

WHO Prequalification of Medicines Programme

WHO launches the PQP Collaborative Registration Procedure

The Collaborative Registration Procedure (CRP) for WHO-prequalified products accelerates registration through improved information sharing between the WHO Prequalification of Medicines Programme (PQP) and national medicines regulatory authorities (MRAs).

The CRP aims to leverage the work of PQP during registration of WHO-prequalified medicines. It enables MRAs to utilize outcomes of PQP evaluations and inspections – thereby eliminating duplication of work, speeding up delivery of quality-assured products and making these more widely available. Since 2012, when the pilot phase began, fifteen MRAs in fourteen countries have decided to participate in the CRP and the present article describes experiences and lessons learned during the launch of this activity.

Given current resource constraints affecting pharmaceutical regulation in many regions of the world, international organizations increasingly rely on the rigorous standards of the WHO Prequalification of Medicines Programme (PQP) (1) and stringent regulatory authorities to ensure the quality, safety and efficacy of medicines that they fund or procure.

Although WHO prequalified medicines are evaluated and inspected according to international standards, they still have to be approved for use by national medicines regulatory authorities (MRAs) in the recipient countries.

The repeated assessment and inspection of medicines consumes scarce regulatory resources and extends the time needed to make them available to patients. In order to facilitate and accelerate registration, PQP has designed a procedure which helps to assure MRAs that WHO-prequalified medicines comply with high quality standards as documented in detailed reports of WHO evaluations and inspection results.

The WHO Collaborative Registration Procedure (CRP) (2) received final approval from the Sixty-sixth World Health Assembly in May 2013. Not only does the CRP enable MRAs to accelerate processing of registration applications for prequalified medicines, but it allows them to make use of work already carried out by PQP to strengthen their own regulatory oversight processes in line with international best practices.

The CRP has been published in the WHO *Technical Report Series* (3) and is open to all WHO Member States. Its principles can also serve as a model for other regulatory collaborative initiatives.

Principles

Participation of stakeholders is voluntary and MRAs wishing to participate agree:

- To respect the principles of the CRP.
- To treat proprietary information shared with PQP as confidential.
- To take a decision on CRP submissions for registration within 90 days of receiving access to confidential PQP outcomes of assessments and inspections.

Each MRA designates one or two focal points to communicate with PQP on a confidential basis. In the event that the CRP is activated for a specific pre-qualified product, focal points will be granted access to PQP's evaluation and inspection information through a secured Internet server.

Because PQP expertise outcomes shared within the terms of the CRP do not interfere with national decision-making processes, participation by MRAs may only require modification of regulatory procedures exceptionally. PQP has posted a list of participating MRAs on its web site.

The CRP is applicable only to medicines which have been subject to PQP evaluation and inspection and follows three steps.

- Firstly, a WHO prequalification holder wishing to register a prequalified product in a participating country should submit an application for registration to the MRA accompanied by an Expression of Interest (EOI) in which the company confirms that the product is technically the same as that prequalified, that submitted data correspond to the dossier as approved during pre-qualification and that it authorizes the MRA to communicate with PQP on product-related issues.

In parallel, the company authorizes PQP, in a pre-defined document, to share with the respective MRA the full outcomes of WHO's assessments and inspections confidentially through the PQP password-protected web site.

- Secondly, the MRA decides whether to apply the CRP to the specific submission — depending on whether it considers its execution to be expedient in the particular case — and informs PQP of its position. In the event that the MRA decides to make use of the CRP, PQP grants the focal point access

to product-related assessment and inspection reports and other relevant documents providing detailed insight into the prequalification decision-making process and outcomes, including approved product specifications and the applicant's commitments. PQP is also prepared to provide additional explanations and responses to the MRA's questions. It is dependent on the discretion and resources of each individual MRA to decide whether the PQP outcome is recognized directly, whether it is considered for verification purposes, whether to organize a partial risk-based evaluation, or whether to use the shared data for quality assurance of its own independent assessment.

In any event, participating MRAs should issue a decision on each submission within 90 days of receiving access to confidential PQP outcomes of assessments and inspections.

