounter	Dosage form	Information Labeled on the product			Quality analysis findings	Proportion of poor quality sample	References
			Batch N	Man. date	Exp. date			
Chloroquine phosphate	Nigeria	All Tablet	NI	NI	NI	Assay (NC)	94%	(55)
Chloroquine sulfate							79%	
Quinine sulfate							24%	
Metronidazole	Nigeria	Tablet	NI	NI	NI	Assay (NC)	72%	(55)
		Suspension					100%	
Artemeter 20 mg + lumefantrine 120 mg combination	Cameroon	Tablet	NOF 2153	01.2013	11.2015	Assay (NC)	100%	(60)
			F2929	01.2012	01.2016		100%	
			F1901	01.2012	01.2014		100%	
			F2261	01.2012	01.2014		100%	
Quinine	Congo	Tablet	NI	NI	NI	Assay (NC)	100%	(54)
Albendazole 600 mg	Ethiopia	Tablet	NI	NI	NI	Assay (NC)		(58)
Chloroquine amoxycillin	Nigeria	Tab.,syrup, inj.Caps.&oral susp.	NI	NI	NI	Assay (NC)		(59)

NI, not indicated; NC, non-complaint.

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TABLE 3 Regulatory setup in African countries as categorized by target regulated product category.

Regulated product category	Country	Regulatory body	Accountability
Veterinary medicines & pesticides	Ethiopia	EAA	MOA
Human medicinal products/cosmetics	Ethiopia	EFDA	MOH
Veterinary medicines/human medicinal products	South Africa/	SAHPRA	MOH
Agricultural pesticides	South Africa	DAFF	DAFF
Human medicinal products/veterinary products/agricultural pesticides	Nigeria	NAFDAC	MOH
Veterinary medicines	Kenya	VMD	MoA
Human medicinal products	Kenya	PPB	MOH
Agrochemicals for pest control	Kenya	Pest control products board	

pharmaceuticals have been regulated together with human medical supplies. Resource scarcity in developing countries challenges the ability to follow American and European pharmacopeias monographs (82).

Lack of integration and disorientation among hierarchical stakeholders in controlling illegal drug trade has been indicated as a problem in Ethiopian veterinary pharmaceutical quality assurance (83). African health services are known to be marred by the availability of analytic infrastructure that is needed to support the analytic quality needed in both regulatory and diagnostic procedures. New drug discovery and product development are also hampered by the level of analytic procedures and institutional credibility. The unreliability of analytic laboratory tests in Africa makes healthcare ineffective in terms of both time and expenditure (84).

3.5.4 Regulatory quality reference platform

From modern global trends in product quality regulation, product quality assurance relies on officially established and agreed-upon facts and parameters from the scientific community. In this regard, pharmaceutical quality assurance relies on pharmacopeia references prepared by a group of experts, even at earlier times before the establishment of respective national regulatory bodies. For example, the initial USP compilation was prepared in 1820. Among the most common ones, USP (8) and BP in 1864 (MHRA) (85), INP (Indian Drug Control Authority), CP Chinese pharmacopeia, or pharmacopeia, in its modern sense, is a legally binding collection, prepared by a national or regional authority, of standards and quality specifications for medicines used in that country or region.

A quality specification is composed of a set of appropriate tests that will confirm the identity and purity of the product, ascertain the strength (or amount) of the active substance, and, when needed, its performance characteristics (86). Reference substances, i.e., highly-characterized physical specimens, are used in testing to help ensure the quality, such as identity, strength, and purity, of medicines. National medicines regulatory policy recommends the inclusion of Pharmacopeia used in their respective quality regulations (87). World health organizations has prepared IP and encourage member states to use it in a bid to globally harmonize regulatory schemes (WHO), the texts cover pharmaceutical starting materials, excipients, intermediates and finished pharmaceutical products (FPPs).

General requirements may also be given in the pharmacopeia on important subjects related to medicine quality, such as analytical methods, microbiological purity, dissolution testing, stability, etc. Unfortunately, no standard pharmacopeia except Egyptian pharmacopeia issued from any one of the African countries can be obtained (9). Instead, many African countries adopt any one of the popular pharmacopeias either through inclusion in their national medicines authorities quality document or informal use according to the ease of its use in a product-specific context. However, the problem arises when marginal quality findings are obtained and judgement via the use of different pharmacopeia results in different outcomes, as recommended acceptance ranges differ between pharmacopeia (88).

3.6 Trends and constraints for local pharmaceutical production in Africa

Low and middle-income countries in the African Region are the only group of countries in which mortality rates due to acute diseases are expected to remain in excess of those for chronic diseases, according to the World Health Organization (WHO) (89). Africa is thought to account for 73% of the AIDS-related fatalities worldwide each year. Only a lack of access to dependable medications and therapy is to blame for this intolerable human cost; thanks to advancements in modern medicine, people living with AIDS can lead happy, meaningful lives. Indeed, mortality increases when people lack access to high-quality medications (89).

Africa's pharmaceutical business is growing because the continent's 13 percent of people have more disposable income and are better able to make ends meet than in the past. Analysts note that between 2010 and 2020, the pharmaceutical market in Africa is expected to grow at an average annual pace of 10% (90). Together with the effects of AIDS, the main factors driving the rise of the pharmaceutical markets in Africa include the development of health insurance programs, greater investments, a better business environment, a developing regulatory framework, and growing trust in generic drugs.

The African pharmaceuticals market—excluding COVID-19 vaccines—has reached $25 billion 2022 and is expected to grow at a 6% five-year CAGR to reach $34 billion by 2027 future base-case scenario (91). This scenario is the same as estimated global pharmaceutical market growth. The implementation and/or growth of universal healthcare across the continent will lead to improved access to medicines. In the future scenario, IQVIA analysts forecast the African pharmaceutical market to reach $40 billion.

However, strong barriers to local pharmaceutical production exist across the African continent; such as, human resource constraints, inadequate infrastructure, high operating costs, weak links between local and international suppliers, and high cost of local commercial capital, poor regulation, industry fragmentation, and low production quality standards. Early experience in countries like Tanzania has shown that majority of the employees in some major drug facilities are from countries like India, due to lack of skilled local workers (92).

Insights from the Analysis of the Local Manufacturing Dynamics in Mozambique and Zimbabwe indicated that, development for local pharmaceutical manufacturing: a favorable economic outlook and support from the international community created the necessary conditions for the development of the nascent pharmaceutical industry in Mozambique, while in Zimbabwe, the presence of an established local industry was instrumental in bringing in favorable, if not always coherent, government regulation (93).

3.7 Trends in the life science of industry

The pharmaceutical sector in Africa is significantly underdeveloped in terms of both production capabilities and innovative practices. The continent's pharmaceutical supply chain is heavily reliant on external funding and imports, with approximately 70% of the pharmaceutical products utilized in Africa being sourced from abroad. This industry is predominantly made up of small, privately-owned enterprises that cater primarily to their local markets. In addition to prominent multinational corporations like Sanofi and GlaxoSmithKline, which have historically maintained a robust presence in the region, a variety of drug manufacturers have recently begun to establish a notable foothold in the market (94).

Africa (kpmg.com/Africa) now hosts some of the leading global innovators and generic manufacturers. Starwin in Ghana, Saidal in Algeria, Universal in Kenya, and Aspen (one of the top 10 generic manufacturers in the world) in South Africa are home grown manufacturers. In some pockets of the continent, predominantly in North Africa and in South Africa, the status of local manufacturing of pharmaceutical products has gained a sturdy foothold (95).

In 2011, South Africa, Egypt, Algeria and Morocco accounted for more than half of the continent's pharmaceutical sales. South Africa has a relatively well-developed pharmaceutical industry, which consists of manufacturers, distributors and dispensers forming the supply-chain (94). South African research-based pharmaceutical companies that previously belonged to either Innovative Medicines SA (IMSA) or the Pharmaceutical Industry Association of South Africa (PIASA), integrated to form a new association named the Innovative Pharmaceutical Association South Africa (IPASA) in April 2013. This created a single entity representing 25 leading pharmaceutical companies operating in South Africa. IPASA currently represents approximately 43% of the pharmaceutical private sector in the country. Overall, 37 African countries have some pharmaceutical production. Significant production capacity is being developed and enriched in Tanzania, Kenya, Uganda, Ethiopia, Ghana, and Nigeria, while Mozambique has recently commissioned an antiretroviral plant with the help of Brazil (94).

3.8 The pharmaceutical market in Africa and the situation of falsified and substandard medicines

The African region represents one of six WHO regions and includes 14% of the world's population spread across 47 countries. The African region is the second most populated region with 95% of the population aged < 60 year (46). The region also faces a high (and increasing) burden of communicable diseases (CDs) and non-communicable diseases (NCDs) (46). Africa's pharmaceutical market is growing in every sector, with a net value worth of US$28.56 billion in 2017, which has increased from a value of US$5.5 billion a decade earlier (96).

In Africa, the reliance on imported pharmaceutical products from foreign countries, coupled with quality assurance management flaws, exacerbates the issue of substandard drugs in the market (97). The issue of defective products in the pharmaceutical market is indeed a critical concern, particularly in the African industry, where poor manufacturing practices contribute significantly to the prevalence of substandard drugs (98). These defective products not only fail to meet therapeutic standards but also pose severe risks to public health, including the potential to exacerbate antimicrobial resistance and cause treatment failures. Implementing a quality-by-design (QBD) approach throughout the pharmaceutical manufacturing process can effectively address these issues. QBD emphasizes the importance of quality being built into products from the very beginning, rather than relying solely on end-product testing. This approach involves a thorough understanding of the manufacturing process and the factors that affect product quality, ensuring consistent performance throughout the product's lifecycle (99).

3.9 Quality by design as solution for quality assurance

The quality-by-design concept is documented to have been coined since the time of 1992 (13) and recommended in toin the area of pharmaceutical manufacturing in 2002 after the FDA realized pharmaceutical quality assurance under conventional quality assurance inefficiency (100). Quality by design refers to a systematic approach to ensuring the quality of medicinal products by utilizing analytical, statistical, and risk management techniques throughout the various stages of design, development, and production. This concept is grounded in the examination of numerous input and process variables, necessitating a comprehensive understanding of both theoretical and analytical aspects related to these parameters (101). Besides the application of QBD in pharmaceutical manufacturing, it has also been described in the improvement of service setting as a systematic approach to design and develop a service through scientific research and quality risk management (19). QBD principles have also been defined for raw material registration (102), non-health related manufacturing activities like automobile industry (103) and non-manufacturing daily life activities like election quality assurance in USA (104) indicating its role in management of diverse human daily life activities.

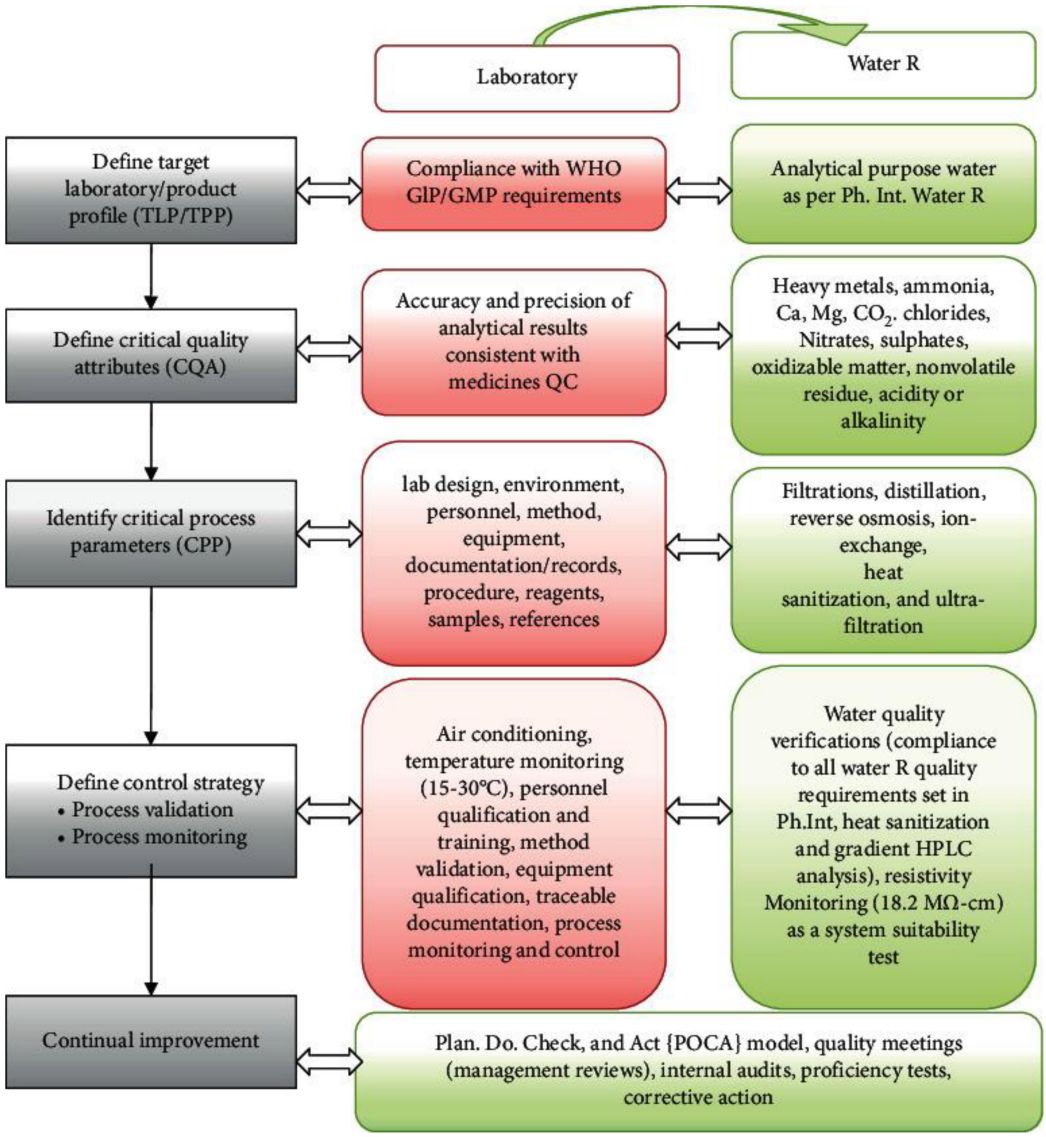

FIGURE 2
Lab QBD workflow and its application to lab water (19). GLP, good laboratory practice; GMP, good manufacturing practice.

The quality-by design approach includes the following components: (93). The target product or service we aspire to obtain is referred to as the quality target product profile (QTPP), which is used to define the characteristics of the final intended output, and this component of QBD helps to identify critical quality attributes (CQA) of the final output. CQA is a set of measurable characteristics for QTPP (93). The product design and knowledge of critical material attributes (CMA), which are characteristics of each input for the desired final outcome; (3) process design and knowledge of critical process parameters (CPPs), relating to CMAs and CPPs to critical quality attributes; (93) a control strategy that includes specifications for the final output, input component parts, as well as controls for steps of the production processes, often referred to as process analytical technologies (PAT); and (93) capability for processes and subsequential improvement (103).

Prior knowledge, mechanistic models, risk evaluation and analysis, quality by design experiments (DoE) and analysis of data, and process analytical technology (PAT) are all necessary QBD tools (100, 103). A study conducted by Suleman et al. (19) in Ethiopia emphasizes that the Drug Quality Control (DQC) laboratory at Jimma University was in accordance with ISO standards. This alignment was evidenced by a comprehensive assessment of quality by design (QBD) parameters, as depicted in Figure 2. A significant element of the study involved the utilization of laboratory water as a representative yet essential example of the QBD-flow, demonstrating how compliance with globally accepted laboratory water quality standards enhances the overall quality control process (19).

3.10 Regulatory harmonization and ICH

In the current era of pharmaceutical marketing, products in countries can be manufactured for domestic consumption and/or

for export, at least to other countries. However, due to the separate regulatory authorities they owe, there are differences in regulatory procedures and customs within each country, which present difficulty and long bureaucratic procedures for manufacturers in registration and product marketing authorization (74). Besides the existing traditional way of quality assurance, no country is found to have documented the mandatory QBD procedure for marketing registration, which holds the same for all countries in the world. There are initiatives for medicine regulatory harmonization (MRH) in Africa. The SADC-MRH of the Southern African Development Community for medicines regulatory harmonization, the ECOWAS-MRH of the West African States Economic Community for medicines regulatory harmonization, and the EAC-MRH of the East African Community for medicines regulatory harmonization are underway. However, the concept of QBD, at least with theoretical concepts, is not on the agenda.

However, the regulatory harmonization committee, commonly referred to as the International Conference for Harmonization (17), was conceived in 1990 with founding members from Europe, the USA, and Japan and reformed into a non-profit legal entity in 2015, now incorporating the above 10 regulatory members. Since its establishment, it has established harmonized regulatory guidelines for quality (Q1-Q14), safety (S1-S12), efficacy (E1-E1) and multidisciplinary (M1-M15) to be used for member regulatory institutions. Among the ICH guidelines, Q8/Q9/Q10 incorporated after 2003 the concept of quality by design with better regulatory flexibility and greater room for continuous product performance improvement (105) .

Under the QBD paradigm, design space and process analytical technologies are key components. Design space is defined as the range of critical process parameters (CPP) that bring critical quality attributes (CQA) of the medicinal product within the acceptable limit, and process analytical technologies refer to the scientific tools to continuously monitor processes and output at every stage of the cycle (106). Thinking quality assurance via quality by design is therefore not easily thinkable without regulatory system harmonization. Some of the variations to be considered for harmonized quality by design perspectives therefore need to look for the following issues (Table 4).

TABLE 4 Comparison of pharmaceutical manufacturing by quality by design and traditional approach (103).

Component	QBD based approach	Traditional approach
Medicinal development	Empirical knowledge	Systematic multivariate experiments
Manufacturing process	Fixed	Adjustable within the design space
Control of processes	Offline analysis wide or slow response	PAT used for feedback and support for real time correction
Specification of final product	Based on batch data	Desired product performance specification
Method of control	intermediate product and finished product testing	Risk based controlled, shifted upstream, real time release
Life cycle management	Post approval changes needed	Continual improvement enabled through design space
Batch failure and recall	Reduced	To high

3.11 Implementing quality by design (QBD) in pharmaceutical manufacturing companies: Can the African medicine environment benefit from it?

Woodcock characterized a high-quality pharmaceutical product as one that is devoid of contamination and consistently provides the therapeutic advantages that are guaranteed on the label to the consumer (12). The US Food and Drug Administration promote risk-based methodologies and quality by design (QBD) principles in pharmaceutical development and manufacturing. This approach emphasizes embedding quality from the design phase rather than relying solely on increased testing. QBD involves understanding the manufacturing process and identifying potential risks to product quality, allowing manufacturers to implement controls that ensure consistent quality (107). This proactive strategy is considered more effective than traditional methods that focus on extensive end-product testing.

Medicine is widely recognized as a specialized commodity, yet the advancement of the pharmaceutical industry relies heavily on innovation and production processes. Nonetheless, numerous grievances have emerged from the pharmaceutical sector regarding stringent regulations aimed at addressing defective products in the market, especially in African nations where the regulatory framework remains underdeveloped (6). The implementation of quality by design principles and methodologies in the development of pharmaceuticals in Africa is crucial for ensuring the production of defective free quality products. This is achieved through the analysis of root causes, as illustrated in Figure 3.

The pharmaceutical industry faces increased global competition and the impact of information technology, prompting a need for improved operational performance and product quality (41, 42). Key challenges include time to market, product quality, regulatory compliance, waste management, cost reduction, and cycle time. This has led to a rapid transformation in the sector, supported by regulatory authorities' willingness to embrace innovative approaches for enhancing quality and safety. Quality by design (QBD) is now seen as essential for achieving these performance improvements (11, 72).

The advantages of implementing quality by design (QBD) in manufacturing are extensive and cover multiple dimensions (41, 42). This is especially pertinent in Africa as well as on a global scale. A comprehensive examination of the benefits associated with the incorporation of quality by design principles in the industrial sector was discussed in the current review. QBD minimizes variability and defects, leading to fewer rejected batches and less rework. This reduction in waste and inefficiency significantly cuts production costs. For instances, in several African nations, drug regulatory authorities have withdrawn a specific batch of Johnson & Johnson children's cough syrup following reports from officials in Nigeria indicating elevated toxicity levels in that particular batch

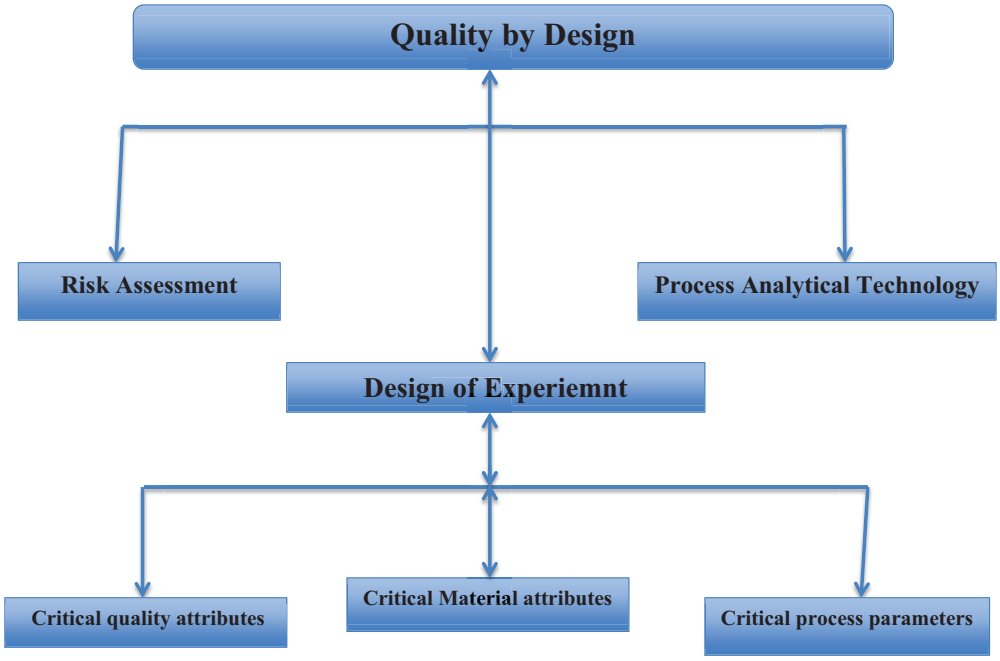

FIGURE 3
Terms and tools of quality by design in drug development.

of the medication (86). This situation would not have occurred if the companies had implemented quality by design in their manufacturing practices.

By understanding the critical quality attributes (CQAs) and critical process parameters (CPPs) early in the development phase, companies can streamline their processes, reducing the time needed for product development (89). Quality by design is a systematic approach to pharmaceutical development that emphasizes understanding and controlling variability in manufacturing processes to ensure consistent product quality. However, many local manufacturers in Africa are still in the early stages of adopting these practices. As a result, the pharmaceutical markets in many African countries heavily rely on foreign imported medicines to meet their healthcare demands. This dependency on imports is often due to the higher standards of quality and reliability that these foreign products are perceived to have compared to locally produced medicines. Strengthening local manufacturing capabilities through the adoption of QBD and other advanced practices is essential for reducing this reliance and ensuring that the continent can sustainably meet its health needs with locally produced pharmaceuticals (91). This is especially pertinent in Africa as well as on a global scale. The general benefit associated with the incorporation of quality by design principles was discussed below:

3.11.1 Higher operational flexibility

With improved process understanding made possible by QBD, producers may adapt their operations to changing raw material or environmental conditions without sacrificing quality (90). Companies can continuously optimize their manufacturing processes according to the methodology of quality by design (QBD) principle (93).

3.11.2 Material sourcing flexibility

Diverse material sourcing: Because QBD places a strong emphasis on identifying material properties, manufacturers can get raw materials from a variety of vendors without compromising the final product's quality (92). Because supply networks may be less dependable in African countries, this flexibility is especially important. According to a Ghanaian assessment, poorly controlled drug supply chains seriously undermine confidence, and doubt regarding the quality of medicines is not eradicated but rather handled (94). Consequently, using quality by design principles may aid in resolving these supply chain issues.

3.11.3 Reduced end-process testing

Real-time quality control: By incorporating strategies for real-time monitoring and control, QBD lessens the dependence on end-process testing. This method guarantees that any problems are identified and fixed as soon as possible while speeding up the manufacturing process (95).

3.11.4 Improved product consistency and robustness

Enhanced product quality: By focusing on designing quality into the product from the beginning, QBD ensures that the final product consistently meets predefined standards, resulting in safer and more effective products for patients. A report has been shown that the issue of substandard pharmaceutical products in Africa remains a significant challenge, with an estimated prevalence of 18.9% (95% CI: 14.3–23.5%) (46). Quality by design (QBD) is an essential instrument for pinpointing the root causes of quality failures in finished pharmaceutical products; however, its implementation in Africa has not yet been thoroughly explored. A study in Turkey showed that preformulating core

excipients improved insights into tabletability and compatibility (97). It examined process parameters like compaction force and formulation variables such as super-disintegrant concentration within a quality by design framework. The optimized formulation was tested and validated within the established design space.

