Reliance: a smarter way of regulating medical products - The IPRP survey

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ABSTRACT
Introduction: A survey was conducted among national regulatory authorities’ members of the International Pharmaceutical Regulators Programme (IPRP) to collect and share experiences of reliance approaches. Reliance allows formally, or informally, one regulatory authority to use assessments made by other regulatory authorities while remaining responsible for the final decision. Reliance is an essential concept to increase the efficiency of the global regulatory oversight of medical products by national regulatory authorities.

Areas covered: This article describes the findings and recommendations from the IPRP survey. It shows that reliance in the area of medical product oversight is broadly accepted. The first part presents the acceptance and reasons for accepting reliance including the need for trust, then gives examples of the most common areas for reliance, and explains the difference between unilateral or reciprocal reliance. Finally, the article analyzes the lessons learned including challenges and opportunities for reliance on regulatory authorities to facilitate patient access in their jurisdictions.

Expert opinion: Regulatory reliance facilitates regulatory approvals and allows to use resources in a more efficient way and ultimately serves patients by facilitating earlier access to quality-assured, safe, and effective medicines.

1. Introduction

In the context of increasing complexity of supply chains, globalization of markets, rapidly evolving science combined with limited human and financial resources, regulators must ensure they make the best use of the available resources and expand global regulatory oversight by increasing international collaboration. The World Health Organization (WHO) supports reliance as a general principle and has recently released draft Good Reliance Practices for public consultation [1]. Reliance is defined as

The act 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. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.

Leveraging the output of other regulators allows the relying authority to focus their resources on national activities with added value. By facilitating access to quality medical products, reliance benefits all stakeholders, i.e. patients and consumers, national governments, the pharmaceutical industry as well as the funding/donor community and international development partners.

Reliance is regularly discussed by members of the International Pharmaceutical Regulators Programme (IPRP) [2]. To collect experience and suggestions on approaches to reliance, a questionnaire was circulated to IPRP members in October 2018 [3]. Responses from 17 IPRP regulatory authorities informed the WHO draft Good Reliance Practices, along with focused consultations with key stakeholders, and are analyzed in this article.

2. Survey and results

The survey was addressed to all 30 IPRP members (of which 5 are Communities, groups of countries, or regulatory network) and 2 Observers. The survey was performed by e-mail. Seventeen authorities responded (17/30, 60%). The questions were unstructured and covered acceptance, reasons, and criteria for the use of reliance and reliance practice and benefits with some lessons learned [4].

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On behalf of the International Pharmaceutical Regulators Programme (IPRP)

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2.1. Acceptance of reliance

The results of the survey clearly show that reliance in the area of medical product oversight is broadly accepted and currently practiced by 16 of 17 responders. The extent of its application differs among respondents, ranging from application in specific cases (e.g. marketing authorizations for a specific type of products) to systems fully built on reliance and even recognition (e.g. the European Union and the Gulf Health Council).

2.2. Reasons and criteria

All responses pointed out the following four main pillars of reliance: to increase efficiency or avoid unnecessary duplication, make the best use of resources, facilitate access to safe and quality medicines, and participate in convergence and harmonization of standards.

Reliance is a tool for authorities to be more efficient, to improve regulatory timelines and quality of scientific or regulatory outcomes, to avoid repeat assessments or inspections where possible, and to broaden the global regulatory coverage while maintaining robust oversight of the quality, safety, and efficacy of medical products. Reliance allows resources to be used in a strategic manner, allows the relying authority to learn from the assessment reports provided, and, in some cases, to access a wider pool of expertise. The need for reliance has been highlighted in the responses in particular for small- to medium-size markets. One of the respondents indicated ‘we cannot do everything alone,’ and this statement applies to any size or resource-type regulatory authority in view of the globalization of the supply chain and the complexity of global regulatory oversight.