- Thirdly, in line with the CRP, WHO and the applicant are informed of this decision within 30 days from when it is taken. The MRA is free to deviate from PQP opinion. However, deviations from WHO PQP conclusions should be explained and communicated to PQP. This process enables PQP to publish on its web site a list of those medicines that have been registered in participating countries under the same conditions as prequalified by PQP. For such products, it is possible to collaborate further with respective MRAs in product post-registration and product regulatory maintenance.

In the post-registration phase, stakeholders should work together to minimize differences between the nationally-registered and the WHO-prequalified product. Companies should submit the same variations to PQP and to participating MRAs, and the parties should inform each other of any major decisions regarding the product.

Information sharing

PQP does not share the full prequalification dossier with participating MRAs because the same technical data are submitted as part of the national registration process. Only assessment reports, variation reports and inspection reports are shared. Dossier assessment reports are in the form of PQP Quality Overall Summaries (QOS) — annotated with the assessor's colour-coded remarks, requests for additional information and the applicant's responses at each round of evaluation until prequalification.

Variation assessment reports are similarly annotated reports on changes to a prequalified product as per PQP variation guidelines. Inspection reports and signed-off Corrective and Preventive Action plans are shared for each manufacturing site of the finished product, as well as for those active pharmaceutical ingredient (API) manufacturing sites and clinical trial sites that PQP has inspected. PQP only shares data owned by the prequalification holder. Data provided by API manufacturers for the purposes of an active pharmaceutical ingredient master file (APIMF/DMF) procedure are not shared, unless there is a specific agreement with a data owner.

The MRA is free to use information to the extent it considers appropriate, subject to its participation agreement and confidentiality undertaking. Shared information enables the MRA to verify that the national submission conforms to WHO prequalification standards in all respects. In addition, examples of PQP process steps and documents followed in prequalifying each product may be useful for an MRA's own training activities. Assurance that the regulatory status of the product remains in line with PQP conditions helps MRAs to define risk-based post-marketing surveillance measures that can be carried out in addition to PQP's re-assessment and re-inspection. Quality control can be

performed according to the same methods and specifications and in cooperation with other countries that have registered the product under the same conditions.

Experience

Ten MRAs participated in the pilot phase organized during the second half of 2012. Staff from seven of these MRAs have worked with PQP through rotational fellowships, while others have either participated in joint bi-monthly prequalification assessment sessions or other assessor training events offered by PQP. These regulators are largely familiar with PQP standards and procedures and have welcomed the opportunity to collaborate.

Since May 2013, the CRP is open to all WHO Member States. By October 2013, participation in the CRP had grown to 15 MRAs, including 12 in Africa that jointly cover more than 45% of the population of the WHO African Region. Three MRAs from Eastern Europe and Central Asia participate and others are considering participation.

PQP informs pharmaceutical companies about the CRP avenue for accelerated registration at its stakeholder meetings and training events, and provides information on its web site and in the standard letter sent upon acceptance of each product for prequalification and after prequalification is achieved. Several participating MRAs have also referred applicants to the CRP.

So far, fifteen prequalification holders have been in contact with PQP concerning collaborative registration of their medicines, including two prequalified "firsts" — zinc dispersible tablets and artesunate + mefloquine fixed-dose combination tablets. Swift registration of these products in relevant countries will be of particular interest for international procurement. WHO has reached out to

additional MRAs in some potential target countries, inviting them to adopt and participate in the CRP.

Registration procedures

By October 2013, five prequalification holders had submitted a total of 29 EOs for collaborative registration of 15 WHO-prequalified products (11 ARVs, one reproductive health product, two antimalarial and one second-line anti-TB product) in a total of seven countries. Participating MRAs agreed to apply the procedure in 18 cases. The most common reason for rejection was that already pending applications for registration in the respective country were at an advanced stage of evaluation.

Thirteen registration procedures were successfully completed for ten prequalified products (nine ARVs and one reproductive health product) through registration in six African countries (Ghana 5, Zimbabwe 3, Namibia 2, Kenya 1, Nigeria 1, Uganda 1).

Adherence to timelines

PQP had shared assessment and inspection information for the accepted EOs within 0 to 42 days after receiving consent from the prequalification holder and confirmation of interest from the MRA (median: 10 days). The longest delays occurred early in the pilot phase while the confidential web site was undergoing upgrading.