3.11.5 Fewer rejected batches and rework

Increased yield: The thorough understanding and control of manufacturing processes under QBD result in fewer batch failures, leading to higher yields and reduced costs associated with rework or disposal (98). This reduced the daily quality product notifications, especially in Africa. For instance, the Ministry of Health Advisory regarding the Medical Product Alert issued by the WHO pertains to the recall of substandard pediatric medicines contain un-acceptable amount of diethylene glycol and ethylene glycol, which have been identified in the WHO Region of Africa (99). These contaminants when consumed in unacceptable amounts are detrimental to ones health.

3.11.6 Faster manufacturing, testing, and approval times

Efficiency gains: Streamlined processes and reduced testing requirements lead to faster manufacturing cycles, quicker testing procedures, and more efficient batch approval processes. This speed is critical for getting products to market more rapidly (108). In Africa, the limited application of quality by design (QBD) has resulted in an extended drug registration approval process. For example, a report from South Africa revealed that the median approval time reached a lengthy 2,092 calendar days between 2011 and 2017, as determined by the Medicine Control Council's procedures (109).

3.11.7 Simplified regulatory compliance

Regulatory alignment: QBD principles align with global regulatory expectations, leading to fewer regulatory hurdles and a smoother approval process (110). The comprehensive documentation generated during QBD-based development simplifies compliance efforts.

For manufacturing companies in Africa and across the globe, the adoption of QBD can lead to more competitive operations, improve product availability, and enhance patient safety. The paradigm shift toward QBD fosters innovation, reduces dependency on reactive measures, and builds a stronger foundation for sustained quality, ultimately benefiting both manufacturers and patients worldwide (96).

4 Concluding remarks and future roadmaps

The review highlighted the considerable challenges faced in ensuring the availability of high-quality, safe, effective, and affordable essential medicines across African nations, aligning with the third priority objective of the global sustainable development agenda. Key obstacles include: Financial constraints limit access to quality medications, particularly in resource-poor regions. The prevalence of substandard medicines and ineffective regulatory systems was exacerbated by gaps in regulatory enforcement and poorly structured penalties for non-compliance. A regional analysis from the WHO indicated that 42% of reports concerning defective-quality medicines originate from Africa, underscoring the continent's regulatory shortcomings. Problems like inadequate law enforcement, corruption, a shortage of human resources, and inconsistent regulatory frameworks exacerbate the complexity of product regulation in African countries. Therefore, strengthening regulatory framework, adoption of the principle of QBD, capacity building and training, financial support and investments, strengthening surveillance and reporting systems, and regional collaboration and harmonization should be taken into account to enhance the African medicine landscape.

Authors contribution

HKH: Writing – review & editing, Visualization, Validation, Methodology, Investigation, Data curation. YTM: Writing – original draft, Writing – review & editing, Data curation, Validation, Methodology, Visualization, project administration, Investigation. AT: Writing – review & editing, Visualization, Validation, Methodology, Data curation. YO: Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Unmet medical needs definition and incentives: stakeholders perspectives on the reform of the EU pharmaceutical legislation

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Introduction: The 2020 pharmaceutical strategy for Europe stressed that rethinking regulatory policies to foster innovation in disease areas with unmet medical needs (UMN) is one of the European Commission's (EC) priority areas. To understand stakeholders' views regarding appropriate UMN criteria and incentives, the EC developed a survey and launched it for public consultation between September and December 2021. This study aims to assess stakeholders' views on the policy revisions proposed by the EC, particularly those regarding the definition of UMN, its criteria and incentives and evaluate how stakeholders' views are reflected in the proposed reform of the EU pharmaceutical legislation of 2023.

Methods: The public consultation survey comprised 14 questions including multiple-choice and open answer questions about the reform of the pharmaceutical legislation. A mixed-method analysis was conducted on publicly available data of stakeholders' responses, including descriptive and quantitative statistics for multiple-choice questions and a qualitative thematic framework analysis for open answer questions. A subgroup analysis was performed to assess differences and similarities in stakeholders' views, and results were compared with the proposed reform of the EU pharmaceutical legislation.

Results: A total of 478 participants completed the survey consisting of 36% industry, 19% end-users, 17% healthcare providers, 7.5% researchers and 7.5% public bodies. All stakeholder groups favored including "absence of satisfactory authorized treatment" and "disease seriousness" as defining criteria for UMN. However, stakeholders disagreed on including the criterion "lack of access for patients," with public bodies and industry being less in favour. Industry favored maintaining or having additional incentives like transferable exclusivity vouchers on top of current intellectual property rights to foster innovation. In contrast, other stakeholders supported alternative proposals, namely enhancing the use of scientific advice and implementing expediting measures for regulatory evaluation of medicines targeting UMN.

Conclusion: Stakeholders agreed on including availability of alternatives and disease seriousness in the UMN definition but highlighted its ambiguity. Industry participants supported additional incentives like transferable exclusivity vouchers, whereas others preferred scientific and regulatory support. These findings underscore the need for further discussion on UMN criteria and incentives to stimulate innovation while ensuring patient-centric outcomes and equitable access to medicines across Europe.

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KEYWORDS

unmet medical need, pharmaceutical legislation, healthcare policy, medicines development, patient need, innovation, sustainability, incentives

1 Introduction

In response to the COVID-19 pandemic, Europe has been re-evaluating its regulatory and health policy framework, resulting in proposals for significant legislative changes, especially in pharmaceutical development. This began with the publication of the Pharmaceutical Strategy of 2020 for Europe, describing general policy initiatives for developing a patient-centered, future proof and crisis-resistant pharmaceutical regulatory framework (1). The aims of the pharmaceutical strategy were (i) ensuring timely and equitable access to safe medicines across the EU, (ii) enhancing supply security regardless of geographical location, (iii) fostering innovation in medicine research and production, (iv) promoting environmental sustainability, and (v) addressing antimicrobial resistance (AMR) and pharmaceutical pollution (1). To achieve these objectives, the European Commission (EC) published its roadmap for the reform of the existing EU pharmaceutical legislation (Regulation EC726/2004, Directive EC83/2001), proposing concrete policy priority areas for legislative change (Figure 1) (2). Subsequently, the EC developed a survey which was made available for public consultation between September and December 2021, containing concrete policy proposals related to the reform of the EU pharmaceutical legislation. This public consultation aimed to collect views of stakeholders and members of the general public on the pharmaceutical policy measures proposed by the EC. On the 26th of April 2023, the EC published its proposal for the reform of the EU pharmaceutical legislation (2).

In both the Pharmaceutical Strategy of 2020 for Europe and the proposal for the reform of the pharmaceutical legislation, there is a notable increased emphasis on strategies to steer research and development (R&D) to address unmet medical needs (UMN) (1, 2). The EC highlights the importance of addressing UMN, as many patients suffering from serious diseases still lack appropriate treatments and current investments in developing medicines do not always prioritize the greatest UMN. Moreover, the EC's proposal for the reform of the EU pharmaceutical legislation aims to shift innovation from a supply-driven model to a more needs-driven approach, and contribute to better serving patients and health systems (2).

Currently, the EC defines the concept of UMN as *"a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorized in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected."* (3). This concept has been officially applied as an eligibility criterion for innovative medicines to facilitate marketing authorization under the form of conditional marketing authorization[1] (3, 4). Additionally, it has been informally applied in various regulatory practices such as accelerated assessments, priority medicines (PRIME) scheme, authorizations under exceptional circumstances, and scientific advice procedures. Thus, already today the UMN concept enables, to a certain extent, regulatory flexibilities to support development and evaluation of medicines targeting UMN. However, in 2019, Vreman et al. reported differing understanding between stakeholders on the UMN concept, its scope and practical application in regulatory frameworks (5).

The EC's proposal for the reform of the EU pharmaceutical legislation includes a new definition for UMN [Proposal for a Directive (EC) No 2023/0132, Art. 83(1)] and, within the context of rare diseases, an additional definition for high UMN [Proposal for a Regulation (EC) No 2023/0131, Art. 70(1)] (6, 7). Nevertheless, considerable reaction and commentary has emerged on the proposed legislation, particularly concerning the UMN definition and its connection to anticipated incentives for medicines aimed at addressing these needs (8). Whilst agreement exists that targeted incentive measures are key to fostering innovation in pharmaceutical development, it remains questionable which type of incentive measures are most appropriate to steer innovation in disease areas with UMN (9, 10). The diverging interpretation of the UMN concept results in a lack of systematic interpretation and application of the UMN definition and its associated incentives in practice (5).

This study aimed to assess the views of stakeholders (including industry, public bodies, patients, healthcare providers and researchers) and the general public on the EC's policy proposals outlined in the Pharmaceutical Strategy of 2020 for Europe regarding (i) general perceptions on the UMN definition, (ii) criteria to characterize UMNs, and (iii) incentive measures to support innovation in UMN areas. Additionally, the study seeks to perform an inter-stakeholder comparison to understand differing perspectives and assess how these are reflected within the proposed reform of the EU legislation. Finally, this study aims to formulate actionable recommendations based on these insights.

2 Materials and methods

This study consisted of (i) a quantitative and qualitative analysis of stakeholders' responses on the EC's public consultation survey in preparation of the reform of the pharmaceutical legislation and (ii) a comparison of stakeholders input with the final content included in the proposed reform of the EU pharmaceutical legislation published in April 2023. It is important to note that this research is a secondary

Abbreviations: AMR, Antimicrobial resistance; HCPs, Healthcare professionals; HUMN, High unmet medical need; HTA, Health Technology Assessment; IPR, Intellectual property rights; MA, Marketing authorization; MAH, Marketing authorization holder; MPs, Medicinal products; PED, Patient experience data; PP, Patient preferences; PRO, Patient reported outcome; RDP, regulatory data protection; R&D, Research & development; SPC, Supplementary protection certificate; UMN, Unmet medical need.

1 *Conditional marketing authorization* is a pragmatic tool for the fast-track approval of a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks, and the applicant should be in a position to provide the comprehensive clinical data in the future.

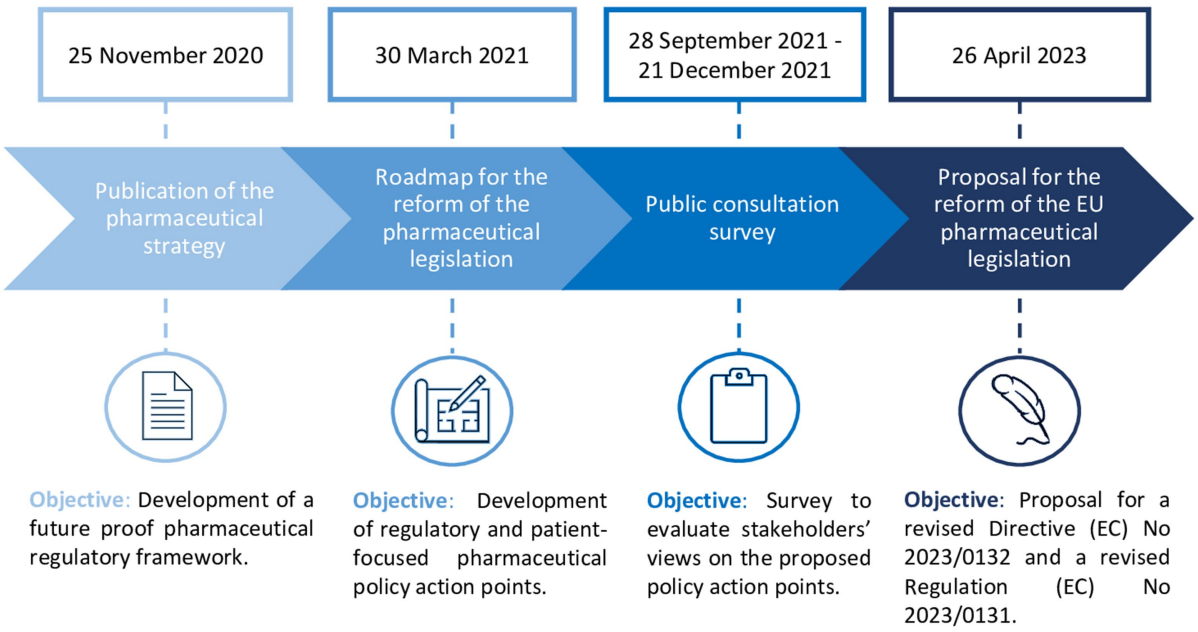

FIGURE 1
Timeline of the European Commission's proposal for the reform of the EU pharmaceutical legislation (4).

analysis of publicly available data, not primary research. While the EC has published a summary report of this data, this study provides an additional independent academic examination of the empiric data focusing on the UMN definition and related incentives to steer R&D (11). This study supplements the EC summary report with additional quantitative assessments and in-depth inter-stakeholder comparisons of both quantitative and qualitative data.

2.1 Public consultation survey analysis

The public consultation survey consisted of 14 questions including 10 multiple-choice questions and 4 open-ended questions. Each multiple-choice question contained several multiple-choice sub-questions as well as an open-ended answer field in which respondents could further clarify their choice. For the scope of this research, survey questions 1, 3, 4 and question 14 were analyzed as they primarily focused on proposed policy measures for (i) defining the concept of UMN and (ii) potential regulatory incentive measures for driving pharmaceutical development. More specifically, questions 3 and 4 were multiple-choice questions related to the UMN definition and incentives to drive R&D, with both questions also containing an open answer box. Questions 1 and 14 were open-ended questions which were also screened for input relating to the research topic. The exact survey questions can be found in Supplementary Table S1.

The data extraction table including all stakeholders' responses to the public consultation was consulted via the website of the EC and used for secondary analysis (1). Respondents were categorized into five overarching stakeholder clusters including (1) public body, (2) industry, (3) researchers, (4) end-users, (5) healthcare providers (HCPs). This cluster classification was performed based on which stakeholder subtype respondents mostly identified itself with. All respondents who identified as "other" in the public consultation survey were clustered separately as "other" and their responses were excluded from the analysis. The cluster classification maintained in this analysis slightly differs from the EC's summary report as the EC screened respondents who identified as "other" and partially re-allocated them to another stakeholder group, causing slight differences in the included number of respondents per cluster (11).

TABLE 1 Scoring of multiple-choice answer options using the VLOOKUP formula.

Score	Multiple-choice answer option
0	Do not know
1	Not important
2	Slightly important
3	Fairly important
4	Important
5	Very important

2.1.1 Quantitative analysis

The answer options from the multiple-choice questions included in this analysis ($n = 2$) were scored from 0 to 5 using the VLOOKUP formula in Microsoft Excel (Table 1).

For each stakeholder cluster, the individual scores from respondents were summed to calculate the average score for each stakeholder cluster per question. The multiple-choice sub-questions that were answered with "do not know" (i.e., score 0), were excluded from this calculation as they would negatively impact the calculated average score. Additionally, the overall average of these stakeholder group averages was calculated. Subsequently, heatmaps were developed in Microsoft Excel to visualize each stakeholder cluster's level of satisfaction with the proposed policy measure. The conditional

formatting tool in Excel was used to automatically color (i.e., green, orange, yellow and red) each average value in the heatmap relative to another.

2.1.2 Qualitative analysis

An extraction table was made in Microsoft Excel including all responses on the open-ended questions ($n = 586$) as well as the open-answer text fields ($n = 500$) of the multiple-choice questions per stakeholder cluster. Subsequently, a thematic framework analysis was conducted, and inductive coding was performed to categorize and classify stakeholders' responses under specific topics (2). A framework matrix was developed and the answers for each question were summarized per stakeholder cluster to perform an inter-group comparison of stakeholder responses.

2.2 Comparative analysis with the proposed revised legislation

A systematic comparison was conducted between analyzed average quantitative results and qualitative stakeholder suggestions and the formulation of the UMN definition, its criteria and proposed incentives included in the proposal for the reform of the EU pharmaceutical legislation. First, specific stakeholder recommendations relating to revisions of the EU pharmaceutical legislation were identified. Secondly, a side-by-side comparison of these stakeholder recommendations with the legislative proposal was performed. To do so, the proposed Regulation [Proposal for a Regulation (EC) No 2023/0131] and Directive [Proposal for a Directive (EC) No 2023/0132] included in the reform of the EU pharmaceutical legislation were reviewed to identify legal changes compared to the existing pharmaceutical legislation. The comparison evaluated the degree of alignment between stakeholder recommendations and the proposed policy changes, noting where stakeholder input was directly incorporated, where modifications were made and potentially suggestions were indirectly or implicitly included, and where suggestions were excluded.

3 Results

A total of 478 responses on the public consultation survey were received. The industry group was the largest representing up to 36% of the total number of respondents, followed by end-users (19%), healthcare providers (17%), researchers (7.5%), and public bodies (7.5%) (Figure 2).

3.1 Conflicting suggestions on general stakeholder perspectives related to the UMN concept: qualitative results

Via open answer boxes and open-ended questions, stakeholders highlighted that for many disease areas patients still face (high) UMN and noted that the current UMN definition and regulatory framework lack clarity and comprehensiveness. With respect to the UMN concept and its definition, stakeholders reported on three main aspects (i) scope, (ii) flexibility, and (iii) binary nature of the UMN concept. However, perspectives highly differed between stakeholder groups:

(i) Scope of the UMN concept: HCPs expressed concerns regarding the restrictive nature of the current UMN definition, emphasizing the

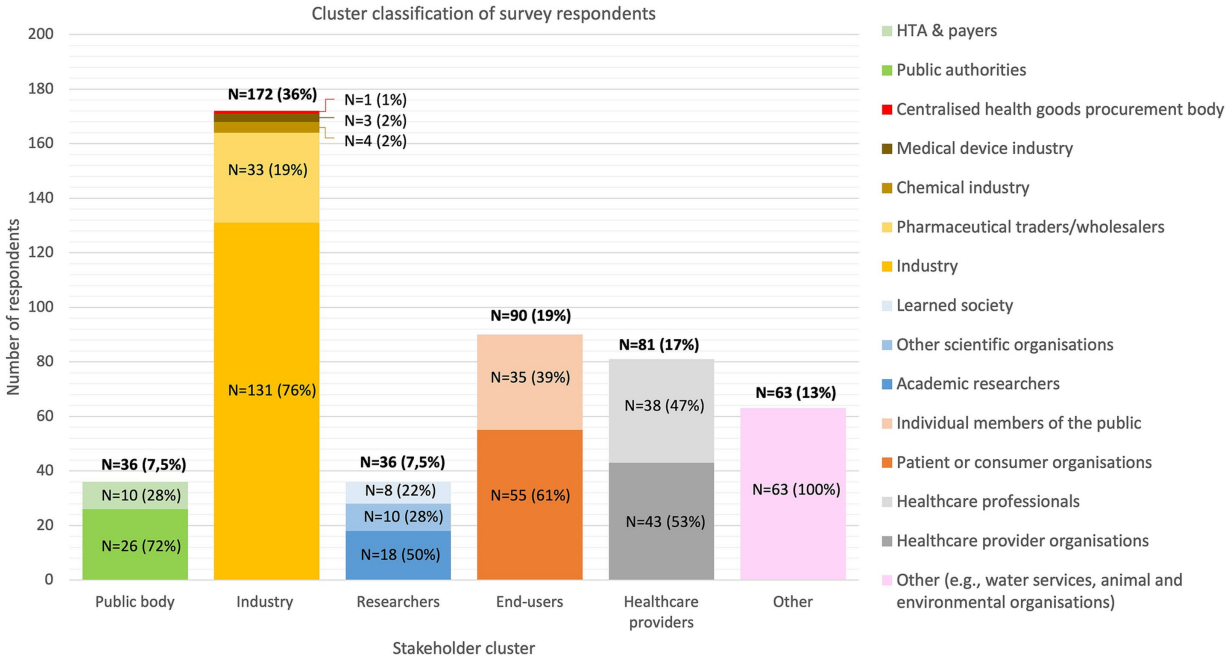

FIGURE 2
Distribution of the survey respondents by stakeholder group and subgroup classification. Stakeholders that did not identify with one of the above-mentioned clusters were assigned to the "other" cluster. HTA, Health Technology Assessment body.

need for a broader scope that considers factors beyond the availability of alternative treatments. Additionally, both researchers and HCPs highlighted the importance of expanding the definition to include diagnostics and HCPs also suggested including supply problems. Rapid and accurate diagnostics were deemed essential for effective healthcare delivery and challenges related to medication supply disruptions were recognized by HCPs as significant contributors to UMN.

(ii) Clarity of the UMN concept: HCPs and researchers cautioned against a rigid UMN definition and one-size-fits all approaches, with strict pre-defined eligibility criteria, suggesting a flexible, multi-stakeholder-endorsed approach to better address healthcare complexities. Conversely, others (i.e., public bodies, industry) emphasized the necessity of clear, quantifiable criteria in a structural framework to guide innovation and address evidence gaps, advocating for an adaptable definition that evolves over time. Proposals and reflections on these UMN criteria are discussed under 3.2.

(iii) Binary approach to the UMN concept: Acknowledging the nuanced nature of UMN, public bodies and end-users emphasized the need for a non-binary approach that quantifies different levels of need. Suggestions included grading UMN based on severity and prioritizing incentives, accordingly, thereby accommodating the diverse healthcare landscape and varying degrees of need across different disease areas. Stakeholders underscored the dynamic nature of UMN, advocating for an adaptable definition that evolves over time to reflect changing healthcare priorities and emerging needs. This approach emphasizes flexibility and responsiveness.

3.2 Stakeholder perspectives on the proposed UMN definition, its criteria and respective implementation in the EU legislative proposal

3.2.1 Quantitative results and the respective implementation in EU legislative proposals

In the public consultation survey, the EC proposed four criteria to be potentially included in the UMN definition: (i) absence of a satisfactory treatment authorized in the EU, (ii) seriousness of a disease, (iii) major therapeutic advantage over existing treatment(s), and (iv) lack of access for patients across the EU to an authorized treatment. Quantitative survey question analysis (Figure 3) showed that stakeholders considered the following criteria as the most important criteria to define UMN: (i) the absence of satisfactory treatment authorized in the EU and (ii) the seriousness of the disease. For the other two proposed criteria the opinions are relatively less favorable; the public bodies and industry stakeholder group indicating on average relatively lower importance for the criterion on lack of access for patients across the EU to an authorized treatment.

Possible criteria for defining UMN as proposed in the public consultation survey

		Public body	Industry	Researchers	End-users	HCPs	Overall stakeholder average	Application in the reform of the pharmaceutical legislation
Proposed criterion 1	Absence of a satisfactory treatment authorised in the EU.	4,78	4,76	4,66	4,62	4,45	4,65	✓
Proposed criterion 2	Seriousness of a disease.	4,47	4,48	4,26	4,36	4,43	4,40	✓
Proposed criterion 3	A new medicine has major therapeutic advantage over existing treatment(s).	4,19	4,20	4,26	4,29	4,22	4,23	◐
Proposed criterion 4	Lack of access for patients across the EU to an authorised treatment.	3,67	3,37	4,19	4,18	4,23	3,93	✗

Legend

- Relatively high average score — ✓ Full application in the proposed legislation
- Relatively medium average score — ◐ Partial application in the proposed legislation
- Relatively low average score — ✗ No application in the proposed legislation

FIGURE 3
Heatmap of quantitative stakeholders' ratings of proposed unmet medical need criteria. Average scores range from 1 to 5 and were colored relatively to another using the conditional formatting tool in Excel. The highest average scores are indicated in green; the lowest average values are indicated in red, and the values in between are colored in orange/yellow. EU, European Union; HCPs, Healthcare providers; UMN, Unmet medical need; QoL, Quality of life.