All responses regarding criteria for the choice of a reference regulatory authority are based on the need to establish that the reference regulator has similar requirements, robustness, or level of control; and where differences exist, they are known and accounted for. Responses also mentioned the following criteria: established experience in working with that regulatory authority and its longstanding recognition in the international community, knowledge of their review processes, application of international standards (e.g. WHO or the International Council on Harmonization – ICH), agreements on exchange of information in place between the regulatory authorities and proximity and commonality of medical products. In some relying countries, an approval from a single trusted source is sufficient for facilitated regulatory pathways, whereas in others a defined number of approvals (e.g. 2 or 3) from stringent regulatory authorities is required for an abridged review.

2.3. Most common areas for reliance

In many examples provided, reliance is a useful tool to improve the efficiency of regulatory processes and pathways with the main objective to provide earlier access to medical products for patients. Examples given cover the full life cycle of medical products and a wide range of regulatory processes and products. Marketing authorizations and Good Manufacturing Practices (GMP) inspections are areas where reliance is most applied. Many respondents (12/17) referred to abbreviated regulatory pathways for marketing authorization using assessments from a trusted source, for example, a stringent regulatory authority, the Pan-American Health Organization (PAHO), National Regulatory Authority of Reference, WHO, and regulatory authorities with equivalent regulatory systems (also referred to as ‘comparable overseas regulators’ in some regions). It should also be noted that in some jurisdictions, a reliance framework may potentially lead to sponsors delaying submission filing in order to take advantage of a reliance pathway, which may cause a delay in patient access. Although this may be correct for those jurisdictions, in the majority of countries, reliance should lead to accelerated access compared to pathways without using reliance. In order to avoid any negative impact on patient access in such situations, work-sharing approaches should be encouraged with parallel submissions to participating countries.

Work-sharing with international organizations or an equivalent regulatory authority was also often cited. The sharing of assessment reports and, in some cases, application dossiers was highlighted as an important tool for reliance on regional regulatory systems (European Union, Gulf Health Council, and Eurasian Economic Union).

Most respondents refer to reliance approaches and mutual recognition agreements in place for GMP inspections and the role of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). A few respondents referred to the use of European Pharmacopoeia Certificate of Suitability for the quality
assessment of medicines. Two respondents refer to effective reliance systems in place to speed up clinical trial authorizations (ANVISA, Brazil, and TFDA, Chinese Taipei). Interestingly, one regulator referred to the use of international regulatory guidelines for areas where the country’s own specific guidance has not yet been developed for industry.

In the area of post-market product surveillance, reliance activities focus more on timeliness and accessibility to emergent safety information.

Examples of integrated regional reliance systems such as in the European Union, the Eurasian Economic Union, or the Gulf Health Council can be seen as the ultimate form of reliance, as they are built on the concepts of reliance, work-sharing, and mutual recognition.

2.4. Unilateral or reciprocal reliance

Reliance is unilateral when a country chooses to rely on the assessment from another authority but the latter does not, or reliance can be mutual. Mutual recognition is a well-established concept built into Mutual Recognition Agreements (MRAs), aimed at reducing technical barriers to trade by reducing the duplication of (mainly GMP) inspections or batch controls (e.g. MRAs between the European Union and Australia, Canada, Japan, New Zealand, Switzerland, and the US FDA, respectively).

3. Lessons learned on regulatory reliance

The lessons learned by most authorities highlighted the need to build mutual trust and to understand the regulatory frameworks of the authority/institution being relied upon. A certain level of convergence and harmonization of requirements or at least the use of common standards are facilitators for reliance. Respondents also highlighted that all internal and external stakeholders, including the pharmaceutical industry, should be involved in building and using reliance approaches. The use of reliance requires a change in mindset and understanding that reliance approaches do not reduce stringency but allow for greater efficiency, reduced review timelines and avoidance of excessive duplication. Many respondents mentioned having a legal basis permitting reliance as a key concept for success. The degree of reliance will vary by regulatory authority; each regulatory authority decides the level of reliance that is appropriate for their agency. It is nevertheless essential for regulatory authorities to maintain and continue to develop expertise within their organizations, especially in areas where reliance is or cannot be applied.