MRAs adhered to the 90-day target timeline for eleven of the thirteen completed procedures (median time to registration 59 days). In seven cases the time taken was less than 60 days. More than 62 days were taken only in two cases (111 and 182 days) — one being due to awaiting the constitution of the relevant regulatory body. However, additional time was taken by MRAs to locate pending applications and identify their status, to respond to EOs, to arrange access to the shared confidential

web site and to provide feedback to PQP and applicants. Considering the above, total time taken from receiving access to confidential PQP outcomes of assessments and inspections to approval of 13 registered products ranged from 19 to 270 days (median: 99 days).

During the pilot phase, a substantial number of cases were initiated for applications which had already been pending for some time in the national registration system. Considering that 12 of the 18 submissions that the MRAs accepted to review under this procedure had been queued in national systems for a year or more, the collaborative procedure has saved time for all parties.

In Zimbabwe — where almost twice as many dossiers were received in 2012 than the registration system is designed to handle — the regulatory focal person states:

«The PQP Collaborative Procedure was a relief for us in Zimbabwe. ... From the pilot phase we established that approval within 90 days is do-able. ... The procedure allows us to save our meagre resources and focus them on risky products which have not been subjected to rigorous PQP quality assurance.» Head, Evaluations and Registrations Division, Medicines Control Authority of Zimbabwe.

Experience with specific aspects of collaboration

Product and data responsibility

In cases where the applicant for national registration is different from the holder of WHO prequalification, the latter must authorize the applicant to act on its behalf for the purposes of the CRP. This situation occurs quite commonly where the prequalification holder has delegated marketing of the product to another entity and/or where the MRA requires that the applicant for marketing authorization must be a local entity. PQP will typically be dealing with only one party, namely

that which authorizes it to share pre-qualification information with the MRA. It is up to the company to define and manage any delegated responsibilities at additional levels.

Format of national submissions

Prequalification dossiers must be submitted in Common Technical Document (CTD) format. In a survey conducted by PQP in 2011, 15 out of 17 MRAs stated that they accept dossiers in CTD format. In most cases preparation of national submissions will require little additional effort by prequalification holders and technical data can be presented as approved by PQP. Wide use of the CTD format facilitates information-sharing under the CRP as well as promoting regulatory harmonization.

Abridged dossiers may be acceptable for MRAs wishing to reduce workload, given that detailed dossiers are on record at PQP and that technical advice on specific issues can be sought from PQP. Such special arrangements should always be confirmed to the applicant by individual MRAs. In any case, the MRA should make sure that it has sufficient technical information at its disposal to enable effective regulatory control. An example of this arose with a hormonal contraceptive that was submitted for registration in a version containing placebo tablets. The WHO-prequalified version contained tablets only with an active hormone.

Dealing with product differences

Some companies prefer to apply for national registration before being granted prequalified status. To ensure that the PQP product and technical data remain the same as that prequalified, the applicant is required to state any differences in its EOL and to upgrade the national dossier in line with the prequalified one. It can also happen that major variations have been approved for the already prequalified product and the dossier submitted in countries should be updated accordingly.

In practice, applicants have submitted upgrades in varying levels of detail and a range of approaches have been adopted by MRAs to deal with product data differences. For example, an MRA may decide to discuss pending prequalification variations with PQP before approving the products concerned, and request an applicant to re-submit upgraded dossiers

The CRP was initially designed on the understanding that national applications would be submitted after completion of WHO-prequalification. The high number of CRP applications for pending submissions reflects a regulatory backlog in some countries. This will hopefully decline over time, as well as the strategy of making parallel submissions to PQP and national authorities at the same time.

Initial experience with handling of product differences highlights the importance of variation control once a prequalified product is registered in a country. Demonstrating that a product meets the same uniform international standards in different national markets offers a clear competitive advantage to prequalification holders. It is the responsibility of the applicant to ensure that the national registration status of the product reflects PQP adopted variations in line with regulations of the country.

