WHO prequalification

Prequalification process quality improvement initiatives: 2010–2016

In the past six years the WHO Prequalification Team (WHO-PQT) has organized a total of four surveys to evaluate client satisfaction among manufacturers that have applied for prequalification of their medicines, vaccines or in vitro diagnostic products. This article provides an overview of the survey findings and some other initiatives to improve prequalification process quality.

WHO prequalification remains an important pathway for quality assurance of key medical products purchased by UN agencies, national agencies and international organizations. The sustainability of the prequalification programme is critically dependent on manufacturers' continued participation. Survey results assist WHO-PQT in designing and implementing targeted improvements to its services.

Background

Ensuring the quality of health products is the responsibility of national regulatory authorities (NRAs). Given the varying regulatory capacity of WHO Member States, WHO provides a "quasi-regulatory" service to identify health products – including affordable generics – that are acceptable for use in UN-funded health programmes. WHO prequalifies vaccines (since 1987), selected medicines for treating priority diseases (since 2001) and selected in vitro diagnostics (IVDs) (since 2010, building on an earlier programme). Prequalification of vector control products to prevent malaria was launched in 2016, and the first invitation for prequalification of selected biosimilars to treat cancer is planned to be issued before the end of 2017.

Prequalification is based on WHO-recommended norms and standards and is performed by the Prequalification Team (WHO-PQT). Regulatory experts from a wide range of settings participate in WHO assessment and inspection activities. Processes are in place for risk management, variation control of constantly changing products, and reliance on stringent assessments performed by other regulators. Prequalification of active pharmaceutical ingredients (APIs) and quality control laboratories have been added as supporting services.

While WHO prequalification was initially controversial, WHO-PQT has become part of what could be termed the regulatory community. Prequalification outcomes are recognized not only by UN agencies, but also by many governments and international organizations that procure medical products, and regulatory authorities in many WHO Member States rely on prequalification outcomes in granting marketing authorizations, thus optimizing the use of limited regulatory resources.

Applicant satisfaction surveys

Prequalification is voluntary for manufacturers, and the sustainability of the programme depends on their continued participation. In 2010, WHO undertook a comprehensive review exercise to seek feedback from applicants on the prequalification service for medicines. This was followed by service quality surveys for vaccines in 2011, for diagnostics in 2015, and again for medicines in 2016.

Method

A survey methodology was developed in 2009 to provide a unified framework for measurement of service quality. An online questionnaire was administered to regulatory and quality assurance professionals in manufacturing organizations, covering a range of aspects related to service design and service delivery *(Annex 1)*. The service design indicators were developed as a result of a process review with WHO-PQT staff and interviews with manufacturers. They measured the respondents' perceptions of the consistency of policies and procedures, feedback mechanisms, resource management, problem-solving options and complaint handling in the various prequalification processes. The service delivery aspects were based on a widely recognized scale of service quality.*(1)* In addition, narrative feedback was sought.

The service quality aspects covered in the surveys were rated on a 7-point scale, together with the minimum and desired expectations for each respective aspect as provided in any regulatory pathway.

Main findings

Medicines – 2010

The 2010 survey on medicines prequalification found that on the whole, the service provided by WHO assessors and inspectors, and the structure of prequalification itself, were meeting or exceeding manufacturer expectations. Areas for improvement included dossier review timelines, opportunities for in-person communications, problem resolution during assessment, consistency of membership in the assessors team, and inclusion of local/national observers in inspection teams.*(2)*

Vaccines – 2012

Manufacturers rated the vaccine prequalification service as acceptable. No service area was scored significantly below minimum expectations. The strengths were in those aspects of service delivery that build applicants' confidence in the prequalification process. Areas for improvement included the structuring of processes and time-related aspects, including both time to prequalification and efficient, predictable time management including for prequalification and sample testing processes.*(3)*

Vaccine products are eligible for prequalification only if the reference NRA of the producing country is shown to be functional in all aspects of vaccines oversight, as defined in a standardized WHO benchmarking tool. NRAs are therefore important partners in prequalification of vaccines. A separate qualitative study included interviews with five NRAs and three organizations procuring prequalified vaccines. These respondents valued WHO's expertise and service highly. They suggested that the efficiency of exchange of information should be improved, as this

