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Streamlining processes – the WHO Collaborative Procedure for Accelerated Registration in Africa

AUTHORS

Lori Alquier, Department of Regulatory & Quality Sciences, University of Southern California School of Pharmacy, US, **Frances J. Richmond**, Director, DK Kim International Center for Regulatory Science, Professor, Department of Regulatory & Quality Sciences, University of Southern California School of Pharmacy, US. **Correspondence to:** alquier@usc.edu

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ABSTRACT

Regulatory harmonisation of drug approval pathways can potentially reduce the time and costs of registration and thus help to improve patient access to important medicines. Many countries only have national registration processes that may not be aligned with those of other national regulatory agencies, so a separate, mostly redundant dossier must be submitted in each country. Multiple regulatory harmonisation initiatives, such as the East African Community Joint Assessment Procedure and the ZAZIBONA initiative, are under way to address these repetitive and low value-added practices by allowing the submission of a single dossier for registration in multiple countries. The World Health Organization Collaborative Procedure for Accelerated Registration, used throughout Africa, is a unique regulatory pathway that is particularly useful to address this redundancy because it streamlines the regulatory approval process in participating countries by incorporating worksharing and regulatory reliance beyond that of using a single dossier.

Introduction

The COVID-19 pandemic has illustrated on a global level the importance of rapidly providing needed medicines to a waiting population. Equitable access to medicines is an important human right. However, a 2008 report from the United Nations stated that over two billion people globally did not have sufficient access to essential medicines; increasing access to high-quality medicines could annually save 10 million lives, including those of four million people who populate Africa and South-East Asia.¹ A robust and agile regulatory authority is a key component to providing that access. It is especially important in Africa because it accounts for approximately 11% of the global population, but carries almost 24% of the global disease burden.²

National regulatory agencies differ substantially in their capabilities, which impacts their ability to protect their citizens by providing them with safe and effective pharmaceutical products. Globally, at least 30% of national medicines regulatory agencies (NMRAs), including NMRAs in Africa, are limited in their capacity to perform core regulatory functions.^{3,4} According to the World Health Organization (WHO), only 7% of the NMRAs have a moderate functional capacity, and more than 90% have minimal or no capacity at all.^{3,5} Further, the speed at which countries approve pharmaceutical products varies significantly from country to country. A typical delay of up to four to seven years has been identified from the time in which the first filing submission is made in a high-income country to its approval in Sub-Saharan Africa.⁶ This delay can have significant health-related implications. Using modelling, PATH, an international, non-profit global health organisation, estimated that accelerating access to just two products (a heat-stable synthetic form of oxytocin for postpartum haemorrhage and a dispersible antibiotic for treating pneumonia in children under five years old) by only two years could save more than 23,000 lives in eastern and southern Africa alone.⁷

Some have attributed the delays in drug registration, in part, to disparate and repetitive regulatory processes.⁸ Many countries have legislation supporting only national registration processes, requiring a dossier to be submitted in each country. The registration requirements and processes are likely not aligned between these countries, yet the different dossiers also have a significant amount of redundancy. Multiple regulatory harmonisation initiatives, such as the East African Community (EAC) Joint Assessment Procedure and the ZAZIBONA initiative, have attempted to address these repetitive and low value-added practices by allowing a single dossier to be submitted for registration in multiple countries simultaneously. An additional initiative, the WHO Collaborative Procedure for Accelerated Registration (WHO-CRP), is an important harmonisation pathway because it is used throughout Africa and in other resource-limited countries throughout the world. It also looks beyond the submission of dossiers to regulatory capacity-building. Improving the capability of NMRAs in Africa therefore becomes an essential goal to improve public health and patient safety.