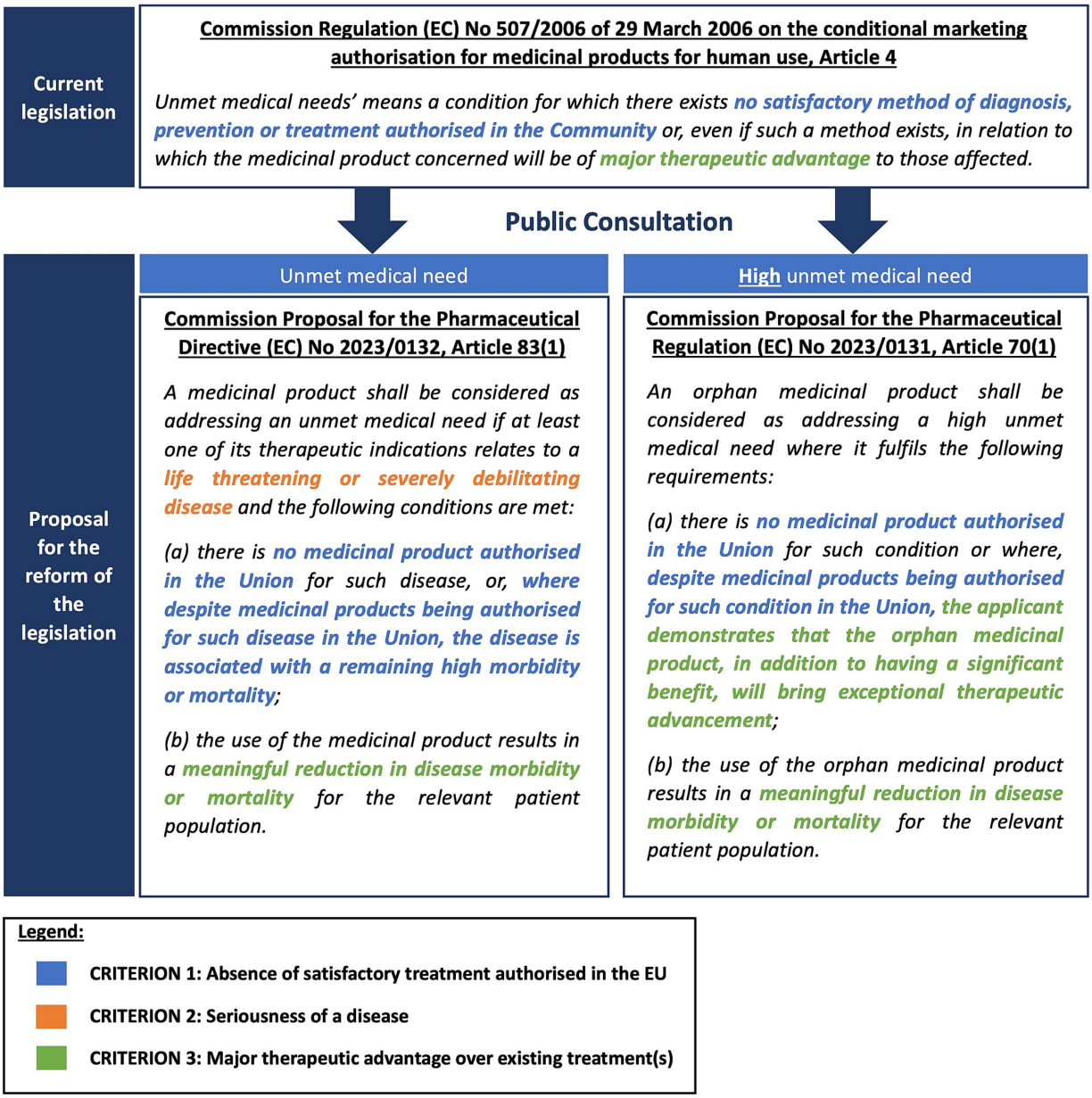

FIGURE 4
The definition of (high) unmet medical need in the existing and proposed pharmaceutical legislation.

Figure 4 provides an overview of the definition of UMN included in the existing pharmaceutical Regulation [(EC) Regulation No. 507/2006], concerning conditional marketing authorization, and the proposed definition included in the proposal for the reform of the pharmaceutical legislation published in April 2023 (Figure 4). The revised legislative package introduces two definitions: one for regular UMN (Proposal for a Directive 2023/0132) and another for orphan medicinal products (Proposal for a Regulation 2023/0131), distinguishing between UMN and high UMN, respectively.

As indicated in Figure 4, both the criterion on the absence of a satisfactory treatment authorized in the EU (Proposed criterion 1) and the major therapeutic advantage over existing treatments (Proposed criterion 3) were retained in the new legislative proposal. The wording for the proposed criterion 3 was updated from "be of major therapeutic advantage to those affected" to "results in a meaningful reduction in disease morbidity or mortality for the relevant patient population." In addition to these two criteria, the seriousness of the disease (Proposed criterion 2) was included in the new legislative proposal. This criterion only applies to the regular UMN definition [Proposal for a Directive 2023/0132] and is not included in the orphan definition of high UMN [Proposal for a Regulation 2023/0131]. One of the proposed criteria, the lack of access (Proposed criterion 4), was excluded from the proposed definition.

3.2.2 Qualitative results and the respective implementation in EU legislative proposals

In addition to the closed multiple-choice questions, participants were given the opportunity to provide complementary

input regarding the proposed criteria. Figure 5 presents an overview of the additional qualitative suggestions offered by participants in the public consultation survey related to the proposed UMN criteria.

3.2.2.1 Proposed criterion 1: absence of a satisfactory treatment authorized in the EU

Both industry representatives and HCPs stressed the importance of addressing diseases where existing medication has poor safety profiles or limited efficacy in some subpopulations. This suggestion is reflected in the new proposed UMN definition since medicines addressing diseases with a remaining high morbidity or mortality are still considered targeting an UMN despite the presence of alternative medicines. Public bodies advocated considering off-label use as part of alternative treatments, while industry respondents argued against including off-label treatments since they believe these treatments lack established safety and efficacy. The proposed UMN definition excludes off-label use, focusing solely on medicines authorized in the European Union. Some industry respondents suggested broadening the definition to include formulations with poor pharmacokinetic profiles, but this suggestion has not been explicitly adopted. It is unclear whether pharmacokinetic improvement would be considered as an exceptional therapeutic advancement (a criterium in the high UMN definition of the Regulation, see Figure 4).

3.2.2.2 Proposed criterion 2: seriousness of the disease

Six suggestions could be identified based on the stakeholder responses to the public consultations. First, end-users proposed to include co- and multi-morbidities in the consideration of UMN. Second, most respondents suggested incorporating the burden of illness and its impact on patients' quality of life (QoL) alongside overall survival when assessing disease seriousness within specific patient populations. However, these considerations are not explicitly included in the proposed definition. Nevertheless, there is implicit recognition in the legislative proposal that diseases severely impacting QoL and burden of illness could be categorized as severely debilitating. The phrase "remaining high morbidity" may also relate to QoL. Beyond the direct health impacts, several other factors affecting patient QoL were noted by stakeholders. Third, end-users highlighted socioeconomic circumstances, and demographics as important QoL indicators. The integration of these aspects into the new UMN definition remains unclear.

Fourth, industry representatives advocated for including disease duration as a criterion for assessing disease seriousness, which is currently absent from the proposed UMN definition. In addition to patient QoL, industry, end-user, researcher, and HCP participants stressed that seriousness should encompass not only the impact on the patient's life but also on their broader environment (e.g., family, society, caregivers). Moreover, industry participants highlighted the need to consider financial impacts on families and caregivers, including indirect costs such as caregiving services and lost income. Sixth, end-users emphasized the importance of using patient-reported metrics to evaluate disease seriousness, though this is not explicitly mentioned and may have been included under the legislation without specific reference.

3.2.2.3 Proposed criterion 3: a new medicine has major therapeutic advantages over existing treatments

Respondents emphasized the necessity for a clear understanding of the terminology "major therapeutic advantage." Although this term is not literally used in the proposed UMN definition, it may be implicitly covered via the terminology "meaningful reduction in disease morbidity or mortality" in part (b) of the definition, which is slightly more concrete and hence partly addresses this reported concern. This terminology, and more specifically the word "meaningful," could potentially point at the perception and experience of patients, which could potentially address the suggestions from public bodies and end-users to incorporate improvements in patient-relevant outcomes. In this regard, end-users underlined the importance of patient involvement and using patient-experience data to gain insight into the "true" benefit that a particular medicine might bring to patients. However, the proposed legislation does not explicitly state whether patient-reported outcomes will be utilized for this assessment. Furthermore, the inclusion of criteria such as ease of self-administration, and improved adherence to assess therapeutic advantage remains unclear in the proposed UMN definition.

3.2.2.4 Proposed criterion 4: lack of access for patients across the EU to an authorized treatment

For "lack of access for patients across the EU to an authorized treatment" no specific additional qualitative suggestions were formulated apart from reflections on the relevance of this criterion. For instance, HCPs and industry respondents expressed concerns about including this criterion in the UMN definition, arguing that access issues are primarily due to economic decisions by Member States or pharmaceutical companies. They warned against attributing lack of access to patients as a criterium, as it is often influenced by national responsibilities and payment systems.

3.2.2.5 Additional proposed criteria: disease prevalence and incidence

For every stakeholder group at least one respondent emphasized the significance of incorporating disease prevalence and incidence rates into the definition of UMN. More specifically, public bodies suggested considering the number of individuals who could potentially benefit from treatment, highlighting the importance of understanding the epidemiological landscape of the disease. Despite these suggestions, disease prevalence and incidence are not included in the proposed UMN definition in the legislation.

3.3 Stakeholder perspectives on the proposed incentive measures to drive R&D in UMN-areas and its respective implementation in the EU legislative proposal

3.3.1 Quantitative results and the respective implementation in EU legislative proposals

The EC proposed in the public consultation survey seven incentive measures to foster innovation and potentially encourage companies to focus R&D in disease areas with (high) UMN. These proposals included (1) public listing of priority therapeutic areas, (2)

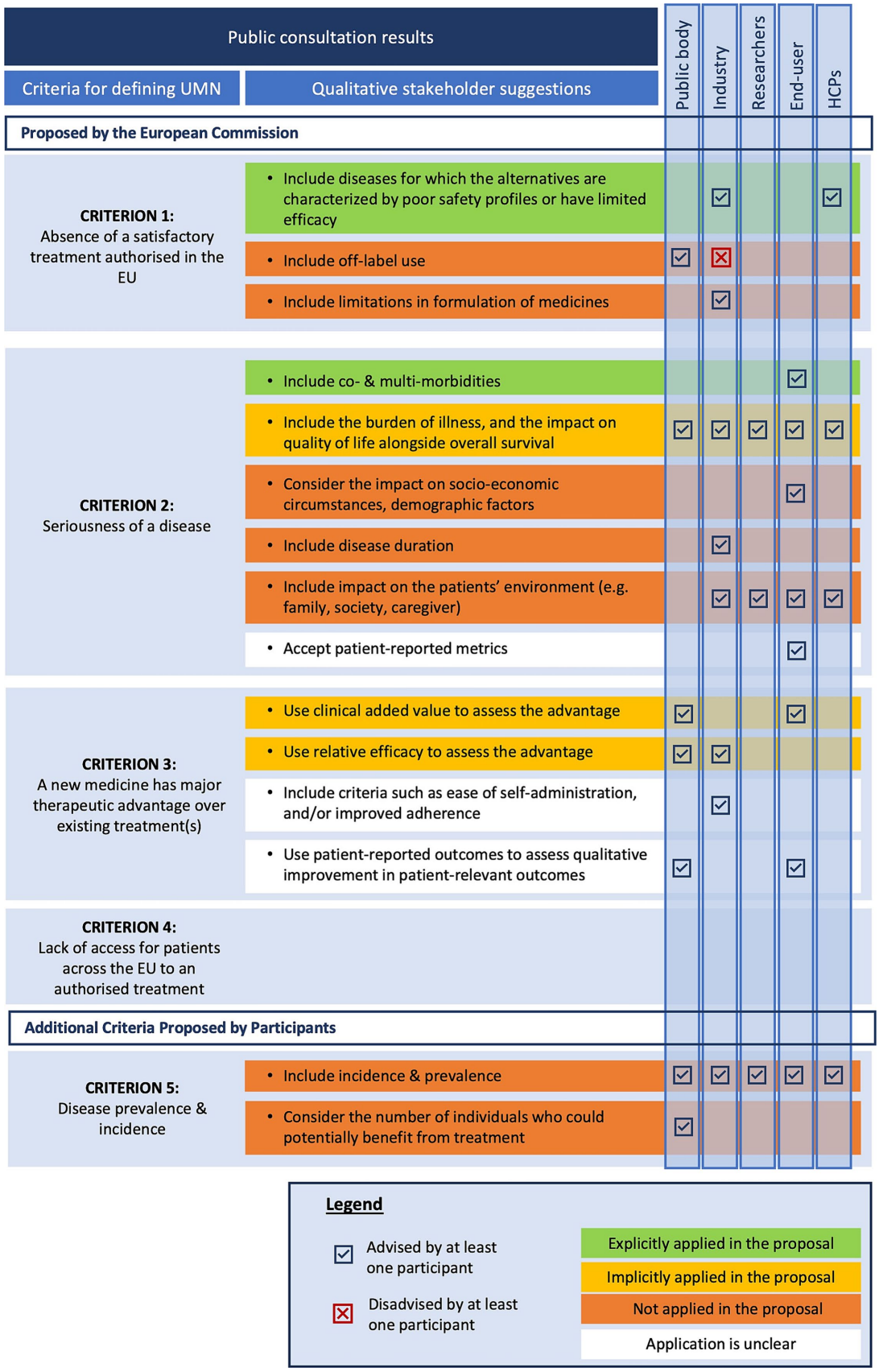

FIGURE 5
Stakeholder suggestions on unmet medical need criteria versus the legislative changes in the reform proposal. EU, European Union; HCPs, Healthcare providers; UMN, Unmet Medical Need.

early scientific support and expediting measures for review/authorization, (3) maintaining current market and data protection periods, (4) introducing new incentives on top of the current regulatory protection periods, (5) providing different regulatory protection periods depending on the medicines' purpose, (6) reducing the current regulatory protection periods and (7) requiring transparent reporting from companies on R&D costs and received public funding.

The quantitative survey analysis (Figure 6) showed that on average, proposal 1 and 2 were relatively most welcomed by stakeholders. While the proposed incentive measures regarding regulatory protection periods (proposal 3, 4, 5, 6) were considered relatively less favorable by most stakeholders, industry respondents in particular indicated to be strongly in favor of maintaining or receiving additional regulatory protection periods for medicines targeting an UMN (proposal 3, 4). Moreover, industry was the only stakeholder group that responded negative to the proposal for enhancing transparency on R&D costs and received public funding for developing novel medicines addressing UMN (proposal 7).

3.3.2 Qualitative results and the respective implementation in EU legislative proposals

In addition to the closed multiple-choice questions, participants had the possibility to provide complementary input regarding the proposed incentive measures outlined in the public consultation survey. Figure 7 presents an overview of the additional qualitative suggestions offered by participants related to the UMN incentives.

3.3.2.1 Proposal 1: public listing of priority therapeutic areas

While most stakeholders were strongly in favor of developing public listings of priority therapeutic areas, industry respondents in particular stressed that more regulation is needed on how such priority lists are being composed and revised. This proposed incentive

Possible incentive measures to support innovation for UMN as proposed in the public consultation survey

		Public body	Industry	Researchers	End-users	HCPs	Overall stakeholder average	Application in the reform of the pharmaceutical legislation
Proposal 1	Public listing of priority therapeutic areas with high UMN to support product development by providing incentives.	4,20	3,30	4,11	4,35	4,33	4,06	◐
Proposal 2	Early scientific support and faster review/authorisation of a new medicine for an UMN.	4,26	4,57	4,20	4,23	4,29	4,31	✓
Proposal 3	Maintain the current data (8 years) and market protection (10 years) periods for innovative medicines.	3,76	4,58	3,46	3,38	3,55	3,75	✗
Proposal 4	Introduce new types of incentives on top of the existing data and market protection for medicines addressing an UMN.	3,00	4,03	3,82	3,80	3,80	3,69	✓
Proposal 5	Provide different data and market protection periods depending on the medicines' purpose.	3,19	2,35	3,39	3,40	3,40	3,15	✓
Proposal 6	Reduce the data and market protection periods to allow earlier market access for generic and biosimilar medicines.	3,22	1,83	2,96	3,24	3,24	2,90	✓
Proposal 7	Require transparent reporting about R&D costs and received public funding as a condition to obtain UMN incentives.	3,96	1,70	3,97	4,51	4,29	3,69	◐

Legend

- Relatively high average score
- Relatively medium average score
- Relatively low average score

- ✓ Full application in the proposed legislation
- ◐ Partial application in the proposed legislation
- ✗ No application in the proposed legislation

FIGURE 6
Heatmap describing stakeholders' responses on the proposed incentive measures for unmet medical need. Average scores range from 1 to 5 and were colored relatively to another using the conditional formatting tool in Excel. The highest average values are indicated in green; the lowest average values are indicated in red, and the values in between are colored in orange/yellow. UMN, unmet medical need; HCPs, Healthcare providers; QoL, Quality of life.

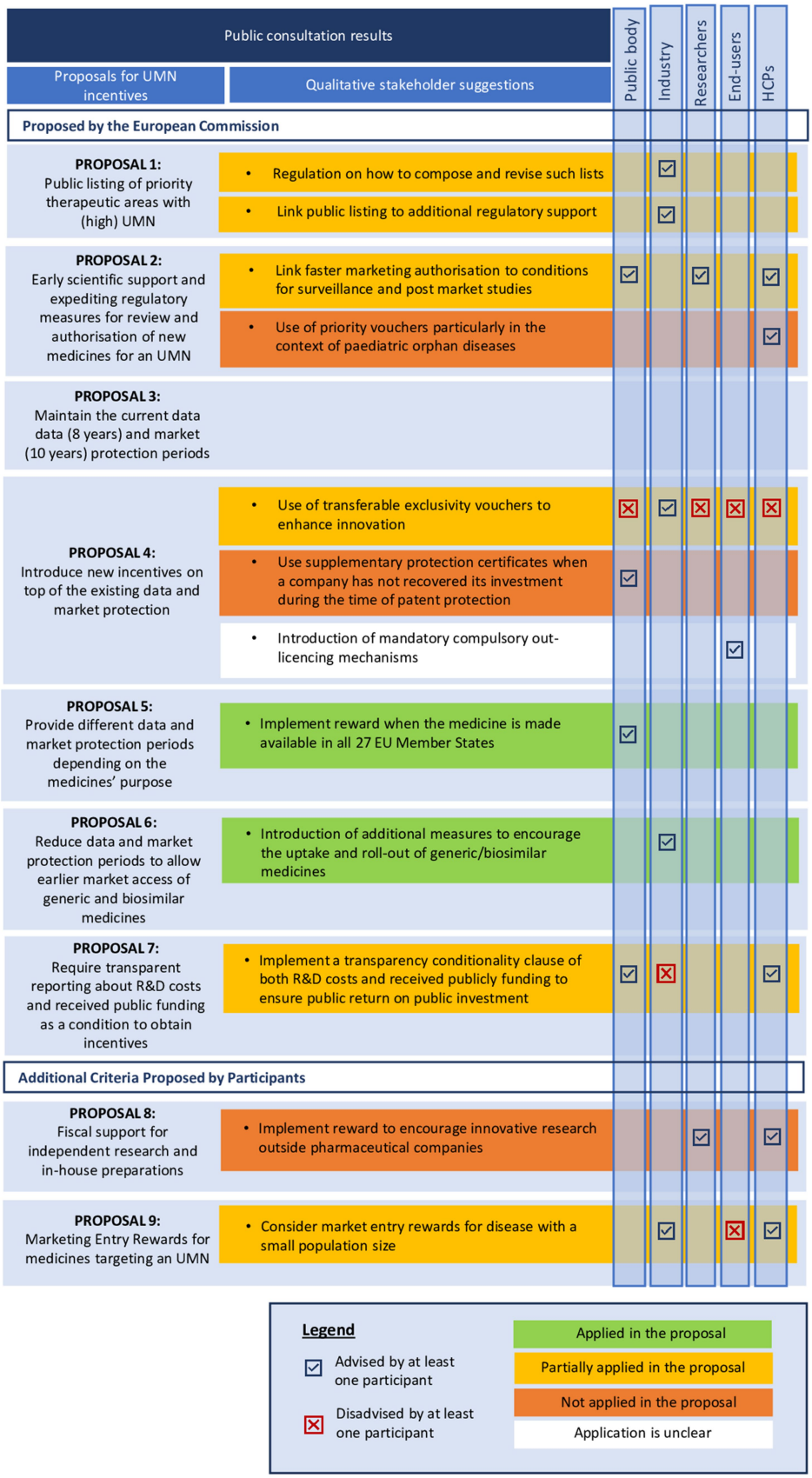

FIGURE 7
Qualitative insights from stakeholders on the UMN-related incentive measures. UMN, unmet medical needs; EU, European Union; IPR, intellectual property rights; RDP, regulatory data protection; R&D, research and development.

measure was partially implemented in the proposal for the revised EU pharmaceutical legislation, limiting its scope to antimicrobials [Proposal for a Regulation (EC) No 2023/0131, Art. 40(3,4)]. More specifically, the legislative proposal refers to the WHO's priority pathogen list and summary report describing the most pressing antibiotic-resistant pathogens as well as the methodological approach for developing the priority list. Industry respondents also emphasized that, to ensure a successful application, public listings for priority therapeutic areas should be combined with additional regulatory support for drug developers. This suggestion was partially implemented in the revised EU legislation [Proposal for a Regulation (EC) No 2023/0131, Art.60 (1), Art.89], given that antimicrobials are considered an area of UMN and thus, companies and not-for-profit organizations conducting R&D for priority pathogens are entitled to receiving (i) enhanced scientific and regulatory support and (ii) accelerated regulatory assessments, as discussed in proposal 2.

3.3.2.2 Proposal 2: scientific advice and expediting regulatory measures for review and authorization

In the existing EU legislation, the UMN definition is officially used as an eligibility criterion in the context of conditional marketing authorization [Regulation (EC) No 507/2006, Art. 4] and implicitly in the context of the orphan designation [Regulation (EC) No 141/2000, Art. 3]. In the proposed reform, UMN as an eligibility criterion is explicitly extended to applications in the PRIME scheme and accelerated assessment [Proposal for a Regulation (EC) No 2023/0301, Art. 60]. This extended application of the UMN concept in these particular regulatory mechanisms corresponds with stakeholders' perspectives, as they were generally in favor of the measure to enhance scientific and regulatory support. However, both public bodies and HCPs emphasized that such incentives must still be applied with vigilance in practice. For example, they warned that these measures may primarily increase the risk of allowing products of uncertain value to the market. Furthermore, they stressed that the assessment of medicines' safety, quality and efficacy should not be shifted from pre- to post MA to the detriment of patients, therefore suggesting linking the implementation of such measures to conditions for surveillance and post-market studies. These suggestions were partially included in the proposal for a regulation (EC) No 2023/0131 by allowing EMA to impose additional post-marketing studies on companies, if necessary, to evaluate medicines' safety and efficacy. The suggestion of end-users to use priority vouchers for rare pediatric diseases was not applied in the revised pharmaceutical legislation. Although innovative medicines with orphan designation are considered to address an UMN and are eligible for (i) enhanced scientific and regulatory support and (ii) accelerated regulatory assessments, these incentives are not equal to the concept of priority vouchers.

3.3.2.3 Proposal 3–6: incentive measures related to IPR and RDP for medicines targeting UMNs

Industry respondents emphasized the need for maintaining the current regulatory and data protection periods for innovative medicines or providing additional incentives on top of the current regulatory and data protection periods to foster innovation. In this regard, the EC proposed to introduce a transferable exclusivity voucher (TEV) as an additional incentive, which means either granting manufacturers an extra year of data exclusivity on any one of the medicines in their portfolio or allowing them to sell the voucher to other developers. Stakeholders had rather conflicting opinions on this proposal. Whilst industry respondents were strongly in favor of this measure, public bodies, end-users, and HCPs believed this measure would cause overcompensation for pharmaceutical developers. The use of TEVs was partially included in the revised legislation, yet its applicability is restricted to the field of antimicrobials, encouraging the development of novel antibiotics to address the issues of AMR [Proposal for a Regulation (EC) No 2023/0301, Art. 40]. The suggestion of public bodies to introduce supplementary protection certificates as additional incentive for companies to ensure return of investment was not included in the proposal of the reform of the pharmaceutical legislation. Lastly, it remains unclear whether and how the suggestion of end-users to introduce mandatory compulsory out-licensing mechanisms was integrated in the revised legislation.

The reform of the EU pharmaceutical legislation includes a gradual incentive structure allowing pharmaceutical developers to receive additional regulatory protection for medicines targeting an UMN. For example, the proposal for a Directive (EC) No 2023/0302. Art. 80(2)—Art. 81(1,2) includes a reduced standard data protection period for medicines from 8 to 6 years. However, data protection periods may be prolonged with (i) +24 months when medicinal products are released in all 27 EU Member States and continuously supplied or (ii) +6 months when the medicinal product addresses an UMN. Moreover, whilst the regular period for marketing exclusivity is 9 years for orphan medicines, pharmaceutical developers can receive an extra year of marketing exclusivity (10 years) when an orphan medicine addresses a high UMN [Proposal for a Regulation (EC) No 2023/0301, Art. 71(1); Art 72(1,2)]. This gradual incentive structure for regulatory protection periods corresponds with public bodies suggestions to maintain a binary approach for UMN incentives and determine regulatory protection periods based on (i) the degree of UMN (i.e., high or not) and (ii) the extent to which a treatment meets patients UMN, referring to the medicines' scientific efficacy as well as its availability across the Union.

3.3.2.4 Proposal 7: transparency on R&D costs and received public funding as a conditionality clause

The proposal for making UMN-related incentives contingent on greater R&D transparency for drug developers was welcomed by end-users, HCPs and public bodies, as they suggested introducing a conditionality clause on transparency of both R&D costs and received public funding to ensure public return on public investment. In contrast, industry representatives stressed that obligating transparency on R&D costs and public funding as a condition to obtain incentives would increase the burden on companies and would set barriers to innovation. As a result, the EC partially applied this suggestion in the reform of the EU pharmaceutical legislation yet limiting its scope to solely requiring pharmaceutical companies to report any directly received public funding [Proposal for a Directive (EC) No 2023/0302, Art. 57(1)]. Furthermore, the EC did not make this transparency clause a condition for eligibility for UMN incentives.