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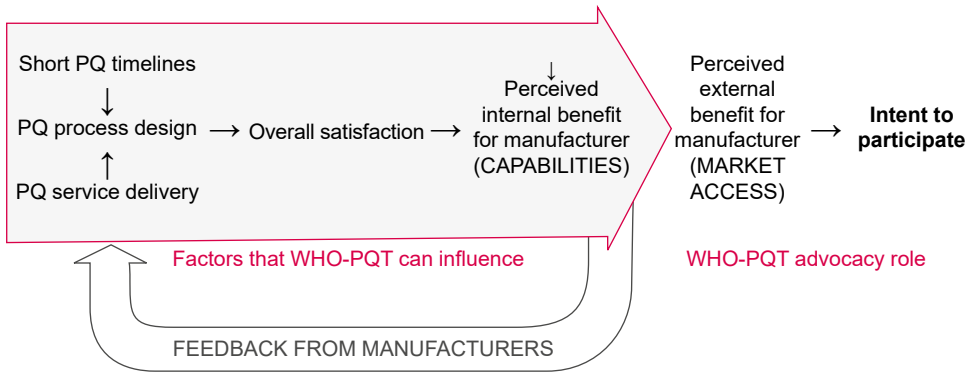
Box 1: **Key drivers of continued participation**



PQ = Prequalification
→ = Positive impact
- - - = Positive impact in diagnostics survey

Source: Adapted from statistical models constructed using survey data

would help to avoid duplication of processes, facilitate a rapid response to emerging issues, and anticipate future needs. They also appreciated the capacity built in some reference NRAs through prequalification and called for advocacy to promote reliance. stating that only WHO can communicate to recipient countries *"why vaccines coming from Thailand are safe"*. Some of these suggestions are now being addressed by the WHO-National Control Laboratory (NCL) Network for Biologicals, established in 2016 among NCLs responsible for lot testing of prequalified vaccines.*(4)*

Diagnostics – 2015

The 2015 survey on IVD prequalification showed that the strength of the programme is in service delivery. The dossier reviewers and site inspectors were found to be competent, dependable, responsive and attentive to each applicant's situation. On the other hand, the processes for dossier assessment, inspections and laboratory evaluation, as well as timelines, were seen as in need of improvement.

In this survey the respondents' ratings of prequalification timelines were very diverse. Interestingly, a subgroup analysis showed that those who rated the process as "fast" also had more favourable perceptions of various other aspects of the prequalification process and even of its benefits for the company.

Medicines – 2016

The follow-up survey on medicines prequalification showed that manufacturers were more satisfied with the prequalification service than in 2010. All aspects measured in the survey had average ratings at or above the manufacturers' expectations for any regulatory pathway; no item had an average score below the minimum required service level. One respondent commented: *"The PQ process has improved dramatically over the past 6 years…They are now on the right track."*

The results of the 2016 survey provided evidence that efforts to reduce the time to prequalification have been successful. The timely progress of dossier assessments is now a strength of the programme, although efficient use of time in inspections could be improved further. Significant progress was also noted in terms of training and assistance provided to applicants before and during the prequalification process. Some respondents would like to see more user-friendly means of data submission. Average ratings were somewhat lower, but still met manufacturer's minimum expectations, with regard to the transparency of selecting products invited for prequalification, as well as a number of aspects related to inspections.

Key drivers of participation

Overall the survey findings provided a picture of the main drivers of manufacturers' continued participation in prequalification, and how these impact each other *(Box 1)*. In the 2016 follow-up survey on medicines, of the dimensions contributing to overall satisfaction, process design was most important for the respondents , followed by time-related aspects and service delivery. In the 2015 diagnostics survey, satisfaction with time-related aspects also had a direct impact on the perceived benefits of prequalification.

Enhancing and sustaining prequalification

In addition to surveying manufacturers regarding prequalification services and incorporating the findings into revised policies and procedures, WHO-PQT initiated other measures to improve the efficiency of its service offerings *(Box 2)*. New internal metrics (KPIs) have been proposed to measure progress in areas important to stakeholders, and a new website was developed to provide a more user-friendly online experience for visitors. A new prequalification fee structure was also developed to increase programme sustainability.