Current regulatory landscape of the continent

The 55 countries in Africa are organised into eight Regional Economic Communities (RECs) to provide an overarching framework for continental economic integration. On average, each country in Africa belongs to two-and-a-half RECs.⁹ This creates difficulties for harmonisation efforts, and initial attempts at harmonisation proved difficult. Obstructions such as inadequate pharmaceutical legislation, poor infrastructure and limited resources proved too formidable for early regional initiatives to overcome.^{10,11}

More recently, two types of harmonisation approaches have been tried. One approach has leveraged international organisations and resources to facilitate harmonisation efforts. The WHO has played a pivotal role in these

activities, as described in more detail below. The WHO-CRP is an example of this type of initiative. A second type of harmonisation is a more regionally constructed effort, such as the ZAZIBONA initiative. Approximately 85% of Sub-Saharan Africa is involved with one or more medicine regulatory harmonisation projects.^{12,13}

WHO prequalification procedure

One of the most notable of the WHO's accomplishments in the medicines sector is the WHO prequalification procedure, which has been responsible for bringing important medicines to multiple resource-limited countries. Its formation was driven by the AIDS/HIV epidemic in Africa that illuminated the shortcomings of the healthcare systems. The prevalence of locally purchased medicines of poor quality led outside entities that were funding the drug acquisitions to demand a process that would stretch their investments as far as possible without compromising medicine quality.¹⁴

In 2001, the WHO formed a partnership with UNICEF, UNAIDS and the United Nations Population Fund and obtained support from the World Bank to establish the Prequalification (PQ) of Medicines Program (PQP).¹⁵ Originally designed for UN procurement, the PQP was initially set up to assure that high-quality medicines would be available for HIV/AIDS, but quickly expanded to meet pressing drug needs for other diseases, such as tuberculosis and malaria. It also enlarged its scope to encompass vaccines and in vitro diagnostic products.

The PQP helps to assure product safety and efficacy by providing a transparent, scientifically robust quality assessment of the low-cost generic drugs, vaccines, and in vitro diagnostics that were becoming increasingly available in resource-limited countries. It was created as an alternative to costly registration by stringent regulatory authorities (SRAs). The output of the process is not drug registration. The PQP operates as a centralised process using multinational teams composed of in-house and external assessors (mostly from SRAs) to spare individual countries from having to perform individual assessments (see Figure 1).

The assessment starts when the WHO solicits an Expression of Interest for certain selected medicines. Only products listed as essential medicines or those recommended by the WHO treatment guidelines can be prequalified.^{16,17} Sponsors of individual brands then provide either product dossiers developed specifically for this purpose or marketing application dossiers that have been submitted to SRAs that are accompanied by the SRA Assessment Report.

A multinational team performs a dossier review, a performance assessment and, if appropriate, site inspections, using WHO, ICH and specific PQP guidelines as well as the standards in the International Pharmacopoeia and other pharmacopoeias to ensure consistency. By making the assessments transparent and adding extensive training programmes, the PQP allows individual countries to focus their valuable resources on more specialised issues important to promoting healthcare in their jurisdictions. The programme is voluntary and minimal fees have been assessed to sponsors using the service since 2013.

The PQP programme has been remarkably effective in supporting access to high-quality medicines in developing countries.¹⁸ As of 2019, the WHO PQP has prequalified over 1,600 products.¹⁹

WHO Collaborative Procedure for Accelerated Registration

While the WHO prequalification procedure facilitates the procurement of pharmaceutical products, it does not directly improve the lengthy methods used by NMRAs to register pharmaceutical products. Thus, the WHO has developed a two-component programme called the "Collaborative Procedures for Accelerated Registration" (CRP).