3.3.2.5 Additional proposed incentive measure by stakeholders: financial support

Both HCPs and researchers pointed out that the focus should not be primarily on introducing additional incentives for industry but rather on funding (i) independent academic R&D and (ii) in-house hospital preparations for particular treatments. End-users agreed with these suggestions, underlining the importance of allocating more public funding to hospitals and academic research to tackle the issues

of academic knowledge commercialization. However, these suggestions were not mentioned in the proposal for the reform of the EU pharmaceutical legislation.

3.3.2.6 Additional proposed incentive measure by stakeholders: marketing entry rewards

Industry representatives highlighted that the lack of reimbursement for many innovative drugs makes it difficult to meet patients' needs in practice and suggested that, in those disease areas for which the target population is rather small, new pricing mechanisms (e.g., de-linkage payment models) and additional market uptake or entry rewards such as lump sums could further support innovation. HCPs agreed on this, adding that HTA bodies should give preference to therapies targeting an UMN. However, the proposal for the reform of the EU pharmaceutical legislation did not include any specifications on the introduction of marketing entry rewards (MER) as an incentive to stimulate innovation, which is consistent with the views of end-users who stated that HTA bodies should maintain stringent standards for newly authorized therapies, especially when the added therapeutic value seems to be marginal or negligible.

4 Discussion

Upon the publication of the proposed reform of the EU pharmaceutical legislation, stakeholders across the drug development landscape have argued against the proposed criteria related to the UMN definition and the associated incentives (12, 13). To better understand how the public consultation has informed the current legislative proposal, this study provides an in-depth analysis of stakeholder responses to the public consultation of the proposal for the reform of the EU pharmaceutical legislation, that covered proposed criteria and incentives for UMN to inform the general EU pharmaceutical legislation, and assessed how stakeholders' perspectives and recommendations were implemented in the current proposal for the reform of the EU pharmaceutical legislation. This analysis focuses specifically on the definition of UMN and incentive measures to stimulate innovation and development in disease areas with (high) UMN and offers an academic perspective, employing rigorous methodological analysis.

Regarding the UMN definition, this comprehensive analysis of stakeholder responses highlighted three key recommendations: (i) extending the scope of the definition beyond pharmaceutical developments, (ii) ensuring sufficient flexibility, and (iii) approaching UMNs in a non-binary way. All respondents agreed that the absence of a satisfactory treatment authorized in the EU and the seriousness of a disease are the most important criteria, which were subsequently included in the proposed legal definition of UMN. Additionally, the criterion of a major therapeutic advantage over existing treatments is a criterion in the existing UMN definition [Regulation (EC) No 507/2006, Art. 4], but it was not as such included in the new legislative proposal. However, this criterion is rather implicitly included in the reform of the EU pharmaceutical legislation and rephrased as (i) "the medicinal product results in a meaningful reduction in disease mortality or morbidity" in case of the UMN definition [Directive (EC) No 2023/0132, Art. 83(1)] or (ii) "the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement" in the definition for high UMN [Regulation (EC) No 2023/0131, Art. 70(1)]. While disease incidence and prevalence were also qualitatively suggested by some stakeholders, these criteria were not included in the reform of the EU pharmaceutical legislation.

Regarding UMN-related incentives, this comprehensive analysis of stakeholder's responses highlighted two major legislative changes in the proposal for the reform of the EU pharmaceutical legislation: (i) a reduction in regulatory data protection from 8 to 6 years [proposal for a Directive (EC) No 2023/0302. Art. 80(2)—Art. 81(1,2)], and (ii) the introduction of TEVs for antimicrobials [Proposal for a Regulation (EC) No 2023/0301, Art. 40]. While most industry participants opposed changes to the regulatory data protection periods, they supported the introduction of TEVs. In contrast, other stakeholder groups were hesitant to provide any additional incentives, including RDP and transferable exclusivity vouchers, and instead recommended focusing on scientific support and expedited regulatory measures. Subsequently, the revised legislative package extended the application of the UMN concept to the PRIME scheme and accelerated assessment [Proposal for a Regulation (EC) No 2023/0301, Art. 60].

4.1 Enhanced clarity on UMN criteria

While this study highlighted the need for clarity from both industry and public bodies regarding the eligibility criteria for UMN, many of these criteria in the current legislative proposal remain open to interpretation. This aligns with suggestions from HCPs and researchers to maintain a flexible and dynamic approach to the UMN concept. However, the European Federation of Pharmaceutical Industries and Associations (EFPIA) warns that less ambiguous criteria could lead to uncertainty for medicine developers, especially in areas reliant on incremental innovation (12). For instance, the proposed criterion of "severely debilitating" raises questions about measurement and cut-offs (12, 14). EFPIA's assessment indicates that most medical products could be considered life-threatening or seriously debilitating, necessitating clearer criteria to enhance predictability (12).

Another ambiguous criterion is "remaining high morbidity or mortality" (12). Similarly, the criterion of "meaningful reduction in disease morbidity and mortality" is seen by EFPIA as challenging and unpredictable due to the underlying value judgment and the implied need for comparative clinical data (12). In the context of orphan medicines, the additional criterion of "exceptional therapeutic advancement" creates uncertainty about its definition, potentially hampering innovation in rare diseases, where only 6% of known rare diseases have an approved treatment (12, 14). Because of this, The European Patient Forum calls for a universally accepted definition of "added therapeutic value," stressing that systematic patient involvement is key to obtain a comprehensive understanding on a medicines' true benefit–risk balance (10). The authors of this study, also question whether there is a meaningful difference in the high UMN definition between "exceptional advancement" and "meaningful reduction," [Regulation (EC) No 2023/0131, Art. 70(1)] and whether the latter is necessary since it is already part of the UMN definition, which is required for high UMN eligibility.

EFPIA argues that this unpredictability could hamper investments and raises concerns about scenarios where high uncertainty persists

at the time of approval, a common issue for orphan medicinal products (12). The authors of this study stress that the primary goal of the UMN definition is to stimulate research and development in areas where investments or therapeutic advancements are currently lacking or limited by linking it to incentives, such as extended RDP. However, predictability is crucial for the pharmaceutical industry; without it, any incentives linked to the UMN definition will be insufficient to make a significant impact and support research in these areas. The authors also believe that UMN will evolve over time, and since pharmaceutical research and development is a lengthy process, the concept must be flexible to accommodate changes over time. Too restrictive criteria can therefore hamper innovation, which is highly unfavorable. A potential solution is to develop frameworks for the identification of needs, such as the one proposed by the Belgian knowledge center (KCE). These results can further support decision-makers in allocating incentives to the appropriate products.

4.2 Increased focus on quality of life and patient involvement

There has been growing attention to the impact of QoL as an outcome measure to evaluate the value of medicinal products, rather than just traditional clinical outcomes such as overall survival or mortality (15–17). Moreover, patient involvement in clinical research has gained importance to ensure that what truly matters to patients is measured through patient-relevant outcome measures (18). This patient-centered focus was reflected in the qualitative stakeholder responses, where multiple participants underscored the importance of patient involvement and QoL in assessing the satisfaction with existing alternatives and the seriousness of the disease. Patient experiences are becoming increasingly important, as confirmed by the EMA through the qualification of a framework for patient preference studies (19). This evolution is reflected in the new proposed legislative definition for UMN by integrating the criterium morbidity and including the term "meaningful," which implies a value judgment and the possibility to include patient perceptions. However, the European Patients Forum (EPF) argues that considering only "mortality and morbidity" is too restrictive, as it ignores other important life-changing indicators. They propose including the impact on QoL more explicitly and involving patients in the definition's development (13).

4.3 Modulation of UMN

The suggestion to move away from a binary approach for the UMN definition has been partially addressed. Some gradation is possible in the context of orphan medicinal products, with a distinction made between UMN and high UMN based on whether there is proof of "exceptional therapeutic advancement." However, questions remain about how this will be demonstrated, and which methods are to be used. EURORDIS, the umbrella patient organization for rare diseases in Europe, requests more clarity on how patient representatives will be involved in regulatory practices (14), a point also noted by EPF (13). This two-level approach partially meets the proposal for a modular system and is welcomed by EURORDIS (14), but it could be extended to a three-level scale: high, medium, and large UMN, as proposed by Horgan et al. (16).

4.4 Incentives to drive R&D in UMN-areas

On the one hand, UMN is in some studies found to be one of the most influential drivers in pharmaceutical sciences (20, 21). On the other hand, factors like market size, scientific grounds, expected return on investment, and historical funding often outweigh the remaining burden of disease in funding decisions (22–25). As a result, the proposed reform of the EU pharmaceutical legislation aims to enhance innovation in areas of UMN (2).

Nevertheless, the European industry organization, EFPIA, warns that the proposed incentive framework will not suffice to create this shift (26). In order to generate real advances in UMN areas, EFPIA suggests additional legislative adjustments, such as the implementation of transferable exclusivity extensions and a predictable RDP system since they believe variable RDP periods based on the "purpose of the medicine" could undermine innovation in Europe (26). Nevertheless, this analysis shows that many other stakeholders are not in favor of extended RDP periods or IPR for companies. Furthermore, stronger pharmaceutical monopolies can increase drug prices and delay availability (27, 28). Therefore, balancing the stimulation of R&D with avoiding monopolies that disrupt the R&D system is crucial.

Besides adjustments in RDP, EFPIA also proposes extending the eligibility scope for the PRIME scheme and allowing earlier PRIME access (26). In its reaction on the proposal, EFPIA emphasizes the need for consistent and predictable application of the PRIME scheme (26). Besides regulatory pathways, adjustments to the orphan drug regulation are believed necessary to further enhance innovation (27, 28).

Lastly, it must be emphasized that basic research is vital for pharmaceutical development, often starting in early research settings (20). Moreover, research shows that developing treatments in non-profit or academic settings could be a viable alternative when EFPIA companies face insufficient incentives to address UMNs (29, 30). Therefore, most stakeholders favor regulatory flexibility such as early scientific advice and faster reviews. Whilst academic-based drug development is becoming increasingly important to address the most persistent UMN, a study by Kallio et al. pointed out the lack of knowledge and skills of academia within the regulatory environment (31). The lack of clear and transparent communication between stakeholders (i.e., academia and authorities) poses a significant barrier for supporting academic development, underlining the need to raise awareness of available regulatory support tools and training to foster academic drug development.

The European Cancer League underscored that enhanced regulatory support alone is not sufficient to foster academic-based drug development, emphasizing the need for (i) non-commercial registration trajectories for marketing authorizations and (ii) public funding for breakthrough innovative medicines developed by academia (32). The latter is considered key in ensuring the translation of academic discoveries into targeted therapies, requiring further efforts in setting up multi-stakeholder partnerships to adequately address the highest UMN (33). One option is public-private partnerships, where academia drives innovation and industry provides resources, which are critical for fostering innovation (29). Moreover, for diseases like Alzheimer's, the federal government is the largest public funder of research, while the pharmaceutical industry focuses on late-stage drugs (34, 35). Additionally, diseases in high-income

countries receive significantly more research attention compared to those in low-income countries, a disparity that regulatory incentives alone cannot address (23). Therefore, expanding support for these initiatives could complement industry efforts, ensuring UMN are addressed even when traditional market-driven incentives fall short.

4.5 Incentivizing equitable access for medicines targeting UMN

When a medicine is eligible for UMN incentives at the European level, it does not guarantee patient access across EU member states. In most member states, extensive pricing and regulatory procedures must be initiated following the submission by the marketing authorization holder (MAH). Currently, there is no obligation for companies to make the drug available in any country upon authorization, leading to reported inequalities in medicine availability across the EU (36–38), with later launches in member states with lower GDP (36).

A key challenge remains achieving alignment across organizations and member states. Currently, there is a lack of consensus between the EMA and national HTA bodies or payers on the UMN concept (5). Although the revised EU legislation aims to enhance and align this understanding among stakeholders, it does not provide concrete guidance on implementation. Therefore, it is still unclear how national HTA bodies and payers will handle medicines that the EMA perceives as targeting a UMN.

Although the proposed criterion on market access in European Member States was not explicitly included in the definition of UMN, it has been included as an eligibility criterion for add-on RDP period incentive. When medicinal products are made available in all 27 member states, the MAH can benefit a prolonged RDP period of 24 months. While this is a step toward achieving more equitable access to medicines in the EU, EURORDIS recommends developing a streamlined pathway that includes regulatory advice, marketing approval, and pricing and reimbursement activities at the EU level to allow early access to medicines for ultra-rare diseases (14). Similarly, in the context of the United Kingdom, the "Innovative Licensing and Access Pathway" (ILAP) was created to support and accelerate the development of medicines targeting UMNs and allows flexible support tools through the life cycle of medicines development using a multi-agency approach from regulators to HTA bodies (39). Alternative recommendations to stimulate earlier patient access include mandatory national pricing and reimbursement submission at the EU level, increased alignment on evidence requirements between the EMA and national payers, and enhanced and aligned national early access programs linked to European decisions (37, 40).

4.6 Strengths and limitations

One of the primary limitations of this study is the dynamic nature of the legislative landscape we are investigating. The laws and regulations under examination are currently in the revision process, and significant changes may occur before the final regulation and directive are adopted. This inherent uncertainty means that some findings and discussions presented in this study may become outdated or less relevant as the legislative process evolves. However, this evolving landscape also presents a unique strength. By analyzing the proposed revisions and stakeholder feedback during the public consultation, this research highlights critical topics and issues that are still under consideration. Our findings and discussions can influence ongoing debates and potentially shape the final content of the regulation and directive, providing valuable insights for policymakers, stakeholders, and researchers, and contributing to a more informed and nuanced legislative development process.

The conduct of both a quantitative and qualitative analysis of stakeholders' responses on the proposed policy optimization measures as described in the public consultation on the Pharmaceutical Strategy to inform the reform of the pharmaceutical EU legislation, allows for an in-depth yet nuanced understanding of stakeholder's perspectives. This approach ensures that agreements but most certainly discussion points among stakeholders on particular policy proposals are put into a broader context. It should be emphasized that stakeholders could voluntarily provide additional qualitative input to further clarify their answers in the public consultation survey. The voluntary nature of these qualitative data may result in a potential imbalance in perspectives among specific stakeholder groups, such as industry who provided substantial qualitative input compared to other stakeholder groups, making it at times difficult to draw general conclusions or find consensus across the diverse views represented. The cluster classification of stakeholder respondents provides the opportunity to make inter-group and between group comparisons of different stakeholder perspectives and allows for a more nuanced interpretation of group level viewpoints. However, it is important to note that the perspectives of stakeholders who self-identified as "other" ($n = 63$) were not included in this analysis. Although their insights could have been valuable to this study, given the heterogeneity of stakeholders in the "other" group, the authors anticipated that drawing generalizable conclusions from their responses would be challenging. The visualization of stakeholders' views and their additional policy suggestions in heatmaps is an comprehensive approach to obtain a clear overview on general tendencies at stakeholder cluster level and allows to compare the different levels of satisfaction between stakeholders regarding the proposed policy measures. Moreover, the calculation of overall group averages indicates which measures received the highest score from all stakeholders and thus, were most widely supported.

An inductive coding approach was maintained for the qualitative analysis of stakeholder's responses in the open answer text fields. As a consequence, there was a primary focus on topics/themes that were recurrently addressed by respondents in each stakeholder cluster. Therefore, the generalizability of the qualitative findings for all participants per stakeholder cluster should be carefully considered. Moreover, the classification of stakeholders into clusters was meticulously conducted in consultation with the entire research team, based on reported affiliations. Stakeholders who did not clearly align with any of the defined clusters were placed in the "other" category and subsequently excluded from the analysis. This approach results in a discrepancy with the stakeholder distribution used by the EC in their summary of results. However, this adjustment affects only 33 participants and is not expected to significantly influence the overall results. Finally, it should be noted that the quantitative analysis was conducted by one researcher, meaning that no cross-check of individual study results was performed. With respect to the qualitative analysis, inductive coding was performed by one researcher while analysis and synthesis were performed by two researchers.

5 Conclusion

This study provides a detailed analysis of stakeholder responses to the proposed EU pharmaceutical legislation revision, focusing on UMN definitions and incentives. Stakeholders proposed, in line with the proposed definition, to include disease seriousness and availability of alternatives in the UMN definition. Nevertheless, many stakeholders continue to highlight the ambiguity of the current definition and underscore a need for further discussion on the UMN definition. The distinction of UMN and high UMN within the legislative proposal was partially meeting the recommendation to apply a modular approach but could still be extended beyond orphan medicinal products. Industry participants opposed reducing RDP but supported transferable exclusivity vouchers as included in the legislative proposal, whereas other stakeholders preferred scientific and regulatory support over additional RDP incentives. The findings underscore the need for further discussion on UMN related incentives to stimulate innovation while ensuring patient-centric outcomes and equitable access to medicines across the EU.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation/public-consultation_en.

Author contributions

IW: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. ZC: Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. AV: Methodology, Writing – review & editing. LB: Conceptualization, Methodology, Supervision, Writing – review & editing. RJ: Conceptualization, Supervision, Writing – review & editing. IH: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1506243/full#supplementary-material

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Comparison of good review practices of seven countries participating in the ECOWAS medicines regulatory harmonisation initiative: identifying opportunities for improvement

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Introduction: When implemented by national and regional regulatory agencies good review practices (GRevPs) support the timely high-quality review of medicines for enhanced patients' availability to safe, quality and efficacious innovative and generic products. It is important that all aspects of GRevPs are continuously evaluated and updated to promote the continuous improvement of regulatory systems at national and regional levels. The aim of this study was to assess and compare the GRevPs of the national medicines regulatory agencies (NMRAs) of Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo, who are active participants of the ECOWASMRH initiative to identify opportunities for improvement.

Methods: The Optimising Efficiencies in Regulatory Agencies questionnaire, was completed by each of the NMRAs, which facilitates the assessment of GRevPs, which in turn affect the regulatory review processes.

Results: Except for Cote d'Ivoire and Nigeria which are autonomous, the other five NMRAs operate within the administrative structure of their respective Health Ministry, to regulate medical products for human use, medical devices and diagnostics. Apart from Togo, the agencies receive partial funding from their governments as well as from regulatory fees. Population in the seven countries ranges from 8.6 million to 211.4 million. All the NMRAs had measures in place to achieve quality in their review processes, although there were some remaining initiatives related to transparency and communication, continuous

improvement and training and education, to be implemented. Of the ten quality decision-making practices Ghana had implemented nine into a framework, Togo eight, Cote d'Ivoire seven, Nigeria six, and Burkina Faso five; while Sierra Leone has partially implemented all ten and Senegal had not implemented any of the quality decision-making practices.

Conclusion: The study compared the organisation, GRevPs and quality decision-making processes of the NMRAs that actively participate in the ECOWAS-MRH initiative. Though some differences were identified with regard to organisation, a significant number of good review practice initiatives and quality decision-making practices were identified yet to be implemented to promote continuous improvement in the regulatory processes of the NMRAs.

KEYWORDS

Economic Community of West African States Medicines Regulatory Harmonisation (ECOWAS-MRH), good review practices, African Medicines Agency (AMA), regulatory reliance, Optimising Efficiencies in Regulatory Agencies (OpERA)

1 Introduction

In 2015, the World Health Organization (WHO) issued guidelines on good review practices (GRevPs) for national and regional regulatory authorities for medical products to support the continual improvement of their effectiveness, efficiency and consistency. The review of medicines has been broadly defined by the WHO as "that part of the regulatory work that forms the scientific foundation for regulatory decisions on marketing authorizations. It requires a highly complex, multidisciplinary assessment of product data to ensure that products submitted for regulatory approval meet adequate scientific and evidentiary standards for safety, efficacy and quality" (1, 2).

GRevPs are defined by the WHO as "documented best practices for any aspect related to the process, format, content and management of a medical product review. The objective of GRevPs is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews. This is carried out through the development of guidelines, review tools (for example, standard operating procedures (SOPs) and templates) and reviewer learning activities (for example training courses, mentoring, orientation packages and discussion sessions). To promote continuous improvement, all aspects of GRevPs should be continuously evaluated and updated" (2). This definition has been supported and expanded by the European Medicines Agency, the United States Food and Drug Administration (3, 4).

The ten key principles of a good review are that it is balanced, considers context, is evidence-based, identifies signals, investigates and solves problems, makes linkages, utilizes critical analyses, is thorough, well-documented and well-managed activities, and guides regulatory authorities in their regulatory practices. Similarly, the benefits of implementing GRevPs by national and regional regulatory authorities include the timely quality review of medical products and the enhancement of patients' availability to safe, quality and efficacious medicines in individual countries and regions (1).

Owing to the dynamic nature of the global regulatory landscape for medical products, it is necessary to assess the efficiencies of the relevant regulatory authorities available in the countries within the sub-region with a view to continually update the regulatory systems (3).

According to Al-Essa and colleagues, "quality measures may be evaluated on a regular basis to determine their impact on the quality and speed of the drug approval process. Review of human resources and the workload must always be assessed and updated according to the needs, challenges and opportunities for improving regulatory review practices" (3). Very useful insights on the implementation of quality measures by regulatory authorities have been provided by these same authors in their recent publication (3).

Therefore, in addition to assessing the quality measures, human resources and workload, this study will also assess transparency and communication parameters and continuous improvement initiatives, as well as training and education programmes.

To further highlight the regulatory importance of GRevPs, it was reported that the Asia Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee instituted the implementation of the 2020 Good Review Practices roadmap. Two international workshops were successfully organized by the Taiwan Food and Drug Administration including other objectives which addressed the building blocks of a regulatory review system in line with the roadmap. From the workshops it was noted that regulatory authorities associated the implementation of quality measures with efficient and transparent regulatory systems (5).

Lin and colleagues reported that "there is a lack of uniformity in review practices for medical products among APEC economies, as each economy has different regulatory practices, levels of expertise and capacity…" and "…the implementation of GRevP could be essential for strengthening the performance of regulatory authorities and enhancing mutual trust between economies in the APEC region" (5).

In the Economic Community of West African States-Medicines Regulatory Harmonisation (ECOWAS-MRH) initiative, there are seven national medicines regulatory agencies (NMRAs) that are active in the assessment of applications for marketing authorisation in the

Abbreviations: EAC-MRH, East African Community–Medicines Regulatory Harmonization; ECOWAS, Economic Community of West African States; NMRAs, National Medicines Regulatory Agencies; WHO-GBT, World Health Organization Global Benchmarking Tool.

subregion. As all the 15 NMRAs in the ECOWAS region collaborate to implement this initiative, it is expected that assessing and improving the GRevPs in the seven active NMRAs will in turn benefit all the NMRAs in the ECOWAS region (6).

According to the WHO, "good communication is critical and has many advantages for regulatory authorities, applicants and the public. It can improve the efficiency of the development and review processes and thus ultimately speed up patients' access to quality medical products" (1).

Because successful assessments of GRevPs of countries participating in the ZaZiBoNa and East African Community (EAC)-MRH initiatives have been conducted (7, 8) it is appropriate that the GRevPs of countries participating in the ECOWAS-MRH initiative are assessed. This study, therefore, is aimed at assessing those GRevPs and to communicate the findings to other regulatory authorities, stakeholders and the public to serve as a reference for future comparative analyses and to promote best practices in ECOWAS

This publication, which is one of a two-part series, provides an insight into the implementation of GRevPs of countries participating in the ECOWAS-MRH initiative. The other publication will compare their review models and regulatory timelines.

2 Methods and materials

2.1 Study participants

All seven active NMRAs of the ECOWAS-MRH initiative namely, National Pharmaceutical Regulatory Agency-Burkina Faso, Ministry of Public Health-Republic of Cote d'Ivoire, Food and Drugs Authority (Ghana-FDA), National Agency for Food and Drug Administration and Control (NAFDAC), The Federal Republic of Nigeria, Ministry of Health and Social Welfare, Republic of Senegal, Pharmacy Board of Sierra Leone (PBSL) and the Directorate of Pharmacy, Medicine and Laboratories-Togo, participated in this study between August 2021 and November 2023.

2.2 Data collection

The Optimising Efficiencies in Regulatory Agencies (OpERA) questionnaire was used to collect data. The development and validation of the OpERA Questionnaire followed the standard methodology for design of such tools. Initially, the content was based on a focus group of regulatory and pharmaceutical industry experts and then tested for validity and reliability in the field with the regulatory authorities and pharmaceutical companies as study participants. Completion of the OpERA questionnaire facilitates the assessment of the regulatory review processes, which affect approval times. Upon completion of the OpERA questionnaire, a country report, specific to each NMRA, is generated, which enables the sharing and adoption of GRevPs (9).

The OpERA questionnaire consists of six modules: module 1 covers structure, organisation and resources of the agency; module 2 explores the review models used for the scientific assessment of medicines; module 3 identifies the key milestones in the review process; module 4 captures regulatory measures that have been built into the regulatory review process; module 5 explores the quality of decision-making processes and module 6 documents the agency's perception of the key drivers and barriers that influence the effectiveness and efficiency of its review and decision-making processes.