On the main challenges to overcome to facilitate reliance, many respondents referred to the need for transparency and unredacted commercially confidential information, along with communication between authorities. In addition, adapting the benefit-risk assessment to the local context was also highlighted as critical. Regarding limitations, respondents referred to resistance from regulators to rely on others because of technical barriers (such as lack of standard harmonization or lack of confidentiality agreement) or non-technical barriers (such as a lack of trust, political barriers, and concerns about losing control). Regulators also highlighted challenges with changes in laws and regulatory practices happening across the world at different times and the different thresholds of evidence for approval between authorities.

Reliance approaches require planning and upfront investments to be effective: time and effort are required to establish similarities and differences, including report formats, level of detail, language, regulations and technical requirements, regulatory practices, standards for employees, etc. Buy-in from all key players is needed, most importantly from the pharmaceutical industry who must see the benefits of reliance and have clear guidance on its application (regulatory pathways well defined).

4. Opportunities for reliance

Opportunities for reliance can be grouped in five main categories: scope and models of reliance, harmonization and convergence of standards, globalization and economical context, framework to establish authorities of reference, and finally advocacy work to reinforce positive aspects brought about by reliance.

Concerning increasing the scope, authorities indicated examples of extension to inspections other than GMP, inclusion of more post-authorization activities such as major variations, safety information, post-authorization surveillance, and pharmacovigilance. Suggestions also included making better use of European Pharmacopoeia Certificates of Suitability or Certificates of Pharmaceutical Product and more pre-market work-sharing activities, where authorities review the same initial application in parallel.

Increasing harmonized guidance and converging standards were mentioned as opportunities to increase the use of reliance, along with increased communication, coordination, and capacity building between authorities. The fact that more and more authorities across the world are joining the ICH initiative and plan to implement ICH guidelines is a great facilitator of harmonized guidance and supports coordination efforts between authorities.

The increasingly globalized but complex world of medical products is perceived by respondents as an opportunity to promote reliance to make the best use of limited resources and expand global regulatory oversight.

Regarding reference frameworks for authorities of reference, different ongoing initiatives with the assessment of National Regulatory Authorities using the Global Benchmarking Tool (GBT) of WHO/PAHO [4] and the WHO-listed authorities (WLAs) [5] should provide more reliable evidence of National Regulatory Authorities’ performance, and facilitate trust in the decisions of National Regulatory Authorities. Finally, some respondents highlighted the need for advocacy about reliance to clearly establish the benefits of reliance.

5. Conclusion

The survey results show that there is a growing body of regulatory experience with reliance approaches. The application of reliance should not be seen as a risk for shrinking resources within regulatory authorities, but rather as a means to ensure that regulators avoid unnecessary
duplication and focus their own limited resources on key activities that cannot be relied upon but bring value to the populations they serve. The active decision to ‘regulate through reliance’ is a positive attribute making the most out of limited resources while retaining a high degree of regulatory stringency and achieving the best outcomes for patients at the national level.

Looking at the dynamic and expanding development of reliance around the globe, it appears that the regulatory community is transforming itself. But are all regulatory authorities and stakeholders ready? The timing is right with the work ongoing at WHO with the publication of the draft Good Reliance Practices and within a number of regulators and regulatory networks/systems. In addition, in times of a global pandemic, like COVID-19, reliance approaches offer essential tools to speed-up the approval of much needed new medical products. Ultimately, wider acceptance and application of reliance and work-sharing worldwide should allow for these approaches to move from pilot stages to ‘daily business.’ Only then, it will become clear that the expected benefits for patients are fully realized.