Prequalification services in context

International donors and procurement agencies have harmonized their quality policies, and require either WHO prequalification or stringent regulatory approval for key categories of products that they purchase. In strategic decisions on which pathway(s) to pursue, companies will weigh the cost and time to be invested against the expected benefits in terms of market access.*(6)* The impact of prequalification timelines as a key driver of manufacturers' perceptions of benefits is therefore not altogether surprising.

Box 2: **Recent initiatives to enhance prequalification services**

Timeline-related KPIs

As in many regulatory systems, prequalification timelines are calculated separately for WHO actions and applicant actions ("stop-clock time"). In July 2017 WHO-PQT proposed a new set of timeline-related key performance indicators (KPIs) for public comment, with a harmonized calculation approach across product categories. The new KPIs will be applied when the new prequalification IT system, currently under development, is launched.*(5)*

Website

A new medicines prequalification website with greatly enhanced search functions was launched in early 2017. A model dossier was also made available on the website. It illustrates how data for finished pharmaceutical products should be submitted to WHO, providing valuable practical guidance to applicants, with added value for regulatory training and harmonization initiatives.

In comparing the service quality of prequalification processes with those of stringent regulatory authorities (SRAs), some of the more intangible benefits may also be considered that result from the different mandates of WHO and SRAs.

Stringent approval, in international procurement, is defined as marketing authorization by a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). These authorities cater mostly for the needs of high-income countries. Mechanisms for assessment of medicines to be used outside the SRAs' own territories include the U.S. FDA approvals for the President's Emergency Plan for AIDS Relief (PEPFAR)[1] and the EMA "Article 58" procedure[2]. However, the former applies only to antiretrovirals and the latter has had limited uptake. For IVDs the SRA route also has some limitations: international organizations recognize the relevant authority's approvals only if they were achieved through the authority's stringent "high-risk classification" procedures, which typically apply to HIV and hepatitis tests but not malaria or tuberculosis tests.

In the long term, ICH is set to become more relevant to low- and middle-income countries as it is expanding its membership to become a truly global organization. In light of these changes a concept for revising the definition of "stringent regulatory authority" has been proposed.*(7)* For the time being, however, stringent regulatory processes are mostly designed for products supplied to each SRA's own territory.

WHO prequalification on the other hand aims to cater for the needs of the Organization's 194 Member States. Based on WHO's mandate to serve its Member States globally, prequalification services are geared to provide some added benefits for global suppliers of health products to donor-funded markets:

- **Product suitability in target countries.** Prequalification considers the requirements of products in the settings of their intended use, *e.g.:* stability of medicines in hot and humid climates, suitability of vaccines in the target countries, or ease of use of diagnostic tests at the point of use.
- **Collaborative oversight.** From its beginnings, WHO has involved regulators from across its Member States in prequalification. This has opened up communication channels that provide added assurance of effective oversight of product quality[3], which is valued by procurers.
- **Support for market access in target countries**. WHO's collaborative registration of prequalified medicines and vaccines offers an accelerated pathway for registration in participating countries.[4] And for global suppliers of vaccines the newly established control laboratory network *(4)*, which aims to promote reliance and reduce redundant lot testing, could remove some significant regulatory hurdles.

[1] www.fda.gov/internationalprograms/pepfar/ucm119231.htm. Used frequently but limited to antiretrovirals.

[2] www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp

[3] **Example:** An African regulator who had worked with WHO-PQT on collaborative initiatives approached WHO about a batch of bilayered tablets found on the local market that differed from the registered specifications with regard to appearance. The WHO-PQT assessors provided advice and requested the WHO-PQT inspectors to take up the issue in their next inspection of the manufacturing site concerned.

[4] See https://extranet.who.int/prequal/content/collaborative-registration-faster-registration

Conclusions

WHO prequalification was established to bridge regulatory gaps in Member States by offering all manufacturers, regardless of where they are based, a stringent assessment mechanism for their medical products. But gaps persist, and global regulatory challenges are growing. Even well-resourced regulatory authorities are increasingly dependent on collaboration with other NRAs and reliance on other NRAs' regulatory outputs to perform all regulatory functions.