FIGURE 1

The WHO prequalification process

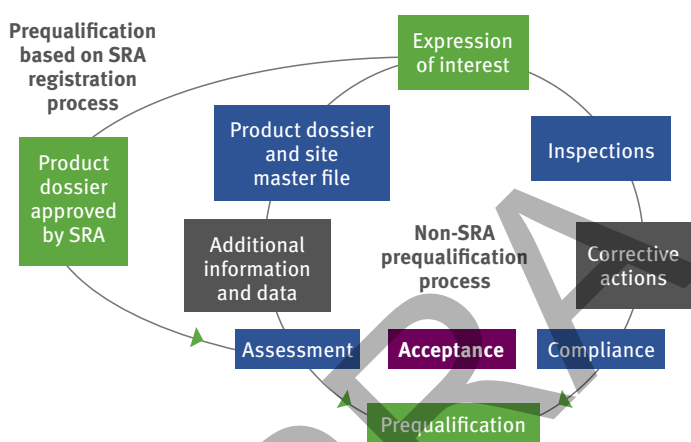
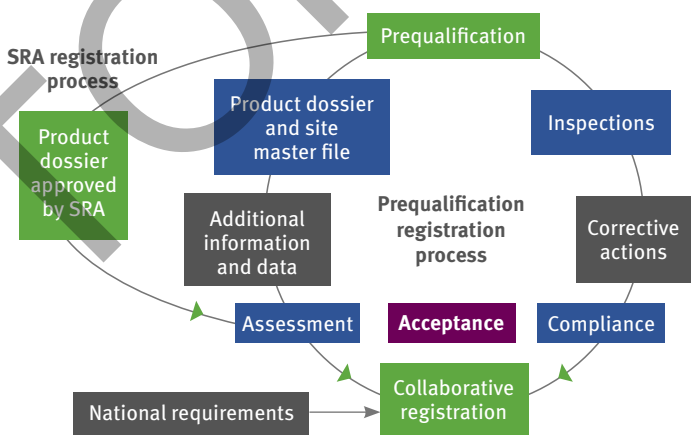


FIGURE 2

The WHO Collaboration Registration Procedure Process



The accelerated registration of prequalified finished pharmaceutical products

The first component, the accelerated registration of prequalified finished pharmaceutical products (FPPs) (CRP-PQP), facilitates the national registration reviews of WHO prequalified pharmaceutical products. The process was created after a WHO assessment of regulatory systems in 26 sub-Saharan African countries concluded that few NMRAs effectively used the WHO PQP to improve their registration processes.¹¹ The CRP-PQP process starts when the applicant supplies the dossier of the prequalified medicine that is listed on the WHO prequalification website. In parallel, the applicant gives the participating NMRAs permission to access the WHO's assessments. The NMRA then has 90 days to decide whether the WHO assessments are applicable for this programme. Finally, the NMRAs decide whether the product will be approved for sale in their respective countries (see Figure 2).

The CRP-PQP can support applications for national registration of any FPP that has been successfully assessed for WHO prequalification and has WHO-prequalified status. It is a voluntary programme that accelerates registration timelines and conserves regulatory resources by improving information sharing between NMRAs and the WHO Prequalification of Medicines Program (PQP).²⁰ Over 40 countries around the world, including more than 25 countries in Africa, participate in this programme.²¹

NMRAs may decide how to use any information provided by the prequalification process in their own registration assessment or whether the procedure should apply to a dossier that they receive. Rarely, an NMRA may decline to apply the procedure because the FPP does not conform with specific national treatment recommendations, or the FPP evaluation by the NMRA is already well advanced, so that the NMRA prefers to complete registration conventionally through its national route.

The WHO recommends that the NMRA should verify essential data to ensure that the FPP under review is the same as the prequalified product. If an NMRA chooses, the NMRA's own independent conclusions after its review can be compared with the WHO prequalification outcomes (as described in the assessment and inspection reports) for training or other purposes. The NMRA may also provide its own assessment with special attention to specific aspects of the product that may be especially relevant to the local population or to the national context. If the assessment of the NMRA differs from the PQ assessment, it should provide the reason to the WHO.

Differences in product name, name of the applicant/registration holder, data format, language, level of detail related to product information, or details of package labelling can be acceptable deviations if they do not affect product quality. However, no deviations would be expected in other aspects, including the manufacturing processes and controls of materials and final product; specifications of active pharmaceutical ingredient and finished product; or the elements in the drug profile including its indications, contraindications, dosing, special warnings and precautions for use, adverse drug reactions, storage conditions and shelf-life limitations.²²

WHO Collaborative Procedure for Accelerated Registration approved by SRAs

The second component of the WHO Collaborative Registration Procedure is the accelerated registration of FPPs approved by SRAs (CRP-SRA). The programme was piloted in 2013, and then converted into a final programme in 2018. The programme was created for drug manufacturers that wish to register in countries that participate in the programme by leveraging the regulatory review and/or inspection for an FPP already accepted by a globally recognised NMRA, such as the US FDA or European Medicines Agency (EMA). The programme follows a similar process as that defined in the CRP-PQP process for collaborative registration, but instead relies on assessments conducted by SRAs that are accessed confidentially by the NMRAs. The process is designed to augment the CRP-PQP process by providing a voluntary, alternative pathway to facilitate product registration.