> *While this manuscript covers the first three modules of the OpERA Questionnaire, because of the extensive nature of the remaining three modules including models of review, timelines (metrics) and challenges, it was agreed that these will be provided in a separate manuscript.*

3 Results

For the purpose of clarity, the results of this study cover three out of the six OpERA modules. These are presented in the following three parts: (1) Organisation of the authorities, (2) GRevPs building quality into the review process and (3) Quality decision-making processes.

3.1 Part 1. Organisation of the authorities

The NMRAs of Burkina Faso, Cote d'Ivoire, Ghana, Nigeria, Senegal, Sierra Leone and Togo were all established within a span of three decades (from 1992 to 2022). With the exception of Cote d'Ivoire and Nigeria, which are autonomous, the other NMRAs operate within the administrative structure of their respective Health Ministries. All the authorities regulate medical products for human use, medical devices and diagnostics. The population in the seven countries varies from 8.6 million to 211.4 million. A summary of the human resources of the NMRAs is provided in Table 1. The ratio of the staff per million residents ranged from 2.5 to 23.3, with five of the authorities having a ratio of less than 10. All the authorities, with the exception of Togo, receive partial funding from their governments as well as from regulatory fees. Table 2 details the fees charged for the review of marketing authorization applications for new active substances (NASs) and generics, respectively.

3.2 Part 2. GRevPs building quality into the review process

For the purpose of clarity, the documentation of review procedures that include general measures used to achieve quality, transparency and communication parameters, continuous improvement initiatives as well as training and education strategies that the authorities have in place, are presented as follows.

3.2.1 General measures used to achieve quality

A summary of the comparison of the quality measures implemented by the NMRAs within the ECOWAS region is provided in Table 3.

All the authorities have measures in place to achieve quality in their review processes namely; a good review practice system, an internal quality policy, standard operating procedures (SOPs) for the guidance of assessors, SOPs for the advisory and /or registration

TABLE 1 Comparison of country population, NMRA size and workload in 2022.

Country	Burkina Faso	Cote d'Ivoire	Ghana	Nigeria	Senegal	Sierra Leone	Togo
Population (millions)	22.7	28.2	30.8	211.4	17.3	8.6	8.8
Number of staff	64	71	683	2080	50+	200	30
Staff per million residents	2.8	2.5	22.2	9.8	2.9	23.3	3.4
Number of internal reviewers	34	15	26	44	37	15	4
Reviewers in agency, %	53	21	3.8	2.1	74	7.5	13.3

TABLE 2 Comparison of fees charged and source of funding in 2022.

Country	Burkina Faso	Cote d'Ivoire	Ghana	Nigeria	Senegal	Sierra Leone	Togo
Source of funding	93% government, 7% fees	63% government, 37% fees	35% government, 65% fees	22.41% government, 77.59% fees, 5.5% international partners	government and fees	90% government, 10% donor funds	100% government
Fees for review of new active substances (USD)	494	808	1,080	1,280	2,511	750	327
Fees for review of generics (USD)	247	808	720	1,280	1,674	250	818

committee consulted during the review process, assessment templates, assessment report, SOPs for completing the assessment report, SOPs for any other procedures in the regulatory review process, a dedicated quality department, a scientific committee and also shared and joint reviews. Only Togo has a few of the quality measures that are informally implemented; however, SOPs for the advisory committee are not in place.

3.2.2 Transparency and communications parameters

A summary of the comparison of the transparency and communication parameters implemented by the NMRAs within the ECOWAS initiative is provided in Table 4.

It was noted that out of the nine listed parameters, Ghana and Sierra Leone have formally implemented seven and informally implemented the remaining two parameters. Burkina Faso, Cote d'Ivoire and Togo have also implemented six parameters. Nigeria and Senegal have formally implemented five and four parameters, respectively.

3.2.3 Continuous improvement initiatives

Sierra Leone is the only country that has formally implemented all the five listed parameters in line with continuous improvement initiatives. Nigeria and Senegal have formally implemented four of the parameters and Cote d'Ivoire and Togo have informally implemented one and two parameters, respectively. A summary of the comparison of the continuous improvement initiatives implemented by the NMRAs is provided in Table 5.

3.2.4 Training and education strategies

A summary of the comparison of the training and education strategy implemented by the NMRAs is provided in Table 6. It was noted that Ghana and Sierra Leone have formally implemented all the nine listed initiatives. Senegal has formally implemented seven of the initiatives while Cote d'Ivoire has informally implemented seven of the initiatives. Burkina Faso and Togo have only implemented three initiatives.

3.3 Part 3. Quality decision-making processes

According to the WHO guidelines, NMRAs are encouraged to have a framework in place that forms the basis of the quality decision-making practices (QDMPs) to approve or reject a marketing authorisation application (2). The following ten principles should be implemented into the framework and also adhered to in practice: namely have a systematic, structured approach, assign clear roles and responsibilities(decision makers, advisors, information providers), assign values and relative importance to decision criteria, evaluate both internal and external influences/biases, examine alternative solutions, consider

TABLE 3 Comparison of the quality measures implemented by the NMRAs.

Indicator	NMRA						
	Burkina Faso	Cote d'ivoire	Ghana	Nigeria	Senegal	Sierra Leone	Togo
Good review practice system	✓	✓	✓	✓	✓	✓	✓
Internal quality policy	✓	✓	✓	✓	✓	✓	✓
Standard operating procedures (SOPs) for guidance of assessors	✓	✓	✓	✓	✓	✓	✓
SOPs for the advisory / registration committee consulted during the review process	✓	✓	✓	✓	✓	✓	x
Assessment templates	✓	✓	✓	✓	✓	✓	✓
Assessment report	✓	✓	✓	✓	✓	✓	✓
SOPs for completing the assessment report	✓	✓	✓	✓	✓	✓[a]	✓[a]
SOPs for any other procedures in the regulatory review process (e.g., validation)	✓	✓	✓	✓	✓	✓	✓[a]
Dedicated quality department	✓	✓	✓	✓	✓	✓	✓[a]
Scientific Committee	✓	✓	✓	✓	✓	✓	✓
Shared and joint reviews	✓	✓	✓	✓	✓	✓	✓

[a]Implemented but not formally documented.

uncertainty, re-evaluate as new information becomes available, perform impact analyses of the decision, ensure transparency and provide a record trail and finally effectively communicate the basis of the decision (10, 11).

It was noted from the study that Ghana has implemented nine of the ten quality decision-making practices into a framework and additionally these nine practices are also adhered to in practice. Togo and Cote d'Ivoire have implemented eight and seven of the quality decision-making practices into a framework, respectively. Nigeria and Burkina Faso have implemented six and five of the quality decision-making practices into a framework, respectively, and additionally these practices are also adhered to in practice.

Sierra Leone has partially implemented all ten quality decision-making practices into a framework and has also partially adhered to the practices. Senegal has neither implemented quality decision-making practices into a framework nor adhered to these quality decision-making practices. A summary of the comparison of the quality decision-making practices implemented by the NMRAs is provided in Table 7.

4 Discussion

This study compared the GRevPs of countries participating in the ECOWAS-MRH initiative and identified opportunities for improvement. The analysis, which is similar to the Southern Africa Development Community (SADC) (8) and EAC (7) regional studies, was also designed to widely share the regulatory good practices in the ECOWAS region to all stakeholders. These practices could interest manufacturers in increasing investment in the region for the ultimate benefit to patients.

It is of interest to note that out of the seven NMRAs, Nigeria and Ghana had the lowest percentage of reviewers in their authorities. It was also noted that Nigeria and Ghana had the highest contribution of their funds from regulatory fees. Coincidentally, Nigeria and Ghana have achieved WHO Global Benchmarking Tool maturity level-3 status, signifying that they have stable, well-functioning and integrated regulatory systems. It can therefore be inferred that these two authorities are demonstrating efficiency in utilizing their human and

TABLE 4 Comparison of the transparency and communication parameters implemented by the NMRAs.

Indicator	NMRA						
	Burkina Faso	Cote d'ivoire	Ghana	Nigeria	Senegal	Sierra Leone	Togo
Post-approval feedback to applicant on quality of submitted dossiers	✓	✓	✓	x	✓	✓	✓
Details of technical staff to contact	x	x	✓[a]	x	✓	✓[a]	✓[a]
Pre-submission scientific advice to industry	x	x	✓[a]	✓	x	✓	✓
Official guidelines to assist industry	x	✓	✓	✓	x	✓	✓
Industry can track progress of applications	✓	✓[a]	✓	✓	✓	✓[a]	✓[a]
Publication of summary grounds on which approval was granted	✓	✓	✓	x	x	✓	✓
Approval times	✓	✓	✓	✓	x	✓	✓
Advisory committee meeting dates	✓	✓	✓	x	x	✓	✓
Approval of products	✓	✓	✓	✓	✓	✓	✓[a]

[a]Implemented but not formally documented.

TABLE 5 Comparison of the continuous improvement initiatives implemented by the NMRAs.

Indicator	NMRA						
	Burkina Faso	Cote d'ivoire	Ghana	Nigeria	Senegal	Sierra Leone	Togo
External peer review	x	x	x	x	x	✓	x
Internal peer review	x	✓[a]	✓	✓	✓	✓	x
Internal tracking systems	✓[a]	x	x	✓	✓	✓	✓[a]
Review of assessors' feedback	✓	x	✓	✓	✓	✓	x
Review of stakeholders' feedback	✓	x	✓	✓	✓	✓	✓[a]

[a]Implemented but not formally documented.

financial resources to strengthen their regulatory systems. This could serve as a major learning point for other NMRAs who seek to make improvements to their regulatory systems.

The ratio of the staff per million residents in five of the authorities was less than 10, similar to that reported by Sithole and colleagues with regard to the SADC region (8); only two authorities had a staff per million residents' ratio of about twenty.

The lack of autonomy for most NMRAs in the ECOWAS region is a major challenge that also exists in the EAC and SADC regions (7, 8) and relevant provisions have been made in the African Union Model Law to promote the autonomous NMRAs, enabling independent decision making as well as their financial structure.

This study assessed the regulatory GRevPs of these NMRAs with regard to the implementation of quality measures,

TABLE 6 Comparison of the training and education strategies implemented by the NMRAs.

Indicator	NMRA						
	Burkina Faso	Cote d'ivoire	Ghana	Nigeria	Senegal	Sierra Leone	Togo
Training programme for assessors	x	✓[a]	✓	✓	✓	✓	x
International workshops/ conferences	x	✓[a]	✓	✓	✓	✓	x
External courses	x	✓[a]	✓	x	✓	✓	x
In-house courses	x	✓[a]	✓	x	✓	✓	x
On-the-job training	✓[a]	✓[a]	✓	✓	✓	✓	x
External speakers invited to the authority	x	✓[a]	✓	x	x	✓	✓
Induction training	✓	✓[a]	✓	✓	✓	✓	✓[a]
Sponsorship of post-graduate degrees	✓[a]	x	✓	x	x	✓	✓
Placements and secondment in other regulatory agencies	x	x	✓	✓	✓	✓	x

[a]Implemented but not formally documented.

transparency and communication parameters, continuous improvement initiatives and training and education programmes. It was noted that the quality measures had been largely implemented by the NMRAs within the ECOWAS region, serving as a useful reference for other NMRA implementation. Some transparency and communication parameters remain to be implemented by the ECOWAS-MRH authorities, presenting an opportunity for the exchange of strategies in order for each of the NMRAs to implement all remaining parameters. Analysis further revealed that Sierra Leone was the only studied country that has fully implemented all continuous improvement initiatives at this time, representing another instance for potential learning for other authorities in the region. According to O'Brien and associates, "Regulators may elect to use external experts from academia, external experts must have appropriate knowledge, skills and experience to conduct an assessment; have no conflicts of interest; meet pre-agreed deadlines and respect the confidentiality of data" (12). Finally, comparing the training and education initiatives that have been implemented by the NMRAs showed that implementation of these programmes in Sierra Leone and Ghana could both serve as references to the other authorities in the region. There appears to be a correlation between implementation of training and education initiatives with the number of staff. This study shows that due to the relatively small number of staff in these agencies, Sierra Leone and Ghana have prioritised the implementation of training and education initiatives to improve GRevPs in their respective authorities.

This study has therefore shown that resources are available in the ECOWAS region for the NMRAs to rely on to improve their respective GRevPs; however, since it was also demonstrated that none of the NMRAs had fully implemented a quality decision-making framework nor had fully adhered to these decision-making practices, this can be considered to be a challenge that needs to be resolved.

5 Recommendations

The following are the recommendations for improving the GRevPs of countries participating in the ECOWAS-MRH initiative.

I *Autonomy of regulatory authorities*: The NMRAs in the ECOWAS region should work towards achieving autonomy, enabling them to have independent decision-making as well as having appropriate financial structure.

II *Regulatory strengthening:* Consideration should be given to employing the services of external experts for the review of marketing authorisation applications in view of the limited resources currently within some of the NMRAs in the ECOWAS region.

III *Transparency and communication strategies:* Authorities in the region would benefit from implementing additional good review practice measures as well as sharing of assessment reports with applicants.

IV *Quality decision-making practices:* It is recommended that all authorities implement the 10 quality decision-making practices underpinned by initiating appropriate structured training.

6 Conclusion

This comparative study of the GRevPs of countries participating in the ECOWAS-MRH initiative has highlighted both the similarities

TABLE 7 Comparison of the quality decision-making practices implemented by the NMRAs.

Practice	Burkina Faso		Ghana		Nigeria		Cote d'Ivorie		Senegal		Sierra Leone		Togo	
	Implemented into framework	Adhered to in practice	Implemented into framework	Adhered to in practice	Implemented into framework	Adhered to in practice	Implemented into framework	Adhered to in practice	Implemented into framework	Adhered to in practice	Implemented into framework	Adhered to in practice	Implemented into framework	Adhered to in practice
Have a systematic structured approach	✓	✓	✓	✓	✓	✓	✓	✓	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓
Assign clear roles and responsibilities	✓	✓	✓	✓	✓	✓	✓	✓	×	NV	✓ (in progress)	✓ (in progress)	✓	✓
Assign values and relative importance to decision criteria	✓	✓	✓	✓	✓	✓	✓	✓	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓
Evaluate both internal and external influences/biases	✓	NV	✓	✓	✓ (in progress)	✓ (in progress)	×	×	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓
Examine alternative solutions	✓	NV	✓	✓	✓ (in progress)	✓ (in progress)	✓ (in progress)	✓	✓	NV	✓ (in progress)	✓ (in progress)	×	×
Consider uncertainty	×	NV	✓	✓	✓ (in progress)	✓ (in progress)	✓	✓ (in progress)	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓
Re-evaluate as new information becomes available	×	NV	✓	✓	✓	✓	✓	✓	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓
Perform impact analysis of the decision	×	NV	✓ (in progress)	✓ (in progress)	✓ (in progress)	✓ (in progress)	×	×	NV	NV	✓ (in progress)	✓ (in progress)	×	×
Ensure transparency and provide a record trail	✓	✓	✓	✓	✓	✓	✓	✓	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓
Effectively communicate the basis of the decision	✓	✓	✓	✓	✓	✓	✓	✓	NV	NV	✓ (in progress)	✓ (in progress)	✓	✓

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among the authorities and also the differences that should be addressed in order to improve the regulatory systems in these countries. The full implementation of GRevP should be essential for strengthening the performance of regulatory authorities and enhancing mutual trust between the NMRAs in the ECOWAS region.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom (Reference Protocol number: LMS/PGR/UH/05160).

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Challenges and ongoing initiatives towards better integrated EU scientific advice

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Scientific advice is the main avenue for clarification of EU regulators' scientific evidence requirements during medicines development. There are multiple avenues for seeking scientific advice in the EU with partially overlapping scope which creates room for divergence and contradictions; simplification and better integration among them could help harmonize EU regulators' requirements. Interaction with other decision makers providing advice along the lifecycle of medicines and other healthcare solutions reduces development uncertainties. The proposal for a new EU pharmaceutical legislation solidifies existing advice mechanisms and creates new avenues for enhanced integration of development support.

KEYWORDS

Research and Development (R&D), scientific advice, clinical trials, medical devices, innovative combination products, health technology assessment, new EU pharmaceutical legislation

1 Introduction

Scientific advice refers to several different interactions with European Union (EU) regulatory authorities during medicines development aimed at clarifying regulators' scientific evidence requirements applicable during the development, most notably prior to the initiation of clinical trials, and/or for the eventual market approval (marketing authorization). These requirements are often detailed in international and/or EU-specific scientific guidelines, but scientific advice may provide clarity in situations where there is little or outdated guidance. Scientific advice may also help clarify how existing guidance should be applied in a case-specific context. It constitutes the core and main form of regulatory support to medicines developers towards optimization of scientific evidence generation to support approval of new medicines, new uses of existing medicines and/or other major (usually manufacturing) post-authorization changes.[1] Other forms of regulatory development support include both formal (e.g., orphan designation,[2] pediatric medicines support,[3] priority medicines-PRIME designation)[4] and informal[5] interactions which are outside the scope of this manuscript.

The EU medicines development support ecosystem comprises regulators and other, parallel or subsequent, decision-makers and has been criticized as being too fragmented, sometimes leading to conflicting advice and recommendations. The proposal for the new

1 Scientific advice and protocol assistance | European Medicines Agency (europa.eu).
2 Orphan designation: research and development | European Medicines Agency (europa.eu).
3 Paediatric medicines: Overview | European Medicines Agency (europa.eu).
4 PRIME: priority medicines | European Medicines Agency (europa.eu).
5 Supporting innovation | European Medicines Agency (europa.eu) | advice mechanisms.

pharmaceutical legislation published by the European Commission in April 2023[6] attempts to simplify regulatory decision-making at European Medicines Agency (EMA) level, but the proposal is still in the legislative process and, more importantly, it does not address the complexity outside the remit of the EMA in the wider ecosystem. Main challenges preventing integrated and hence more coherent EU scientific advice will be analyzed in the following, with a focus on clinical development where the fragmentation notably occurs.

2 Policy options and implications

2.1 The current scope of scientific advice and its proposed amendment in the draft legal proposal for reform of the EU pharmaceutical legislation

According to the EU legislation,[7] scientific advice is about 'advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products for human use and of veterinary medicinal products'. In the absence of a legal definition, undertakings could be understood as medicine developers at large, mainly pharmaceutical companies and, less commonly, other entities developing new or existing medicines. In practice, scientific questions on any aspect of medicines development and any part of the dossier supporting a clinical trial or marketing authorization application fall within the scope of scientific advice.

Scientific advice focuses on prospective development planning aspects and refrains from pre-assessment of the actual data produced in the course of development. The assessment of such data takes place at marketing authorization application stage, when an authorization decision is made focusing on the balance of benefits and risks and going well beyond experiment and study design aspects into the evidence that ultimately supports the conclusion on benefits, risks, uncertainties around them and necessary post-authorization follow-up. Although focused on future development plans, scientific advice cannot ignore but is instead informed by early exploratory evidence which is critical for scientific advice at any stage of development. This is best exemplified in the case of tailored scientific advice for biosimilars,[8] where reduced non-clinical and clinical development programs can be proposed based on promising, rather extensive analytical comparability data. Review of such data informs the advice given, but it is without prejudice to their eventual detailed assessment during the marketing authorization application.

On the other hand, scientific advice formally assesses evidence in the case of qualification of novel methodologies (QoNM). Such qualification implies regulatory acceptability of novel methodologies for use in medicines development within a specific context in which they have been validated.[9] Examples of such methodologies include novel biomarkers to be used for enrichment of patient populations in early clinical trials or novel patient reported outcomes (PROs) to be used as secondary endpoints in confirmatory clinical trials. Scientific advice can be sought in early stages of method development on the proposed validation plan, but can also be used for the assessment of the evidence leading to regulatory qualification. Once it has been concluded that the proposed method can be qualified for a well-defined context of use, a qualification opinion is published[10] and subjected to public consultation before being finalized.

The revised Regulation[11] included in the European Commission proposal for reform of the EU pharmaceutical legislation expands the legal provisions for scientific advice (articles 58 and 59), albeit for the most part formalizing practices already in place or mirroring other recent pieces of legislation. Notable changes, the majority of which address the EU development support fragmentation, include:

1) Contrasting 'undertakings' to not-for-profit entities as scientific advice applicants. This implies that undertakings are to be understood as pharmaceutical companies and generally as for-profit entities in contrast to purely academic applicants, learned societies and other not-for-profit entities. The new Regulation further foresees fee reductions and waivers for not-for-profit entities which the new EMA fee Regulation (EU) 2024/568,[12] applicable as of January 2025, has already put in place
2) leveraging of clinical trial and medical device expertise from national competent authorities to support centralized scientific advice, as necessary
3) consultation of other authorities and public bodies, as applicable
4) parallel consultations with health technology assessment (HTA) bodies and with the expert panels for medical devices
5) publication of high-level information from scientific advice at the time of marketing authorization.

2.2 Options for seeking scientific advice from regulators in the EU and associated challenges in medicines development

There are multiple avenues for applicants to seek advice from EU regulators[13] and these include national, simultaneous national (SNSA) and centralized (also called EMA, SAWP, or CHMP) scientific advice. This is in contrast to the US system with the existence of the centralized Food and Drug Administration (FDA) solely responsible

6 Reform of the EU pharmaceutical legislation – European Commission (europa.eu).

7 Article 57(n) of Regulation (EC) No 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency.

8 Scientific advice and protocol assistance | European Medicines Agency (europa.eu).

9 Qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu).

10 Opinions and letters of support on the qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu).

11 Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency.

12 Regulation (EU) 2024/568 on fees and charges payable to the European Medicines Agency (europa.eu).

13 Advice on medicines for Human use in the EMRN (europa.eu).

for a multitude of meeting types[14] intended to support both clinical trial[15,16] and marketing authorization applications.[17,18] Underpinning this complexity, which understandably creates challenges for navigating the EU regulatory development support landscape, is a compartmentalization of remits between the EMA and National Competent Authorities (NCAs) for medicines with the former being responsible for EU-wide marketing authorizations while the latter are responsible for any clinical trial and national marketing authorizations.

The scopes of national, simultaneous national and centralized scientific advice are partially overlapping, each one offering advice on any product, any aspect of the dossier supporting subsequent regulatory applications and at any stage of the medicine's development. However, as scientific advice is sought in preparation for subsequent regulatory decisions, each advice option is more commonly used in different stages of medicines development depending on the remit of the regulatory decision-maker providing the advice. The scientific advice strategy is the developer's choice and may entail national advice and SNSA more frequently in earlier stages of development in order to support subsequent clinical trial applications whilst centralized advice is sought most commonly ahead of phase 3 clinical development in order to clarify marketing authorization requirements. SNSA was launched in 2020 in the form of a pilot in two phases to date and, while the scope is generally identical to single national scientific advice, it offers the possibility for applicants to get advice on the same set of questions and data package from different National Competent Authorities (NCAs) of EU member states within a single procedure.[19]

Provision of centralized scientific advice is the task of the Scientific Advice Working Party (SAWP) of the Committee of Medicinal Products for Human use (CHMP). The committee itself is responsible for producing scientific opinions which form the basis of EU marketing authorization decisions by the European Commission. The SAWP comprises experts from the European Medicines Regulatory Network (EMRN)[20] representing different types of expertise involved in medicines development including members from relevant EMA working parties and the majority of EMA scientific committees[21] as well as academic experts. This composition ensures provision of best advice possible and consistency between scientific advice and subsequent regulatory decision-making of different types (maintenance of orphan designation, pediatric investigation plan (PIP) agreement, authorization of advanced therapy medicines and adequacy of post-authorization follow-up and pharmacovigilance plans). It also allows the identification of regulatory guidance gaps, e.g., in case of novel technologies or evolving treatment landscapes, so that existing guidance can be updated or new guidelines can be developed, which a task of EMA working parties other than the SAWP.

On the other hand, the multitude of EMA working parties and especially of scientific committees creates challenges for the agile and coherent provision of regulatory development support. This is, e.g., obvious in the case of pediatric medicines development as both SAWP and Pediatric Committee (PDCO) guide on prospective development plans albeit with different remits. The proposal for the new pharmaceutical legislation foresees refocusing on two main committees for human medicines with a view to simplification of regulatory decision-making and increased efficiency and harmonization. Retention of expertise of outgoing committees would be enabled through alternative means such as a pool of experts to be consulted. The legislative proposal therefore creates the opportunity for more agile decision-making through involvement of subject matter experts in each case without the need for committee-level endorsement and formal opinion adoption.