Existing experience with management of post-prequalification and post-registration variations is still limited. Although the CRP provides principles for post-approval product maintenance and communication between PQP and MRAs, it has not been able to define a protocol due to the highly varying practices of MRAs. Effective management of variations in order to harness capacity of all parties is now a priority in further development of the CRP.

Country-specific conditions

PQP prequalifies products as being acceptable, in principle, for procurement by international organizations. However,

it is up to each MRA to evaluate the acceptability of a product in context. A recent example of this difficulty was noted when a prequalified artemisinin-based antimalarial combination treatment was registered in countries where it is not currently recommended in the national standard treatment guidelines. The situation was presented to the WHO Global Malaria Programme which proposed a registration strategy. While it is not PQP's role to advise on the country-specific risks and benefits of using a product, the CRP provides a platform for discussion between the applicant, the MRA and WHO.

Communication of technical issues

Beyond the formal exchange of pre-defined documents (submission of EOIs, response from the MRA, and communication of outcomes) the CRP also encourages a flow of ad hoc information and communications on technical and administrative issues. Such interaction by telephone and e-mail between PQP and MRA staff is critical to the functioning of the CRP. The confidential PQP web site which hosts the shared prequalification information also offers a functionality for managed discussion forums. However, it was found that the potential of this form of

Benefits of the Collaborative Registration Procedure for key stakeholders

Manufacturers

- Harmonized data for WHO prequalification and national registration.
- Facilitated interaction with MRAs in assessment and inspection.
- Accelerated and more predictable registration.
- Easier post-registration maintenance.

Procurers

- Faster start to procurement processes and wider availability of PQ medicines.
- Access to status of a the same nationally registered and prequalified medicine (web site).

MRAs

- Availability of WHO assessment and inspection outcomes to support national decisions and consolidate internal capacity.
- Opportunity to learn from PQP assessors and inspectors.
- Demonstration of MRA efficiency.

Confirming status of product to that prequalified.
Quality control using harmonized methods and specifications.
Easier post-registration maintenance.
Easier problem management.
Model of work-sharing.

WHO

- Prequalified medicines are available faster to patients.
- Feed-back on WHO prequalification outcomes.

Patients

- Timely access to assured quality products.

communication has not been fully utilized. More work probably needs to be focused on enhancing user-friendliness of the IT system and seeking input from regulators.

The growing number of MRAs joining the CRP from different geographical regions also poses the question of language translation for CRP documents.

Conclusion

Experience and lessons learned show that a fully functional CRP can accelerate approval time, reduce workload and enhance the capacity and capability of MRAs in the registration process of WHO-prequalified products. Additionally, the CRP improves regulatory collaboration among MRAs — especially those interested in setting up worksharing networks at national and regional levels. The CRP provides benefits to all stakeholders while assuring international quality standards of the products in registering countries.

Next steps

At this stage of development, the CRP has progressed from a pilot to a fully operational phase. It is expected that new participating MRAs and manufacturers will bring additional experience which is relevant for the evolution of practical processes.

Good communication on technical issues, including effective post-approval control, will be crucial in sustaining successful implementation of the CRP. PQP will take every opportunity to meet with stakeholders and create a basis for effective communication. Regular meetings are scheduled with participating

MRAs to cultivate use of the CRP and discuss ways to expand beyond its existing scope. Additional supporting documents are planned to be developed at these events.

Future challenges will include post-approval maintenance of registered medicines, cooperation on registration sample testing (which is still routine for some MRAs), and work-sharing in inspections — for example, ongoing collaboration on inspections with MRAs in the East African Community.

A frequent topic of discussion is how to expedite registration of medicines that have been approved by stringent regulatory authorities. The CRP provides certain helpful approaches that can be explored further.

References

1. World Health Organization. Prequalification Programme: A United Nations Programme managed by WHO. <http://apps.who.int/prequal/>
2. World Health Organization. Prequalification of Medicines Programme Collaborative Procedure at http://apps.who.int/prequal/info_applicants/collaborative_registration_main.htm
3. World Health Organization. Expert Committee on Specifications for Pharmaceutical Preparations. Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and nation medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products. Annex 4. *Technical Report Series*, No. 981 (2013). <http://www.who.int/medicines>