Through the SRA-CRP, the drug manufacturer provides the assessment and inspection outcomes from a consenting SRA. The participating health authorities in Africa use that documentation to support their decisions regarding registration, but the evaluation process itself is unchanged from a national procedure. The WHO acts as an intermediary between the applicant, participating NMRAs and the SRAs. The WHO can also participate in a procedure if it considers that the product under review will affect public health. By enabling NMRAs to use the previously performed evaluations and inspections, some work is not duplicated, and approvals can be faster. Its goal is to help NMRAs to decide on registration within 90 days after completing the validation process. The procedure does not include any risk management plans or pharmacovigilance follow-up. No fee is paid to participate in the procedure. However, the usual registration fees associated with registration at the national level will be levied by the NMRAs unless they are waived.

As of January 2020, 43 NMRAs are using the process, including 29 NMRAs in Africa.²³ The programme has also been expanded to new

programmes that encompass diagnostics and vaccines.²⁴ In recognition of the programme's impact, UNITAID recently expressed its support of the programme.²⁵

Today, the programme is widely recognised for having made an enormous contribution in terms of accelerating and increasing access to critical quality-assured products that are affordable and adapted for markets in low- and middle-income countries. It illustrates the WHO's philosophy regarding the beneficial outcomes of harmonisation for its stakeholders. Manufacturers benefit because they can create and use a single dossier for registration in multiple countries; these dossiers may advance quickly and predictably through the registration process. This can also simplify their post-registration maintenance. NMRAs from resource-limited countries can learn from assessors and inspectors of SRAs and thereby build in-country capabilities. National decisions are respected, but collaboration is encouraged. Most importantly, patients receive accelerated access to life-saving and high-quality medicines.

For the WHO-CRP to be effective in reducing the regulatory burden on NMRAs, the legal framework in the country must be structured to support regulatory harmonisation. Differences in national laws can impede effective harmonisation.²⁶ This challenge has been recognised by the WHO, which considers political and governmental support to be a key enabler of good regulatory practice.²⁷ Legislative frameworks in Africa, like most other parts of the world, are based on laws that were developed at the national level at a time when the need to demonstrate sovereignty was more important than a desire for harmonisation. This heterogeneous legislative environment has been recognised to impede harmonisation for more than a decade,¹¹ yet adjacent countries within RECs continue to have different legislative, and therefore different regulatory systems for approving medicines. The African Union (AU) Model Law attempted to remediate this problem by providing a framework to be used by member states to update their current laws in ways that would facilitate regulatory harmonisation in the region. However, this Model Law has been "domesticated" (ie, adopted in principle, but not set into law) by approximately one-quarter of the AU member states.²⁸ Efforts to domesticate and then adopt legislation suggested by the AU Model Law are thus important to facilitate harmonisation of regulatory requirements and elimination of redundant documentation and activities. It would alleviate some of the burden currently placed on NMRAs that must satisfy their national requirements.

Discussion and conclusion

Regulatory harmonisation has the potential to reduce the regulatory burden on NMRAs through worksharing and elimination of redundant, non-value-added activities. It can also encourage industry to provide needed medicines to waiting patients in resource-limited countries more quickly by streamlining the requirements they need to fulfil. The WHO-CRP is a unique regulatory pathway that is particularly useful because it streamlines the regulatory approval process in participating countries by incorporating work-sharing and regulatory reliance. It is used throughout Africa and in other resource-limited countries throughout the world. For the programme to achieve its maximum value, it is important that the participating country's legislature is supportive of the programme without adding national requirements and, in Africa, the adoption and domestication of the AU Model Law can facilitate that integration. ■

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