The proposed new legislation maintains the SAWP as a working party of the CHMP with the sole remit of providing scientific advice and hence also maintains the separation of scientific advice from subsequent regulatory evaluation. The principle separation between individuals in prominent roles during early advice and later assessment, respectively, has been recommended to prevent any perceived conflict of opinion whilst recognizing the need to balance such principle against allowing to employ necessary scientific expertise.[22] Obviously, in depth knowledge of the product and the development is scientifically relevant for the assessment of the marketing authorization application and any post-authorization lifecycle changes of the medicinal product. Applying such principle on those individuals in prominent roles is feasible but requires careful management and sufficient capacity to not add to the existing resource constraints in the EU medicines regulatory network.[23]

The authorization of clinical trials at national level is another major challenge for medicines development in the EU and lack of harmonization of clinical trial application requirements across EU member states has repeatedly been identified as a major obstacle towards conduct of multi-national clinical trials in the EU. The clinical trials regulation, applicable since January 2022, is aimed at ensuring that the EU offers an attractive and favorable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants.[24]

The Accelerating Clinical Trials in the EU (ACT-EU)[25,26] initiative, also launched in January 2022, builds on the clinical trials regulation and aims to transform how clinical trials are initiated, designed and run, in order to further promote the development of high quality, safe

14 Formal Meetings between the FDA and Sponsors or Applicants of PDUFA Products.

15 Investigational New Drug (IND) Application | FDA.

16 Investigational New Drug Applications (INDs) for CBER-Regulated Products | FDA.

17 New Drug Application (NDA) | FDA.

18 Biologics License Applications (BLA) Process (CBER) | FDA.

19 Heads of Medicines Agencies (HMA) EU Innovation Network (EU-IN), section on Simultaneous National Scientific Advice (SNSA).

20 European medicines regulatory network | European Medicines Agency (europa.eu).

21 Committees, working parties and other groups | European Medicines Agency (europa.eu).

22 Decision in strategic inquiry OI/7/2017/KR on how the European Medicines Agency engages with medicine developers in the period leading up to applications for authorisations to market new medicines in the EU | Decision | European Ombudsman.

23 Handling competing interests | European Medicines Agency (EMA).

24 Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

25 Accelerating clinical trials in the EU (europa.eu).

26 Accelerating Clinical Trials in the EU (ACT EU) | European Medicines Agency (europa.eu).

and effective medicines, and to better integrate clinical research in the European health system. The ACT-EU Priority Action 7 focuses on scientific advice ahead of clinical trial applications and two pilots were launched in June 2024[27,28] with the aim to reinforce regulators' advice ahead of clinical trial applications, as follows:

1) Consolidated scientific advice on clinical trial and marketing authorization requirements by the SAWP with the involvement of the Clinical Trials Coordination Group (CTCG):[29,30] this follows the centralized scientific advice process with at least one of the two SAWP coordinators identified from the member states expected to coordinate the assessment of the subsequent clinical trial application. Individual member state comments concerning clinical trial requirements additional to the consolidated advice (if inevitable) are also communicated in the SAWP final advice letter. This initiative is in line with the European Commission proposal for the new pharmaceutical legislation which foresees leveraging of clinical trial expertise from national competent authorities to support centralized scientific advice.
2) Consolidated technical and regulatory advice (not scientific advice) by the CTCG, called pre-CTA advice:[31] this uses the SNSA avenue for submission but follows a shortened timeline, as intended to address technical and regulatory issues towards a smooth clinical trial application (CTA).

2.3 Parallel scientific advice with other decision-makers

Marketing authorization is a critical but not the final decision towards patient and market access for medicines. Health technology assessment (HTA)[32] informs subsequent reimbursement and pricing decisions taken at EU member state level. The EMA has been collaborating with HTA bodies[33] through the European Network for Health Technology Assessment (EUnetHTA)[34] since 2010 towards both provision of parallel scientific advice, started in 2012, and towards building synergies between regulatory evaluation and the HTA. The Regulation (EU) 2021/2282 on Health Technology Assessment[35] foresees joint scientific consultations (JSCs) between HTA bodies to be carried out by the HTA Coordination Group and optionally in parallel with the scientific advice process of the EMA. Well-established processes of parallel scientific advice between EMA and HTA bodies have been used to prepare for implementation and establishment of the new parallel consultation process under the new HTA regulation.

Moreover, use of medicinal products is becoming increasingly linked to medical devices which can be integral to or co-packaged with the medicine or used separately from it but support (*in vitro* diagnostic) or dictate (companion diagnostic) its use. Medical devices and in vitro diagnostics are regulated in the EU via respective Regulations (Regulation (EU) 2017/745[36] and Regulation (EU) 2017/746).[37] Both Regulations foresee scientific advice from expert panels[38] established by them. However, scientific advice from the expert panels is not available to manufacturers of *in vitro* (including companion) diagnostics [such advice is legally available only to the European Commission and the Medical Devices Coordination Group (MDCG)]. Moreover, scientific advice from the expert panels is restricted to high-risk medical devices which are primarily used on their own and not in combination with medicines. Finally, expert panels comprise clinical experts who can only advise on clinical, but not quality, development aspects.

Although clearly of value within its remit, scientific advice from the medical device expert panels cannot address the major device-related issues of current and future medicines development. These issues relate to combination products, i.e., medicines used in combination with medical devices or *in vitro* diagnostics. Most notable examples of innovative combination products are targeted therapies given to biomarker-defined populations for which a companion diagnostic is used to ascertain the status of the biomarker and hence identify patients eligible (or non-eligible) for the targeted therapy. Such combination products are already commonplace, mainly in hematology/oncology but also other therapeutic areas. The issues in the development of combination products stem primarily from the integrated conduct of the clinical investigation for the medical device or the performance study for the *in vitro* diagnostic with the clinical trial for the medicine in the combination. Different frameworks and regulators govern the approval and conduct of clinical investigations, performance studies and clinical trials following different timelines and requirements. Moreover, there is still no EU-coordinated process for multi-national clinical investigation or performance study approval, while coordinated review of clinical trial applications is already taking place since January 2022 following the go-live of the EU Clinical Trials Information System (CTIS).[39]

In many EU member states, medicinal products and medical devices/*in vitro* diagnostics are regulated by the same NCA and the scope of both national scientific advice and SNSA also covers combination products as long as these combination products fall within the remit of the NCA or NCAs participating in the SNSA pilot and their scientific-regulatory advice services. Similarly, questions on medical devices/*in vitro* diagnostics used in combination products are routinely being addressed in centralized scientific advice having access to medical device expertise in NCAs represented in the SAWP.

However, these advice options do not address the needs in terms of scope and capacity while some medical device decision-makers such as

27 Scientific advice – European Union (europa.eu).

28 Scientific advice and protocol assistance | European Medicines Agency (europa.eu) | Scientific advice on clinical trials.

29 Heads of Medicines Agencies: Clinical Trials Coordination Group (hma.eu).

30 Guidance for applicants SAWP CTCG pilot on scientific advice (europa.eu).

31 Guidance for applicants Pre-CTA advice pilot_final (europa.eu).

32 Health Technology Assessment-Overview-European Commission (europa.eu).

33 Health technology assessment bodies | European Medicines Agency (europa.eu).

34 www.eunethta.eu

35 Regulation (EU) 2021/2282 on health technology assessment.

36 Regulation (EU) 2017/745 7 on medical devices.

37 Regulation (EU) 2017/746 on in vitro diagnostic medical devices.

38 Medical device expert panels | European Medicines Agency (EMA).

39 Clinical Trials Information System | European Medicines Agency (europa.eu).

notified bodies are legally constrained from providing advice during device development. In order to address these issues lying at the interface between the Regulations on clinical trials, medical devices and *in vitro* diagnostics, the European Commission has launched the COMBINE project[40] in an attempt to harmonize the approval of combined studies, i.e., studies integrating a medical device clinical investigation or *in vitro* diagnostic performance study within a clinical trial.

Much as the focus in the EU is currently on coordination and harmonization among Member States in both areas of clinical trials and medical devices/*in vitro* diagnostics, there would also be benefits from further exchanges on scientific advice beyond the EU borders with international medicines regulators. The EMA and the US FDA have been operating a process of parallel scientific advice[41] since 2005 with modest uptake by medicines developers to date (1). The reasons may relate to logistical challenges of applicants dealing with two regulatory agencies in parallel in a process that involves additional meetings and effort. Scientific advice interactions between developers and EMA or FDA are relatively short and simple and more cross-border exchanges certainly increase procedural complexity, although they clearly add value and create opportunities for international harmonization of regulators' scientific evidence expectations.

3 Actionable recommendations and conclusions

To be meaningful, development support and guidance for scientific evidence generation need to evolve. Scientific advice is the pillar for obtaining feedback from EU regulators on the development plan. Several initiatives have been taken and pilots have been initiated to strengthen the ecosystem; the proposal for a revised pharmaceutical legislation builds on these experiences. It is recognized that better coordination is needed within clinical trial approval processes to improve consistency and predictability, particularly for studies combining medicinal products with medical devices or *in vitro* diagnostics, and make the EU competitive again in the area of clinical research. Closer links with medical device regulators at national level could help optimize existing and/or develop new scientific advice mechanisms for combination products which are becoming the norm, especially in therapeutic areas like oncology. More intense collaboration of medicines regulators with HTA bodies could improve patient access to new medicines. Critical expertise needs to be retained and remain accessible for the future fewer EMA committees and working parties, while their mode of operation should also adapt to their enhanced responsibilities. Finally, simplification and integration of the multiple EU scientific advice avenues and ensuring capacity of European NCAs to provide EU-level work may help ease resource constraints in the EU medicines regulatory system while making it simpler for medicines developers to seek regulators' advice.

40 Combined studies - European Commission (europa.eu).

41 Scientific advice and protocol assistance | European Medicines Agency (europa.eu) | Parallel scientific advice with the United States.

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Impact of changes in regulatory framework on approval of medicines for rare diseases and applicability to market access policies

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The introduction of the Orphan Drug Act in the USA in 1983, followed by adoption of the Orphan Drug Regulation No 141/2000 in the EU in 2000, led to a change in landscape of drug development for rare diseases. The introduction of regulations, guidance documents and incentives aimed at increasing the availability of new medicines for rare diseases resulted in an increase in approvals of 3 and 11-fold for branded products and generic medicines, respectively, in the decade 2013–2023 compared to 1990–2000. This effort was successful due to the collaboration of Regulatory Authorities, industry, patient groups and other stakeholders keen to leverage an integrated evidence approach using non-traditional approaches. While the regulatory approval landscape moved toward integration, the effective access to those medicines over the same period was globally fragmented with pricing and access determined at a local level. There is growing recognition of the importance of addressing the needs of rare disease patients and a concerted effort to balance innovation with affordability and access.

KEYWORDS

rare disease, orphan drug, market access, regulatory policy, approval, marketing

Introduction

The development landscape for new medicines for rare diseases has undergone significant changes over the last two decades. At the beginning of the 21st century, many countries had limited or non-specific legislation for rare diseases. Orphan drug policies were just starting to gain traction, with only a few countries implementing dedicated programs. The Orphan Drug Act in the United States (1983) had already set a precedent for rare disease drug development by offering incentives like tax credits, grant funding, and market exclusivity (1). European countries started to adopt some policies, though they varied in scope and implementation. Despite these attempts to address some of the barriers which prevented the development of drugs for rare diseases, incentives for pharmaceutical companies were insufficient to offset the high costs and risks associated with these medicines, until implementation of Orphan Drug Regulation No 141/2000 in 2000 (4). In this paper we attempt to quantitate the impact of the introduction of those regulations and associated guidance documents on the availability of new medicines for rare diseases and assess the drivers behind the outcomes we observe. We recognize and acknowledge that in addition to the guidances there were multiple additional incentives introduced to facilitate development and approval of drugs for rare diseases. However, we focus our review on the guidances to establish any potential correlation with the

access to these therapies. Moreover, we deliberately focused on rare disease specific guidances and excluded any general guidance that is applicable to any product development, this includes ICH guidances.

Approval of new medicines is one key factor for the availability of new medicines, however, ensuring that medicines are both accessible and affordable is the other part of the equation. Around 263 to 446 million people worldwide live with a rare disease at any given time, many of these conditions are debilitating or life-threatening and about half affect children (2, 3). This highlights a strong need to provide patients with effective therapies. We therefore also considered the healthcare payer environment over the same period to see if the incentives to develop new medicines for rare diseases were mirrored by incentives for these therapies to be both accessible and affordable.

Regulatory requirements: changes and trends

The introduction of the Orphan Drug Act in the USA in 1983, followed by adoption of the Orphan Drug Regulation No 141/2000 in the EU in 2000, changed the landscape of drug development for rare diseases (1, 4). Both the FDA and the EMA subsequently issued multiple guidances and programs to help drug developers navigate implementation of respective Act and Regulation and provided various incentives to encourage drug development for rare diseases. To evaluate the potential impact that guidances could make on the development of treatments for rare diseases we conducted a search of EMA and FDA websites and identified rare disease specific guidances. 35 FDA guidances and 12 EMA guidances were identified, all guidances are listed under Reference section for ease of the review (5–52). In our opinion, the number of published guidances demonstrates interest and support for the rare disease community by both the EMA and FDA. However, the fact that FDA published almost 3 times more guidances than EMA may indicate that FDA has more dedicated resources and this could encourage sponsor to prioritize engagement with FDA during the product development, approval and access strategy. For ease of comparison and to avoid duplication we excluded general guidances that are applicable to product development for all products. For example, ICH guidances on quality, efficacy and safety are deliberately excluded from the evaluation, as all sponsors should consider ICH guidances during drug development, regardless of whether the drug is being developed for treatment of rare disease or not. It should be noted that while the FDA has a website on Guidance Documents for Rare Disease Drug Development, the EMA guidelines relevant to rare diseases are published separately and could be found through a search of general guidances on the EMA website (53, 54).

The summary of guidances and the trend in guidance publication are presented in Figure 1 with the detailed titles and dates of publications presented in the Reference section (1, 4–53). There was a notable uptick in the annual number of guidances published by the FDA starting from 2015, albeit with an obvious drop in 2020 when everyone was focused on addressing the COVID-19 pandemic. Rare disease guidances publication from the EMA has been consistent since the 2000. In our opinion the most impactful guidances are the ones that encourage sponsor to use innovative and collaborative approaches to drug development, for example, FDA Draft Guidance Pediatric Rare Diseases-A Collaborative Approach for Drug Development Using Gaucher Disease as a Model (12) and EMA Guideline on clinical trials in small populations (43). The evaluation of regulatory guidances reveals some differences in FDA and EMA approaches to providing regulatory directions. In general, the FDA guidances focus on common issues and specifics of product development for all rare diseases with the exception of disease specific guidances for Duchenne and Gaucher diseases, the latter of which was done in collaboration with the EMA. The EMA issues more disease specific guidances, with the intent to help sponsors with drug development guidance for specific diseases. For the purpose of this paper, we only focused on guidances, however, it should be noted that both Agencies expanded their work outside of just publishing guidances. There were multiple

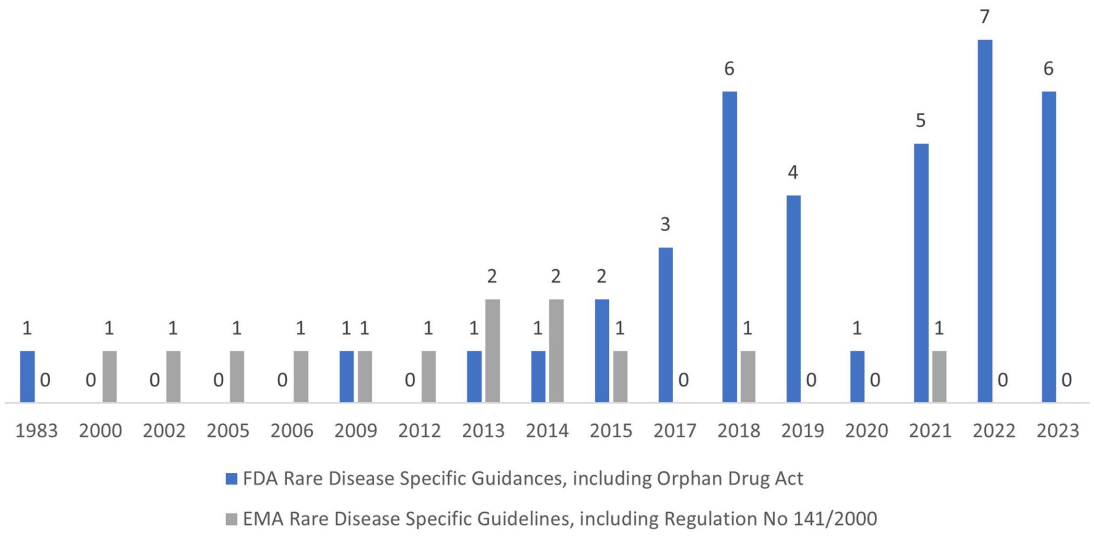

FIGURE 1
FDA and EMA rare disease specific guidances, including Orphan Drug Act and Regulation No 141/2000.

incentives and engagements with major stakeholders in rare disease drug development in addition to collaborative efforts between EMA and FDA in a Rare Diseases Cluster, which was established in 2016. Another noticeable EU initiative, supported by EMA, is Medicines Adaptive Pathways to Patients (MAPPs) which is a concept that seeks to foster access to novel/beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span, in a sustainable fashion. MAPPs is not an official designation and is not intended to create new regulatory or legal frameworks (55). Both FDA and EMA have multiple incentives to facilitate drug development for life-threatening and debilitating diseases. Although, the discussion of these incentives is outside of the scope of this paper, a high-level overview of these incentives and timeline of implementation is presented in Table 1. These incentives in combination with regulatory guidances created a supportive network for rare diseases drug development and reflected in significant increase in orphan drug designation and approvals. For example, FDA approved 470 orphan drugs in the period 2013–2022, which is a 6 fold increase compared to the 80 orphan drugs approvals in the period 1983–1992 (56).

In totality the cumulative efforts that were made by both EMA and FDA resulted in significant increase in drugs for rare diseases, as presented in the next section.

Medicines for rare diseases: overview

To evaluate the impact of changes in the regulatory and access landscapes on the number of rare disease treatments available in US and EU we accessed the GlobalData system. As a "baseline" we extracted all marketed products for the treatment of rare diseases that were listed in the database from 1990–2000, before the ODA and Orphan Drug Regulations in USA and EU, respectively could have reasonably impacted drug approvals. To evaluate the impact of changes in regulatory and access environment we used the same criteria and extracted products for rare disease treatments marketed from 2013–2023. The 1990–2000, timeframe was selected because the drugs marketed during this period were unlikely to have benefited from orphan drug legislative incentives. The 2013–2023 timeframe was chosen, because drugs marketed during this period were considered to have both the time and opportunity to have benefited from orphan drug incentives. We selected all types of products for treatment of rare diseases, including but not limited to small molecules, biologics and combination products. During the EU data analysis it was not possible to establish a clean dataset for EU marketed products due to multiple factors, including but not limited to placement of the same product on the market under duplicate licenses. Therefore, the analysis proceeded with the data from the US only, however, some specific examples of access considerations in EU were evaluated and presented further in this publication. The graphical representation is provided in Figures 2, 3. Figure 2 depicts the total number of products marketed in the USA during the two periods as well as a breakdown of the data by branded and generic products.

Overall, the number of marketed products per decade increased from 255 in 1990–2000 to 1,571 in 2013–2023, a 6-fold increase. This increase clearly indicates that incentives and support, provided to rare disease drug developers, including, but not limited to increase in guidances, had a significant impact on access. When looking at the changes for branded innovator products and generic products separately, both showed a marked increase in availability (3-fold and 11-fold respectively) between 1990–2000 and 2013–2023. The increase in the availability of new treatments is much higher in some therapeutic areas than others, as presented in Figure 3. Therapeutic areas showing a higher increase in new products for Rare Diseases included oncology, metabolic, hematological disorders and central nervous system and cardiovascular disorders. These areas are also ones which in general are current areas of focus for pharmaceutical R&D. Despite the clear increase in the number of products reaching the market for Rare Diseases in 2013–2023 access to these products has presented a variety of challenges, as discussed in the next section.

Access challenges

Timely access to medicines is essential to reduce morbidity and mortality of orphan diseases. However, regulatory approval still does not guarantee access for patients. According to the European Federation of Pharmaceutical industries and Associations there is still considerable variation in time across the EU Member states between the authorization and reimbursement of new medicines with mean time to reimbursement ranging from 102 days in Germany to 993 days in Poland (57).

The US Orphan Drug Act, and the European Orphan Medicinal Product Regulation were big steps toward greater availability of orphan medicines. While orphan designations directly translate into easier access to therapies via compassionate use, and early access programs, the effective access to orphan medicines in a targeted population of interest remains complex as healthcare decision makers need to allocate resources for drug funding within already constrained healthcare budgets. The complexity of access challenges is multifaceted, and may include:

- Requirements for robust evidence by HTA Assessors; Due to low patient numbers, nature of the condition, absence of standard of care orphan disease randomized controlled trials (RCTs) have inherent limitations which may hinder demonstrating therapeutic value for a new therapy, e.g., small sample size, short study duration, use of biomarkers or surrogate study end-points, lack of appropriate comparator in the control arm; [recent examples include elafibranor for the treatment of primary biliary cholangitis (regulatory approval in 2024), talquetamab for the treatment of relapsed refractory multiple myeloma after four prior lines of therapy (regulatory approval in 2023)] which despite regulatory approval failed to demonstrate additional clinical benefit during French HTA assessment [ASMR *Amélioration du service médical rendu* V (absent)] (58–63).
- High cost of therapy, resulting in challenges to demonstrate economic value to local decision-makers (e.g., impact to local healthcare budget high, cost-effectiveness above locally acceptable willingness-to-pay threshold); (the highest costs among orphan drugs are often attached to gene therapies for examples etranacogene dezaparvovec for severe and moderately severe hemophilia B or exagamglogene autotemcel for the treatment of β-thalassemia and sickle cell disease with price tag of $3.5 M and $2.2 M per single administration) (64–69).
- Assessors knowledge and capacity; limited capacity, and/or limited clinical or technical expertise to assess advanced

TABLE 1 Summary of FDA and EMA incentives to facilitate drug development for rare diseases.