Clearly there is a continued need for WHO prequalification. In 2014 the World Health Assembly called on WHO and Member States to support the programme.*(8)* More recently *The Lancet's* Commission on Essential Medicines Policies commented: "*The prequalification programme is a concrete application of WHO's global norms and standards for medicines quality and safety. It has positioned WHO as a global regulatory agency and has greatly shaped the world's generic markets, driving down costs while ensuring the quality of products. It has also become an important training ground for regulators and inspectors, paving the way for regional harmonisation*". It recommended that WHO prequalification should maintain a focus on new essential medicines to help achieve universal health coverage.*(9)*

WHO prequalification is critically dependent on manufacturers' continued participation. Encouragingly, the 2016 follow-up survey for medicines prequalification showed that improvements have been made and sustained, and the service provided meets the respondents' expectations in every respect. Ongoing communication with manufacturers will be critical to ensuring that prequalification services remain attractive for applicants and therefore sustainable for WHO.

References

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9 Wirtz VJ, Hogerzeil HV, Gray AL, Bigdeli M, de Joncheere CP, Ewen MA, *et al.* Essential medicines for universal health coverage. Lancet 2016; published online Nov 7. http://dx.doi.org/10.1016/S0140-6736(16)31599-9.

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Annex 1: **Overview of aspects rated in manufacturer surveys**

Service design – "Process"	
Assistance to applicants	Transparency on how products are selected/prioritized | Training provided to prepare applicants for the process | Applicants made aware of resources to assist them during the process | Assistance provided during process | Applicants kept informed of progress *Website:* Clear guidance on process | Comprehensive information on requirements *Assessment:* Understanding provided of full review process | Convenient dossier submission process *Inspection:* Plan provided with all required information to prepare for inspection *Post-marketing surveillance*:* Required information provided for manufacturer to act on complaints
Consistency of policies and procedures	*Assessment:* Consistent standards applied for quality, safety and efficacy | Consistent process applied for multiple dossiers submitted | | Use of international standard formats for vaccine product summary files *Inspection:* Clear requirements | Clear interpretation provided of good manufacturing practice (GMP) requirements | Explaining non-conformities | Inspection team has full set of required skills *Laboratory evaluation*:* Opportunity to review product testing at the evaluation site prior to actual product testing | Clear protocol | Clear acceptance criteria *Post-market surveillance*:* Clear explanation of obligations *Sample testing***: Clear requirements at time of initial assessment | Clear requirements for annual targetted testing of batches
Problem resolution	Efficient process to resolve issues and questions raised | Clear questions asked | Access to staff *Assessment:* Opportunities for in-person meetings with assessors *Inspection:* Opportunities to address technical questions/non-conformities | Efficient post-inspection processes | Inclusion of local inspectors *Sample testing**:* Addressing manufacturers' questions on testing results
Time-related aspects	Acceptable overall time to prequalification | Process timeline with delivery dates for agency and applicant | Timely process to address technical questions *Assessment:* Timely screening process | Appropriate length of review cycles | Appropriate number of review meetings | Timely overall review | Timely handling of post-approval variations *Inspection:* Timely announcements | Efficient use of manufacturer's time *Laboratory evaluation*:* Laboratory evaluation report sent in a timely manner *Post-market surveillance*:*Timely handling of complaints Sample testing**: Time taken to complete the testing
Service delivery – "People" *(Rated separately for assessors and inspectors)*	
Reliability	Ability to perform the promised service dependably and accurately
Responsiveness	Willingness to help applicants and provide prompt service
Assurance	Knowledge, courtesy and ability to convey trust and confidence
Empathy	Caring, individualized attention provided to applicants
Perceived benefits	Internal: Increased internal capabilities of company | Quality raised of all medicines that company manufactures | Company can easily forecast return on investment for the process External: Increased access to global markets | Can charge higher prices for approved products | Increased market share of company's products | Process prepares emerging companies to enter new, more regulated markets
Participation in prequalification	My company intends to submit additional medicinal products in the future; I expect my company to continue participating | My company is likely to participate in future

** = For diagnostics only; ** = For vaccines only*