The following 17 authorities replied to the survey: Agência Nacional de Vigilância Sanitária (ANVISA), Brazil; Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED), Cuba; Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), Mexico; European Commission/European Medicines Agency, European Union; Food and Drug Administration, United States of America; Gulf Health Council; Health Canada, Canada; Health Sciences Authority (HSA), Singapore; Medicines and Medical Devices Safety Authority (Medsafe), New Zealand; Ministry of Food and Drug Safety (MFDS), Republic of Korea; Ministry of Health, Labor and Welfare (MHLW)/Pharmaceuticals and Medical Devices Agency (PMDA), Japan; National Drug Authority (NDA), Uganda; Roszdraznadzor, Russia; Swissmedic, Switzerland; Taiwan Food and Drug Administration TFDA, Chinese Taipei; Therapeutic Goods Administration (TGA), Australia; Türkiye İlaç ve Tibbi Cihaz Kurumu, TITCK, Turkey.

IPRP membership also includes authorities from Argentina, Colombia, Indonesia, Iran, Israel, Kazakhstan, Malaysia, Saudi Arabia, South Africa, with the Asia-Pacific Cooperation (APEC), Association of South-East Asian Nations (ASEAN), East African Community (EAC), the Pan American Network for Drug Regulatory Harmonization (PANDRH), South African Development Community (SADC), and two observers: the WHO and European Directorate for Quality of Medicines (EDQM).

The full results of the survey are available upon request.

6. Expert opinion

The aim of this article is to ascertain the actual use of reliance by regulatory authorities. The reliance survey performed by the IPRP (International Pharmaceutical Regulators Program) brings to the fore a principle that is often used by regulators across the world, but not so well described. The survey is meaningful because IPRP has true global representativity, involving 25 regulatory authorities from five continents, five Communities of regulatory authorities, and two Observers. Seventeen regulatory authorities shared their responses and experience of reliance.

Regulatory reliance requires and is built on trust; it facilitates regulatory approvals, allows to use scarce resources in a more efficient way, and ultimately serves patients by facilitating earlier access to quality-assured, safe, and effective medicines. Reliance can take different forms, ranging from using another regulatory authority’s assessment as a complement to own assessment to using this external assessment as the sole basis for approval. It can be unilateral or reciprocal. In all cases, the relying regulatory authority remains in full control of the decision.

Reliance can be used informally or formally. In the latter case, a legal framework needs to be set up to accept other authorities’ assessments. The relying authorities may be fully able to perform the assessment, but through reliance aim to avoid duplication of activities, as for example in the case of Mutual Recognition of Good Manufacturing Practice (GMP) inspections. The conclusions of the GMP inspections are accepted (‘recognized’) in place of own inspections, resulting in the ability to focus resources on other critical areas and decreasing the disruption and burden for manufacturing sites. In other situations, the relying authority may not have the full expertise available to assess and use reliance as a way to complement their own scientific capacity, for example, in the case of complex biologics.

Reliance may still be a way to build assessment capacity, for example, with the use of joint assessments whereby parallel assessments are performed, but the robustness of conclusions is ensured by holding discussions between regulators at key time points. Another example is work-sharing where the assessment is split between regulators, who then come together for a joint conclusion.

In any case, there is always the possibility for the relying authority to diverge in its conclusion and decision. Reliance does not mean dependence and is not an outsourcing of decision-making as the sovereignty of the decision remains with the regulatory authority.

The survey provides some lessons on reliance. It shows that reliance is mostly applied in the area of marketing authorizations and GMP inspections. Reliance is more used where there is already a degree of convergence between authorities and transparency. Advocacy work is still needed in many countries to overcome reluctance and get support from policymakers. All relevant stakeholders should also participate in the building of reliance approaches.

Reliance can be and has been used in emergency situations as a way to speed up regulatory processes. We have seen its use increase during COVID-19, both because regulatory procedures needed to be fast and because resources were affected by the disease or lockdown. This will be addressed in further publications.
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