Description	Incentives	Year of implementation
EMA		
Orphan drug designation	• Protocol assistance • Access to the centralized authorisation procedure • Ten years of market exclusivity • Additional incentives for small and medium-sized enterprises (SMEs) • Fee reduction • Grants • Incentives in member states	1999 under Orphan Drug Regulation (4, 57),
PRIME	Enhanced support from EMA, tailored to the relevant stages of development Confirmation of potential accelerated assessment	2016 as European commission initiative (94)
Advanced therapy medicinal products (ATMP)	• Enhance scientific support (PRIME) for ATPs • Facilitate approval of clinical trials • Specific action plan for SMEs • Foster increased interaction between EMA and EUnetHTA on ATMPs • 65% fee reduction for a request for scientific advice for ATMPs (90% for SMEs); • 90% fee reduction for the certification procedure.	2008 under EC Regulation No 1394/2007 (95, 104)
Support for micro, small and medium-sized enterprises (SMEs)/ SME office	• Direct contact the SME office for questions about regulations, administrative requirements or procedures • Request a briefing meeting • Receive translation assistance for the product information into all official EU languages • Receive guidance on clinical data publication; • Stay up to date with SME newsletters; • Participate in training events; • Receive support with looking for academic partners in the paediatric-medicine field	2005, Commission Regulation (EC) No 2049/2005 (105)
Conditional marketing authorization (CMA)	• Fast-track approval of a medicine that fulfils an unmet medical need • Must fulfil specific obligations within defined timelines	2004, Regulation (EC) No 726/2004, further elaborated in Regulation (EC) No 507/2006 (106).
Exceptional circumstances	Marketing authorization granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical	2004, Article 14 (8) of the Regulation (EC) No 726/2004 (107)
Accelerated assessment (AA)	Reduce the timeframe to 150 days if the applicant provides sufficient justification for an accelerated assessment	2004, Recital 33 and Article 14 (9) of Regulation (EC) No 726/2004 (108)
Parallel EMA/FDA scientific advice (PSA)	Receiving feedback from both agencies and ability to align product development with both EMA and FDA expectations	2021, collaborative initiative between EMA and FDA (109)
Parallel consultations EMA/HTA (EUnetHTA)	• Streamlined procedure for applicants; • Increased mutual understanding and problem-solving ability between EMA and HTA bodies through a more structured interaction; • Improved coordination with, and greater participation of HTA bodies in parallel consultations through EUnetHTA 21's committee for scientific quality and consistency in its configuration for joint scientific consultations (CSCQ JSC)	2022, collaborative initiative between EMA, HTAs and EUnetHTA (110)
FDA		
Orphan drug designation	• More frequent communication with FDA • Tax credits for qualified clinical testing • Waiver of NDA/BLA user fees • Eligibility for 7-year marketing exclusivity ("orphan exclusivity") upon marketing approval	1983 under Orphan Drug Act (1)
Fast track designation	• More frequent interactions with FDA • Eligibility for accelerated approval and priority review • Rolling review	• 1997 under Food and Drug Administration Modernization Act of 1997 (FDAMA) (111)

(Continued)

TABLE 1 (Continued)

Description	Incentives	Year of implementation
Breakthrough therapy designation	• Eligible for all Fast Track designation features • Intensive guidance on an efficient drug development program, beginning as early as Phase 1 • Organizational commitment involving senior FDA managers	• 2012 under Food and Drug Administration Safety and Innovation Act (FDASIA) (112)
Regenerative medicine advanced therapy designation (RMAT)	Eligible for all the benefits of the fast track and breakthrough therapy designation programs	2016 under 21st Century Cures Act (113, 120)
Priority review	• Shorter clock for review of marketing application • 6 months compared to 10 months	1992, under the Prescription Drug User Act (PDUFA) (114)
Accelerated approval	Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	2012 under Food and Drug Administration Safety and Innovation Act (FDASIA) (115)
Real-time oncology review (RTOR)	Expedite drug approval review: FDA reviews clinical data throughout the development process, and before a company formally applies for approval	2018 under collaboration of FDA Oncology Center of Excellence (OCE), with the Office of Oncologic Diseases (OOD) (116, 119)

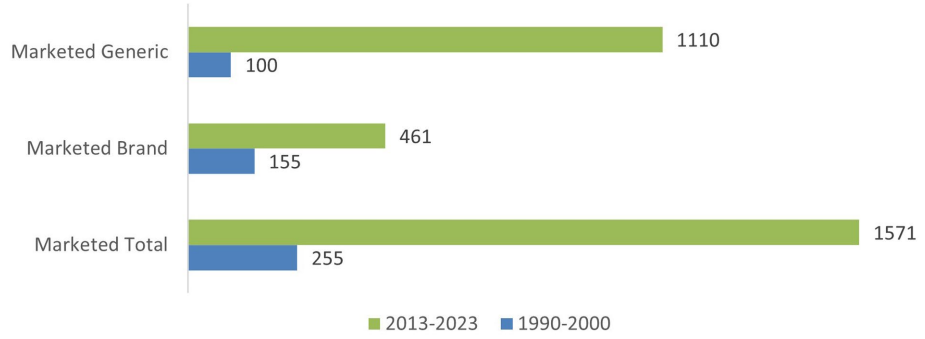

FIGURE 2
Comparison of rare disease products in USA between 1990–2000 and 2013–2023 by type of product: brand or generic.

statistical and health economic methods submitted within product evidence package
- Legislation and policy; lack of uniform value assessment and appraisal process across markets, lack of innovative access models to manage "one-time-administration" potentially curative advanced therapy medical products

Although it is beyond the scope of this publication to describe the evolution of the pricing, reimbursement and access landscape of both the USA and the EU member countries, we have explored access context of the leading European markets such as Germany and France to compare to the evolution of regulatory policies previously described. Although reimbursement legislation and policies vary across the EU member states, they all provide public healthcare coverage. We delve into Germany and France as the first two countries in terms of pharmaceutical market value in Europe (€47.588 billion and €32.077 billion sales in 2021, respectively) (70). Among the key five European markets (4 EU member states and UK) Germany and France had historically the best access indicators for orphan medicines (number of medicines reimbursed and months to reimbursement) (71). In both countries reimbursement is linked to the outcomes of national health technology assessment (HTA) and medicines with positive HTA recommendation are funded through healthcare payer budgets. In contrast to primarily cost-effectiveness HTA framework, both countries have a system driven by assessment of clinical benefit and reimbursed price based on the demonstrated level of additional clinical benefit over standard of care therapies, German policies incentivize access to all medicines through a 6-month free pricing mechanism and availability immediately upon EMA regulatory approval (117). Moreover, access to orphan drugs is facilitated given that these medicines are exempt from the full HTA (i.e., the need to demonstrate benefit versus an appropriate comparator) and approval is granted based on a minimum level of additional benefit. Orphan medicines are required to undergo full HTA only after exceeding the threshold of €30.0 million annual sales (117). In contrast, there is no designated market access pathway for orphan medicines in France, but there are early access (EA) mechanisms in place allowing innovative medicines to be funded prior to the EMA regulatory approval and/or prior to the completion of the HTA (72). The EA mechanism has proven particularly effective for rare genetic conditions that are highly debilitating, especially those with early-onset: since 2016 the EA program facilitated access of three innovative therapies for spinal muscular atrophy (SMA) type 1, 2 or 3: 48 patients were enrolled in the nusinersen EA program (Oct 2016–Jun 2017), 14 patients enrolled in onasemnogene abeparvovec EA program of (Jun 2019–May 2020)

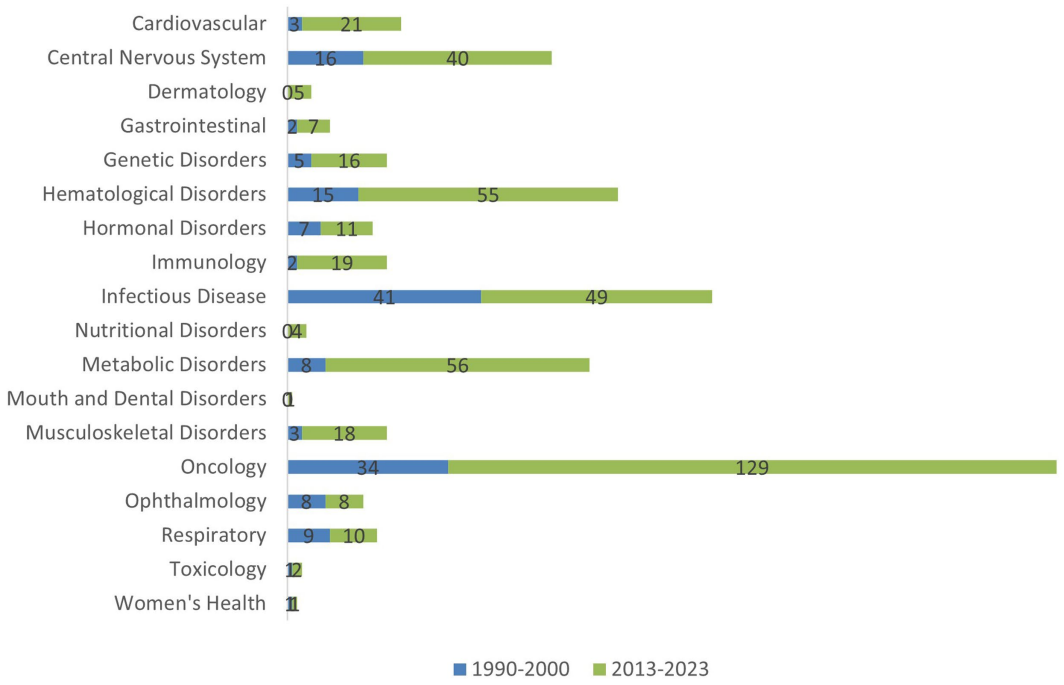

FIGURE 3
Comparison of marketed brand products for rare disease products by therapeutic area in USA.

and 110 patients enrolled in risdiplam EA program (Dec 2020–Apr 2021) (73, 74).

While there are additional similarities and differences in the reimbursement processes between Germany, France, and other EU member states, these are not expected to significantly impact access to orphan medicines and are outside the focus of this publication.

In the US, access to orphan drugs, like other drug products, is governed by the major purchasers of healthcare in the US which are largely the government programs of Medicare, Medicaid, and health insurance exchanges, and the employer-sponsored insurance market. Typically, orphan drugs require prior authorization, which is a mechanism payers use to manage utilization and ensure that physician drug choices are clinically appropriate and within label. Orphan drugs, due to their high cost, usually have fairly detailed prior authorizations, which may require submission of clinical documentation and justification of medical necessity. Prior authorizations for orphan drug products often include some key inclusion/exclusion criteria from clinical trials, in an effort to achieve the clinical outcomes seen in that setting. While a critical tool to ensure appropriate use, prior authorizations can result in delays in treatment. Most patients in the US market experience some form of cost sharing for drugs as well, which can create another barrier to access.

In Germany and France, the reimbursement of orphan medicines in therapeutic areas in which an increase in availability was noted (oncology, central nervous system, hematological and metabolic disorders) has largely followed the regulatory pace with some delays in time to effective access driven by the time taken for the HTA assessment and price negotiation (e.g., in France). The areas with more prominent differences between the number of regulatory approvals, access in the US and that in the EU members states are rare genetic diseases with recent approvals of novel gene therapies. Among the 7 non-oncology gene therapies which had FDA and EMA regulatory approvals (<etranacogene dezaparvovec for severe haemophilia B, betibeglogene autotemcel for transfusion-dependent beta-thalassemia, onasemnogene abeparvovec for spinal muscular atrophy, valoctocogene roxaparvovec for severe hemophillia A, voretigene neparvovec for retinal dystrophy, exagamglogene autotemcel for sickle cell disease and transfusion-dependent β-thalassemia, and lovotibeglogene autotemcel for metachromatic leukodystrophy), all 7 are funded and available in the US, 5 received positive HTA recommendations in Germany and France (etranacogene dezaparvovec, onasemnogene abeparvovec, valoctocogene roxaparvovec, atidarsagene autotemcel, and voretigene neparvovec), but information on effective access including price were not identified for etranacogene dezaparvovec, nor valoctocogene roxaparvovec in France (64–67, 73, 75–91, 118). Potential uncertainties associated with perceived drug value and long-term treatment benefits were mitigated with mandatory data collection and/or re-assessment upon more evidence being available. In addition to the evidence driven hurdles during the HTA process, access to orphan medicines in the EU-member states, such as Germany and France, may be driven by manufacturer decision to opt out in instances when healthcare payer acceptable price is not commercially viable for manufacturers. Although these are rather exceptions, after unsuccessful price and reimbursement negotiations in Germany Bluebird decided to focus betibeglogene autotemcel efforts on the US market citing "*challenges of achieving appropriate value recognition and market access in Europe*" (92). Which lead to complete withdrawal of the EMA authorization in 2022 (75).

Manufacturers of orphan drug products sold in the US are free to set and change price according to market demand, and all payers

are compelled to provide access to products deemed medically necessary (or justify why it is not medically necessary for that patient). This has resulted in multi-million dollar prices for one-time administrations of gene therapies, albeit with substantial authorization criteria from payers, both government and private. Yet, these are sometimes life-saving and life-changing therapies, so from a health economic perspective, many gene therapies are cost-effective in the short and long term views.

The pricing of many orphan drug products in the US has created an access environment in which they are likely to be covered for eligible patient populations, but with real financial impact to public and private payers. This has spurred the development of risk-sharing agreements in which failure to achieve a clinical outcome is tied to some level of financial remuneration. These agreements, when in place, offer some downside protection to payers while also ensuring access to these medications for patients.

Overall, access to orphan medicines is complex and multi-faceted. Local healthcare decision makers have made steps and progress in implementing mechanisms to facilitate access, but the work is still ongoing in making therapies timely available to all the patients in need.

Discussion

It is clear from the data examined that the implementation of legal frameworks and incentives, the availability of guidance documents and the partnerships and support provided by global regulatory agencies has created an environment which has clearly resulted in an increase in the regulatory approval of new medicines for rare diseases, although the speed of this change was slow, despite of the positive trend, for example there were 6 folds increase in rare disease drug approvals by FDA in the period from 2013 to 2022 in comparison to 1983–1992 (56).

In the US and Europe, regulatory agencies support programs (e.g., EMA's support for early access and four FDA's Expedited Programs: Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval and Priority Review Designation) are available to facilitate and expedite clinical development and regulatory approval with the aim to foster timely access to patients with serious conditions and clear unmet medical need (93, 94). The programs consider iterative processes including early dialog with manufacturers in preparation of technical and scientific aspects of the regulatory submissions (93, 94).

In the US over the last two decades, both public and private payers have dealt with the advent of high-cost, clinically innovative orphan drug products by attempting to manage access as close to the clinical trial population as possible. While sometimes onerous and resulting in delays in therapy, this approach has worked well to ensure that appropriate patients are receiving medically necessary treatments.

More recently, with the launch of gene therapies in orphan disease areas, risk sharing agreements have become more commonplace to address the financial impacts on payers (95). While in its infancy, this represents movement toward the objective of aligning payment for value, as defined by clinical outcomes.

In Europe, local decision makers have introduced policies and mechanisms to facilitate access to medicines while managing constrained budgets, yet there are still hurdles to overcome. In 2013, the Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA) was established at the European Level between volunteering EU stakeholders and developers of Orphan Medicinal Products with the aim to support the exchange of information, enable informed decisions on pricing and reimbursement at EU-member state level and assess the value of orphan medicines based on a transparent framework (96, 97). MoCA created a voluntary and flexible framework for non-binding dialog between different stakeholders with the main objective to *"support more equitable access to authorized therapies for people living with rare diseases, rational prices for payers and more predictable market conditions for Orphan Medicinal Products developers"* (98). During the 10-year MoCA pilot program 23 orphan products were discussed involving industry, payer/HTA and patient representatives. Although informal and non-binding, one of the key drivers of accelerating access to orphan medicines of this pilot is the collaboration between industry, payers, and patient advocacy groups with a common goal to ensure that clinical development addresses the unmet needs and ensures access once approved. In 2022, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Organization for rare Diseases (EURORDIS) issued a joint statement bringing forward proposals to bolster HTA process and pricing and reimbursement framework for orphan drugs (99). Finally, the new Joint Clinical Assessment Process (starting in 2025 and applicable to orphan medicines from 2028 on) aims to ensure a uniform clinical assessment at the EU level and facilitate HTA collaboration across EU member states with the final goal of accelerating access to medicines (98, 100).

These changes reflect a growing recognition of the importance of addressing the needs of rare disease patients and a concerted effort to balance innovation with affordability and access.

In looking at the more than three decades over which progress on the number of new medicines for rare diseases has been made, it is difficult to conclude that the implementation of legal regulations alone was sufficient to drive change. It was only when the regulatory agencies, pharmaceutical industry, patient groups and other stakeholders worked together that progress became significant. The requirements around the need to ensure safety, efficacy and quality for orphan drugs is not reduced because patient numbers are small. However, an alignment was created on acceptable, innovative ways to meet these requirements in the context small patient numbers, through the use of non-traditional data sources and integrative evidence approaches. This enables sponsors to develop new orphan drugs in collaboration with regulators and patients and helps to ensure that the needs of both are met.

In contrast to the partnership among multiple stakeholders and the increasing progress of new drug development paradigms in the development and regulatory approval of orphan drugs, the subsequent access to those medicines over the same period was still globally fragmented. In Europe the EFPIA and EURORDIS proposal and the new Joint Clinical Assessment Process should increase the uniformity of clinical assessment and provide a pricing and reimbursement framework for orphan drugs. These changes reflect a growing recognition of the importance of addressing the needs of rare disease patients and a concerted effort to balance innovation with affordability and access. It is hopeful that a similar collaborative approach, that was successful in the regulatory approval space, if successfully translated into the market access and pricing arena would result in a similar step

change in the timely access to new medicines for rare diseases. It may already be too late for companies with gene therapies for rare diseases. These companies struggle to make therapies profitable given a small pool of eligible patients and challenges in scalability. Following layoffs in 2024 and struggles with cash flow, Bluebird Bio, which has been a pioneer in gene therapy development, announced in February 2025 its acquisition by Carlyle to secure a financial path forward for the company (68). At the same time Pfizer announced its decision to stop the commercialization of Beqvez (101). This news follows previous indications that other companies are also struggling with multiple companies pulling their development programs in this space, CSL reporting slower-than-expected sales for Hemgenix and BioMarin's decision to focus commercialization of Roctavian on markets where it is reimbursed (102, 103). We hope that these examples of the challenges to successful commercialization will bring more public and government attention in order to encourage establishment of innovative approaches to the ensure commercial success for gene therapies.

Author contributions

FB: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. MV: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SS: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. GF: Conceptualization, Writing – original draft. OI: Conceptualization, Project administration, Writing – original draft, Writing – review & editing.

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FB, MV, SS, GF, and OI are employed by company Certara.

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Bridging the gap: enhancing blood regulatory functions in African contexts through comparative analysis

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Introduction: Independent assessments of blood regulatory systems, facilitated by tools such as the WHO's Global Benchmarking Tool (GBT) plus Blood expedites development of National Regulatory Authorites (NRAs) and thus promotes increased access to safe, effective, and quality blood, blood components, and products. The aim of this study was to assess and compare the status of implementation and performance of the regulatory functions for registration and marketing authorization as well as the system for approval of blood, blood components and plasma for fractionation or processes.

Methods: We did this by conducting assisted self-benchmarking in 12 African countries using the GBT plus Blood (registration and marketing authorization function, 34 sub-indicators and approval of blood, blood components, and plasma for fractionation or processes function, 24 sub-indicators). Comparative assessments of WHO-designated maturity level 3 (ML3) NRAs for medicines and vaccines against non-designated NRAs were made.

Results: The percentage of implemented sub-indicators was higher for the registration and marketing authorization function with an average implementation score of 73% (range: 51%–92%) compared to the approval of blood, blood components, and plasma for fractionation or processes function which had an average implementation score of 45% (range: 6%–65%). The comparison of group averages for the ML3-designated NRAs against the non-designated NRAs revealed a higher score 91% (range: 71%–100%) for ML3-designated NRAs as opposed to a lower score of 71% (range: 49%–100%) for the non-designated NRAs for the registration and marketing authorization function. This pattern, however, was not observed for the comparison of group averages for the approval of blood, blood components, and plasma for fractionation or processes function where the ML3-designated NRAs scored 47% (range 19%–72%) against 46% (range 23%–88%) for the non-ML3-designated NRAs.

Conclusion: Most of the NRAs excelled in implementing sub-indicators for the registration and marketing authorization (of plasma-derived medicines) function. All NRAs exhibited notable flaws in regulating blood, blood components, plasma for fraction, and approval of processes, indicating nascent regulatory frameworks. This study highlights the urgent need for WHO and African countries to prioritize formal benchmarking of NRAs using the GBT plus Blood to enhance their regulatory capacities in blood and blood product regulation.

KEYWORDS

blood and blood products, global benchmarking tool, Sub-Saharan African countries, availability of safe blood, GHPP BloodTrain

Introduction

The need for blood regulation arises from the inherent dangers of blood and blood products, and the complexities of preparation of whole blood and blood components for transfusion and the manufacture of plasma-derived medicinal products (1–3). Threats to blood quality and blood safety from different viruses and from newly emerging blood-borne diseases have resulted in increased blood quality and safety concerns (4). In Africa, major concerns remain over safety risks posed by high rates of transfusion transmissible infectious diseases in the general population (4–6).

Recognising blood and blood products as essential medicines highlight their crucial importance in healthcare systems (7, 8). Every country needs to have an assured supply of safe, efficacious, good quality and affordable blood, and blood products to promote public health and patient care (9, 10). The lack of effective blood regulatory systems can thus be a barrier in access to blood, blood components, and blood products (11). The need to ensure "appropriate regulatory systems" in the area of quality and safety of blood and blood products was recognized in the 2010 World Health Assembly resolution 63.12 (12). Robust and effective blood regulation therefore plays a vital link between improving equitable access to blood and blood products, promoting adequacy of blood supply and assuring blood quality.

Competent national regulatory authorities (NRAs) have the mandate to ensure consistent compliance with appropriate quality and safety standards for blood and blood products. This is achieved through a set of regulatory control measures such as registration and marketing authorization of plasma-derived medicines and approval of blood, blood components, including plasma for fractionation (concerning the product and/or the manufacturing process) among others (3, 13). The former pertains to the mechanism for issuance of marketing authorizations, or registrations, of plasma derived medicines subsequent to an evaluative procedure assessing their quality, safety, and efficacy (14–16). The approval of blood, blood components, and plasma for fractionation involves a regulatory mechanism ensuring the adherence to established standards for quality, safety, and efficacy, as well as the suitability of product information pertaining to blood and its components, including plasma for fractionation, or the processes involved in their preparation (14–16). NRAs play an integral role in national blood systems destined to ensure equitable access to essential blood and blood products of assured quality, safety, and efficacy (17).

Independent assessment of blood-related regulatory functions (such as those detailed above) and their implementation in a country has the potential to bolster confidence in regulatory competence. Moreover, such assessments have the capacity to catalyse the augmentation of NRA competencies in blood regulation and ultimately improve access to safe, effective, and quality blood and blood products (3, 13). The WHO has included blood and blood product regulation in its Global Benchmarking Tool (GBT) for the evaluation of national regulatory systems for blood and blood products (14–16). The GBT plus Blood is used to assess and measure the performance of each regulatory function, that is the national regulatory system, registration and marketing authorization, vigilance (haemovigilance), licensing of blood establishments, market control and post-marketing surveillance, regulatory inspections, clinical trial authorization, lot release and lab access, approval of blood and blood components including plasma for fractionation (or processes involved in their preparation), and approval of medical devices and associated substances and *in-vitro* diagnostic (IVD) and medical devices (14, 15). The evaluation assesses competencies and maturity of blood regulation at the NRA and identifies deficiencies as a basis for continuous improvement (10).

WHO estimates that only 30% of NRAs have adequate capacity to perform the core regulatory functions for medicines and vaccines globally (18, 19). Further, only 37% of countries in Africa reported having a system for authorization and/or approval of blood establishments as well as licensing of blood establishments in the WHO Global Status Report on Blood Safety and Availability (2018) (11). Detailed information on the performance of countries in blood regulatory functions, however, is lacking. In the meantime, WHO has designated only 8 countries (Egypt, Ghana, Nigeria, Tanzania, Rwanda, Senegal, South Africa, and Zimbabwe) in Africa to be operating at maturity level 3 (ML3), that is having the minimal capabilities of a stable, well-functioning and integrated regulatory system to meet local needs. Of these, only Egypt is ML3 for both medicines and imported vaccines (non-producing) and also ML3 for local vaccines (producing). Ghana, Nigeria, Tanzania, Rwanda, Senegal, and Zimbabwe are only ML3 for medicines and imported vaccines. South Africa is ML3 only for local vaccines (producing).

The aim of this study was to assess and compare the status of implementation and performance of the system for registration and marketing authorization as well as the system for approval of blood, blood components, and plasma for fractionation or the respective manufacturing processes in Africa. We did this by conducting assisted self-benchmarking assessments in 12 countries using the WHO GBT plus Blood over a 5-year period. Further, we compared the implementation and performance of countries that are already deemed to be operating at maturity level 3 (ML3) for medicines and vaccines (non-producing) and/or deemed to be operating at ML3 for local vaccines (producing) against those yet to achieve this status. These comparisons provide vast potential for within and cross-country learning by offering a way to explore different approaches countries take to address similar problems to achieve comparable objectives.

Methods

Study design

This cross-sectional descriptive study examined the existing systems for the registration and marketing authorization of plasma-derived medicines, as well as the approval processes for blood, blood components, and plasma for fractionation in 12 Sub-Saharan African countries: Ghana, Ethiopia, Nigeria, Malawi, Kenya, Liberia, Rwanda, Uganda, South Africa, Tanzania, Zambia, and Zimbabwe. Table 1 provides an overview of the National Regulatory Authorities (NRAs) and the blood regulatory systems that were benchmarked, along with the dates when the data from these systems were updated. The self-benchmarking process is detailed in the WHO Global Benchmarking Tool (GBT) for evaluating national regulatory systems for medical products, and the "Manual for Benchmarking and Formulation of Institutional Development Plans" (20).

Indicators and sub-indicators

The GBT plus Blood employs a comprehensive set of 14 indicators which are utilized for the registration and marketing authorization ($n = 6$), as well as the approval of blood, blood components, and plasma for fractionation or process functions ($n = 8$). These indicators are further divided into 58 sub-indicators to comprehensively compare, evaluate, and measure the performance and implementation of these two blood regulatory functions. For the registration and marketing authorization function, six indicators are used, each covering the following specific themes (1) legal provisions, regulations and guidelines, (2) organisation and governance, (3) human resources, (4) regulatory processes, (5) transparency and accountability, and (6) monitoring progress and assessing impact. Conversely, the approval of blood, blood components and plasma for fractionation or processes function was evaluated using eight indicators, each covering a specific theme: (1) legal provisions, (2) system to ensure quality, safety, and efficacy of blood and blood components, (3) criteria for donor selection and deferral, (4) requirements for transmissible-disease testing, (5) requirements for labelling, (6) approval system for blood and blood components, (7) requirements for post-approval changes, and (8) existence of appropriate expertise. This structured approach ensures consistency in the GBT plus Blood tool (15, 20). Furthermore, the GBT plus Blood tool comprises both common sub-indicators (applicable to medicines, vaccines, and blood and blood products) and specific (non-common) sub-indicators (blood and blood product specific sub-indicators). For the function of registration and marketing authorization, there are non-common sub-indicators ($n = 3$) and common sub-indicators ($n = 31$), while the approval of blood, blood components, and plasma for fractionation or processes utilizes only non-common sub-indicators ($n = 24$).

The WHO GBT also incorporates the maturity level concept from the International Standard Organisation (ISO) 9004:2018 (15, 19). This concept enables the assessment of the status and performance of regulation with a variety of indicators and sub-indicators and gives an overall view of the NRA's maturity based on the achievement of general benchmarks in regulatory practice. The maturity levels for the sub-indicators are distributed as shown in Supplementary Tables 1a, b.

While in some of the countries, sub-indicators for ML4 were also assessed, this was not done in all areas, therefore not allowing a general analysis. Therefore, the results are not included in this publication.

Benchmarking methodology and data collection

Before visiting the participating NRAs, authorization and approval for the benchmarking was sought from the heads of agencies via e-mail in 2018. Key individuals with overall responsibility and knowledge of the respective national system in each country were identified. They were informed about the assessment and asked to share the legal and statutory documents and other relevant information with the external assessment team before the benchmarking visit. The documents requested were extracts of national legislation describing responsibilities of the function of the registration and marketing authorization and/or the systems for approval of blood, blood components, and plasma for fraction, regulations, and guidelines.

A priori data from the previous self-benchmarking by the NRA was also sent to the Paul-Ehrlich-Institut (PEI) BloodTrain team, where it was available and was used to pre-fill the sub-indicators before each visit. The actual assisted self-assessment was carried out on-site at each of the NRA's premises with the NRA's team as an assisted self-benchmarking exercise to complete the WHO GBT plus Blood. The initial self-assessments and data collections in the 12 countries were conducted from 2018. Further, updated data was collected from each NRA, where specific updates and changes were available from in July 2021 and in April 2022 and validated by the same team and where there were updates these were noted (See Table 1).

The benchmarking principles on assessment procedures and conducting benchmarking assessments (how to score, evidence to review) that are enshrined in the WHO Manual for benchmarking of the national regulatory system of medical products were applied

TABLE 1 Benchmarking and updates of national blood regulatory systems across 12 countries.

Country	National Regulatory Authority	Blood Collection and Supply Institution	Initial benchmarking	Blood regulatory systems		
			2018	2021	2022	2023
Ethiopia	Ethiopian Food and Drug Administration (EFDA)	National Blood Bank Service and Red Cross Society	✓	✗	✓	✗
Ghana	Food and Drugs Authority Ghana	National Blood Service Ghana	✓	✓	✓	✓
Kenya	Pharmacy and Poisons Board (PPB)	Kenya National Blood Transfusion Service	✓	✓	✓	✗
Liberia	Liberia Medicines and Healthcare Products Regulatory Authority (LMHRA)	Blood Safety Program, Ministry of Health	✓	✗	✓	✗
Malawi	Pharmacy Medicines and Poisons Board of Malawi (PMPB)	Malawi National Blood Transfusion Service	✓	✗	✓	✗
Nigeria	National Agency for Food and Drug Administration and Control	National Blood Transfusion Service of Nigeria, Regional and State Blood Transfusion Services	✓	✓	✓	✗
Rwanda	Rwanda Food and Drugs Authority (RFDA)	National Centre for Blood Transfusion	✓	✗	✓	✗
South Africa	South African Health Products Authority (SAHPRA)	South African National Blood Service and Western Cape Blood Service	✓	✓	✓	✓
Tanzania	Tanzania Medicines and Medical Devices Authority (TMDA)	National Blood Transfusion Service Tanzania and Regional Hospitals	✓	✓	✓	✓
Uganda	National Drug Authority (NDA)	Uganda Blood Transfusion Services	✓	✗	✓	✗
Zambia	Zambia Medicines Regulatory Authority	Zambia National Blood Transfusion Service	✓	✓	✓	✓
Zimbabwe	Medicines Control Authority of Zimbabwe (MCAZ)	National Blood Services Zimbabwe	✓	✓	✓	✓

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(20). The GBT plus Blood was completed by senior staff from the registration and marketing authorization of blood products and approval of blood (product/process), blood components, and plasma for fractionation teams of the national regulatory agencies with the support of the BloodTrain team. Data were collected and recorded in the data collection module of the WHO GBT application and validated by the BloodTrain team.

To determine whether a sub-indicator was implemented or not, the NRA had to provide documentary evidence and references. When documentary evidence such as legislation (Act or Regulation), policy, and/or guidelines that were being implemented and enforced were available, the sub-indicator would be scored "Implemented" and the system would give a numerical score of 1. When the NRA had documentary evidence (such as legislative provisions, policy, guidelines or procedures) without any further evidence of implementation or was still at the initial stages of implementation of their legal requirements, the sub-indicator was scored "partially implemented" and the system scored the sub-indicator with a score of 0.75 (20). When the NRA had recently drafted legislation or guidelines that were not being followed, the sub-indicator was scored "ongoing implementation" and the system would give a numerical score of 0.25. When the NRA was not implementing the sub-indicator or had neither documentary evidence nor references to satisfy the requirement of the sub-indicator, then the sub-indicator was scored "not implemented" and the system would give this a numerical score of 0.

While in some NRAs the indicators up to ML4 were assessed during the piloting of the tool, this was not done systematically. Therefore, the focus of the data analysis for the 12 African NRAs was up to ML3.

Data analysis

The data from each country's self-assessment were collected in the WHO GBT plus Blood data collection module and exported into a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) template from the WHO GBT plus Blood with all indicators.

To determine the status of implementation of registration and marketing authorization and approval of blood and blood components sub-indicators in each country, the sum of the sub-indicator scores were expressed as a percentage of the maximum score that could be obtained. Similarly, to determine the performance of specific registration and marketing authorization and approval of blood and blood components functions, the sum of sub-indicator responses for each indicator was analysed. The maturity levels of the two regulatory functions of each country were analysed by comparing the sum of the responses to each of the sub-indicators against their maturity levels. Additionally, we compared the implementation and performance of WHO-designated ML3 NRAs for medicines or vaccines (producing or non-producing) against those that are not WHO-designated ML3 NRAs by averaging the groups and expressing this as percentage. The authorities were anonymized randomly for the presentation of results.

Results

Overall, a greater number of sub-indicators were implemented for the registration and marketing authorization function compared to the approval of blood and blood components or processes function. For the registration and marketing authorization function, the average score for implementation of sub-indicators was 73% (range: 51%−92%), with eight countries achieving a score of at least 80% (Figure 1). In contrast, for the approval of blood and blood components including plasma for fractionation function, the average score for implementation was 45% (range: 6%−65%) with five countries having an implementation score of at least 50%. We also noted that, for the two functions, none of the NRAs scored 100% implementation of all sub-indicators and as such none of the NRAs were operating at ML3 level for the 2 functions for blood regulation.

All NRAs had legislative provisions mandating them to perform the registration and marketing authorization function with all NRAs implementing on average 70% (range: 67%−92%) for this indicator (Figure 2A). The procedures to perform registration and marketing authorization were the least implemented indicator among the 12 NRAs with an average implementation score of 57% (range: 27%−85%). The rest of the indicators for the registration and marketing authorization function had good implementation scores. For the same function, we also observed that the non-common sub-indicators were not fully implemented in any of the NRAs.

Among the eight indicators for approval of blood and blood components or processes function, the highest average implementation scores were observed for the following indicators: availability of appropriate assessment expertise 80% (range: 0%−88%), existence of legal provisions for systems to ensure quality, safety, and efficacy of blood and blood components 67% (range: 0%−100%), approval system for blood and blood components is in place 53% (range: 0%−100%) and donor selection and deferral criteria are established 52% (range: 13%−88%) (Figure 2B). The remaining indicators had average implementation scores below 50%.

We noted that those NRAs that operated already on ML3 for medicines and vaccines (producing or non-producing) had a higher average implementation score, which was 91% (range 71%−100%), than those that were not for the registration and marketing authorization (of plasma-derived medicines) function (Figure 3A). Further, the implementation scores were lower for the approval of blood and blood components or processes function both for those NRAs already WHO-designated ML3 (47% range 19%−72%) and those that were not (46% range 23%−88%) (Figure 3B). We further noted that for four indicators of the same function the non-WHO designated ML3 NRAs had the same average implementation scores or better than those of WHO designated ML3 countries.

Discussion

Our study showed good implementation and performance of the registration and marketing authorization (of plasma-derived medicines) function in 9 of the 12 NRAs with scores above 72%, based on the WHO defined scoring system indicated in the WHO

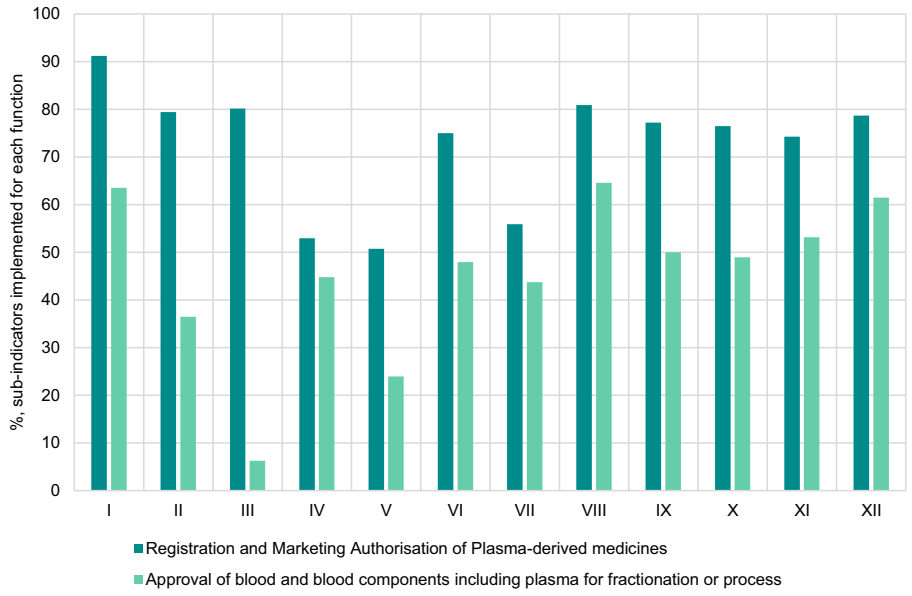

FIGURE 1
Overall implementation of registration and marketing authorisation of plasma-derived medicines and approval of blood and blood components including plasma for fractionation or processes functions in benchmarked country NRAs.

Manual for benchmarking of the national regulatory system of medical products and formulation of institutional development plans (20). However, the approval of blood, blood components, and plasma for fractionation or processes function demonstrated considerable deficiencies in its implementation and performance. We further noted substantial flaws in implementing specific (sub-indicators relating to blood and blood products in both functions. Our findings also showed the approval of blood, blood components, and plasma for fractionation or processes function had lower implementation scores compared to the registration and marketing authorization (of plasma-derived medicines) function. Additionally, the implementation and performance of the approval of blood, blood components, and plasma for fractionation or processes function was comparable between NRAs at ML3 and other NRAs. Notably, no NRAs achieved the stable, well-functioning, and integrated system or maturity level 3 rating for blood and blood products. These insights can be integrated into existing efforts to enhance blood regulation in African countries (13).

In our comparison of the two blood regulatory functions, we observed that 9 out 12 NRAs demonstrated high implementation of sub-indicators (with scores above 72%) for the registration and marketing authorization (of plasma-derived medicines). The implementation of sub-indicators for the approval of blood, blood components, and plasma for fractionation or processes function showed significant shortcomings, with only four NRAs achieving implementation scores above 50%. This observation aligns with the global trend in the development of blood and blood product regulation, where stringent regulation for plasma-derived medicines followed immediately after the tragic scandals of transfusion-transmitted AIDS infections by blood transfusions and plasma derivatives (5, 21, 22). Plasma-derived medicines became subject to pharmaceutical legislation in Europe since 1989 and are similarly regulated in all 12 NRAs and the regulatory function is therefore well-implemented (22–25). Blood and blood components are subject to the blood directive (Directive 2002/98/EC) which has been transposed into national law in all EU states since 2002, much later than the establishment of regulation for plasma-derived medicines (23, 24, 26, 27). Comparable to Europe, other countries such as Australia, Canada, Japan, Singapore, South Korea, and Switzerland also saw the evolution of stringent regulation for blood and blood components occurring later than that for plasma-derived medicines (28).

Despite most NRAs in our study attaining high scores for implementing the registration and marketing authorization function, they fell short of fully implementing the three specific sub-indicators associated with blood and blood products. Notably, the common sub-indicators for medicines and vaccines were consistently well-implemented and NRAs with WHO designated ML3 status demonstrated effective implementation of these common sub-indicators (13, 20, 29, 30). WHO-designated ML3 NRAs and other NRAs in our study have invested effort in strengthening this function, and benefitted from the focused approach to build capacities and strengthen systems that WHO and other development partners have taken to improve the registration and marketing authorization function for medicines and vaccines (29, 31).

We found that most NRAs scored low in implementing the specific function "approval of blood, blood components, and plasma for fractionation or processes." Even the more mature NRAs in our study were struggling in implementing the specific sub-indicators related to blood and blood products only. Coupled with the lack of full implementation of the non-common sub-indicators for the registration and marketing authorization function, it is evident that there are significant challenges for African NRAs in implementation of blood regulation, impacting the provision

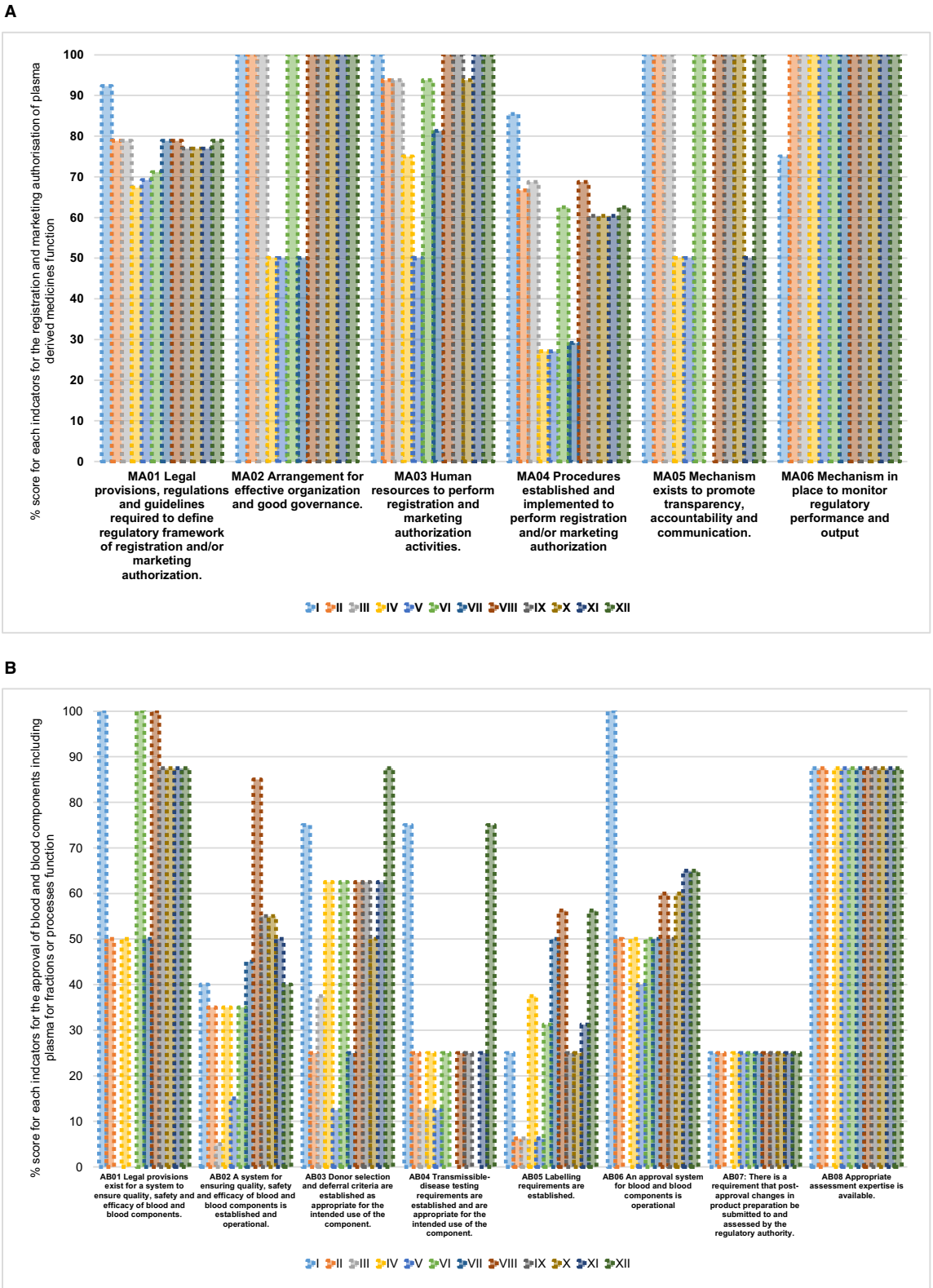

FIGURE 2
(A) Overall performance of registration and marketing authorization of plasma-derived medicines function in benchmarked country NRAs. **(B)** Overall performance of approval of blood and blood components including plasma for fractionation or processes function in benchmarked country NRAs

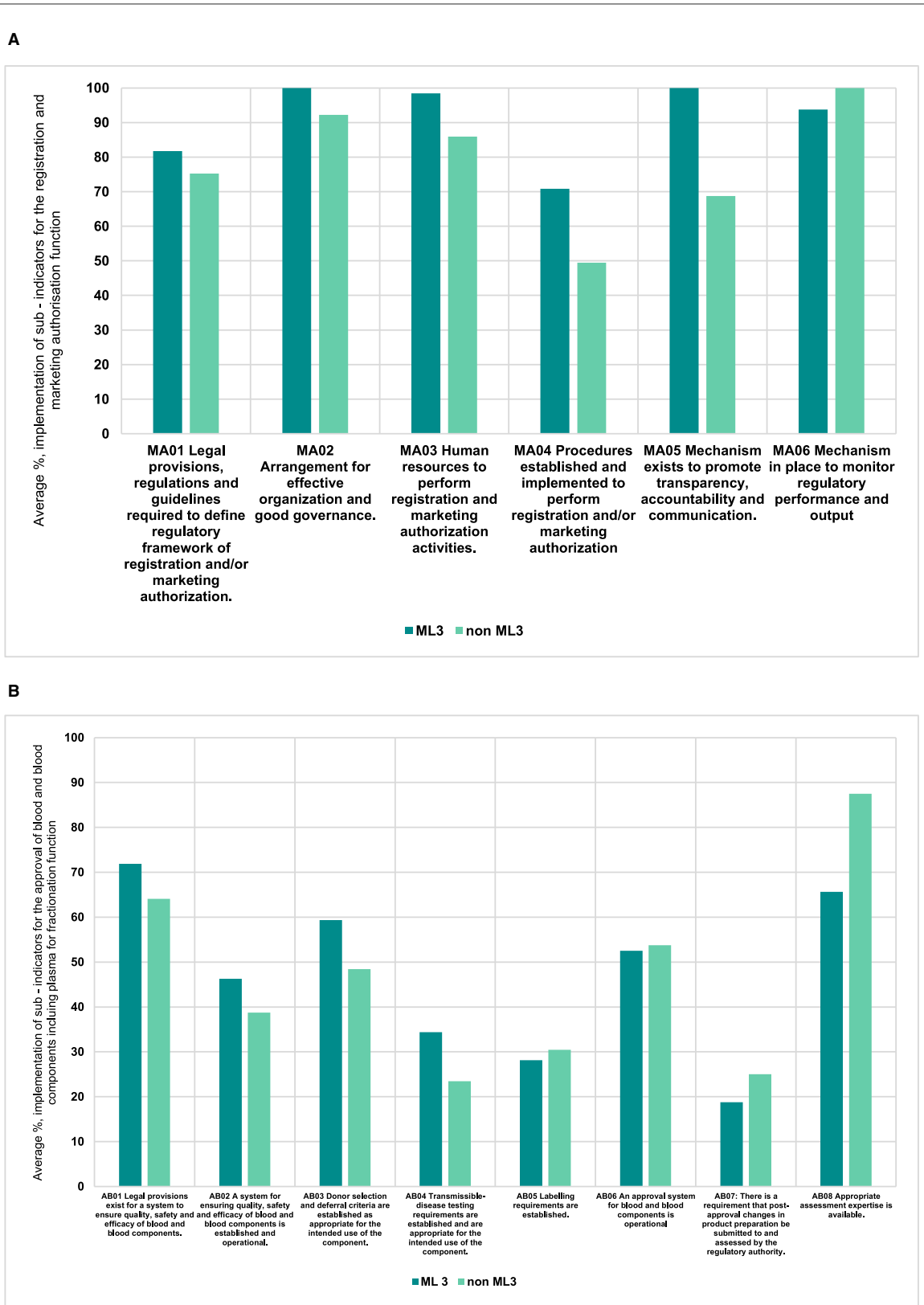

FIGURE 3
(A) Comparison of performance of indicators for ML3 NRAs vs non ML3 countries for the registration and marketing authorization function (plasma — derived medicines). **(B)** Comparison of performance of indicators for ML3 NRAs vs non ML3 countries for the approval of blood and blood components including plasma for fractionation function.

of safe, quality-assured blood and blood components (5, 6, 32). Of note is that independent national blood systems in African countries have developed with less stringent regulatory oversight, a similar observation reported in the EU as well (2, 22). Overall, the results we observed are synonymous with regulatory systems that are still in their early phases of implementation (22, 24, 25). Moreover, there are limited global initiatives to support low-and-middle income countries in enhancing their blood regulatory functions and capacity building. Most notable among the few current international opportunities to support blood and blood regulation in developing countries is the Bundesministerium für Gesundheit (Federal Ministry of Health, Germany) financed Global Health Protection Programme (GHPP)'s BloodTrain project that is implemented by the Paul-Ehrlich-Institut (9, 10, 33–36). The recently ended WHO Action Framework to Advance Universal Access to Safe, Effective and Quality-Assured Blood and Blood Products (2020–2023) was another renewed effort from WHO to among other things strengthen blood regulation (30).

Throughout our study, we came across concrete examples of common problems and challenges in implementing requirements of the WHO GBT plus Blood for the two functions across all NRAs which have been repeatedly reported for medicines and vaccines regulation. We identified four primary issues in our study as major challenges for blood regulation coming from both regulatory functions include: (1) legal provisions (system for ensuring quality, safety, and efficacy of blood and blood components), (2) selection, deferral and transmissible-disease testing requirements for blood, blood components, plasma for transfusion, and plasma for fractionation (6), (3) human resources (37–39), and (4) regulatory processes (38–42).

To improve the implementation and performance of the two functions, particularly the blood and blood product related requirements, sustained political will is necessary to prioritise national blood regulatory systems and national blood systems as the anchors of improving the access to quality-assured blood and blood products. It is imperative to further strengthen legislative measures to establish legal requirements for selection, deferral and transmissible-disease testing for blood, blood components, plasma for transfusion, and plasma for fractionation. It is essential to offer regular in-service opportunities (on the job training, mentoring, internships, joint assessments or supported assessments, workshops) and "twinning opportunities" with competent NRAs to provide continuous professional development, competence (43, 44), and capacity building opportunities for staff and NRAs in this crucial area of healthcare.

To foster collaboration and reliance, it is essential to accelerate global and regional regulatory harmonization and to enhance the overall efficiency in NRAs in Africa, e.g., by relying on WHO-designated ML3 NRAs (45). At the level of the African Union, the African Union Development Agency-Africa Medicines Regulatory Harmonisation (AMRH) programme has included strengthening of blood and blood product regulation through the African Blood Regulators Forum (ABRF)—continental technical working group. The focus of the African Medicines Agency (AMA) does not extend to blood and blood components but will include innovative plasma-derived medicines such as coagulation factors or recombinant analogues (46, 47). To sustainably build capacities in African NRAs, there is urgent need to designate Regional Centres of Regulatory Excellence (RCOREs) specifically dedicated to support blood regulation or any of the core functions of blood regulation. Capacitating and designating one would represent a crucial next step in the current efforts to strengthen blood regulation in Africa.

Benchmarking tools must be carefully designed and implemented to generate meaningful results. However, generating meaningful benchmarking data and properly evaluating performance in this complex domain remains challenging. In this study, the GBT + Blood did not measure regulatory outcomes such as the numbers of approved blood and blood products, timelines for approval or other key performance indicators. Further, while the information gathered was correct at the time of data collection, some NRAs may have updated their systems. Further studies about the positive effects of benchmarking or benchmarking outcomes are warranted to engage continuous commitment into the practice.

Conclusion

This study contributes to our overall understanding of core elements of regulation of blood and blood products and provides insights into how the registration and marketing authorization (of plasma-derived medicines) function is well-implemented in all NRAs. However, the implementation of the approval of blood, blood components and plasma for fractionation reflected a system early in its infancy. Insights from our study can be utilized to expand knowledge on how to enhance blood regulatory systems to increase access to quality-assured blood and blood products. Benchmarking of NRAs with the WHO GBT plus Blood is essential for strengthening blood regulatory systems in Africa. It fosters performance comparisons, maturity level assignments, and targeted WHO advocacy for NRA support. Moreover, the AMRH programme's RCORE concept, with adequate financial resources, can serve as a vital element to enhance regulatory capacities across the continent.

Data availability statement

The datasets generated and/or analysed during the current study are not publicly available due to the confidential nature of the data, but are available from the corresponding author on reasonable request'. Requests to access the datasets should be directed to BloodTrain@pei.de.

Author contributions

WS: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft. VK: Data curation, Investigation, Methodology, Writing – review & editing. CK: Data curation, Investigation, Methodology, Writing – review & editing. KH: Data curation, Investigation, Methodology, Writing – review & editing. JA: Data curation, Investigation, Methodology, Writing – review & editing. AK: Data curation, Investigation, Software, Writing – review & editing. FT: Investigation, Writing – review & editing. EN: Data curation, Investigation, Writing –

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1519719/full#supplementary-material

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