Ariadna Nebot Giralt et al.

WHO’s pre-qualification of medicines

A survey of nongovernmental organizations on their use of WHO’s prequalification programme

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Abstract

Objective To obtain the perspectives of some small- and medium-sized organizations on the World Health Organization (WHO) prequalification programme for medicines and to ascertain organizations’ unmet needs.

Methods We conducted an exploratory, qualitative study in 2018 among 17 representatives of 15 small- and medium-sized Belgian and non-Belgian organizations who purchase medicines for humanitarian, development or public programmes in low- and middle-income countries. We used semi-structured interviews to obtain respondents’ views and experiences of using WHO prequalification guidance when procuring medicines. We identified emerging themes and formulated recommendations about the activities of the WHO Prequalification Team.

Findings Most respondents suggested expanding prequalification to essential antibiotics, particularly paediatric formulations; and insulin, antihypertensives and cancer treatments. Respondents were concerned about irregular availability of WHO-prequalified medicines in the marketplace and sometimes high prices of prequalified products. Small organizations, in particular, had difficulties negotiating low-volume purchases. Organizations working in primary health care and hospitals seldom referred to the prequalified lists.

Conclusion We recommend that the WHO-prequalified products be expanded to include essential antibiotics and medicines for noncommunicable diseases. The WHO Prequalification Team could require prequalified manufacturers to make publicly available the details of their authorized distributors and facilitate a process of harmonization of quality assurance policies across all donors. Prequalification of distributors and procurement agencies could help create more transparent and stringent mechanisms. We urge WHO Member States and funders to sustain support for the WHO Prequalification Team, which remains important for the fulfilment of universal health coverage.
Introduction
A key element of achieving universal health coverage in target 3.8 of the sustainable development goals is “access to safe, effective, quality and affordable essential medicines and vaccines for all.” Ensuring the quality of medicines is a moral imperative for any concerned stakeholder,¹ and failure to do so may have major public health and economic consequences. The globalization of production and distribution, however, coupled with the weakness of national medicines regulatory authorities in many low- and middle-income countries, makes it difficult to thoroughly assess the quality of medicines available in the global market.² Most national medicines regulatory authorities in low- and middle-income countries lack the human and financial resources and infrastructure to assess the efficacy, safety and quality of medical products submitted for marketing authorization or to maintain adequate postmarketing surveillance. The World Health Organization (WHO) has developed a global benchmarking tool for systematically evaluating regulatory systems.³ Yet, as reported in 2018, only 26% (X) of 194 WHO Member States have the capacity to enforce adequate quality assurance systems.⁴ Consequently, low- and middle-income countries are particularly at-risk of having poor-quality medicines that weaken their health systems and erode trust.⁵⁻¹⁰ Based on a literature review of papers that reported on field studies or surveys of the quality of medicines, WHO has estimated that about 10.5% of medicines in low- and middle-income countries are substandard or falsified (that is, 1166 of 11 156 tested samples in low-income countries and 3906 of 35 884 samples in middle-income countries).¹¹

The WHO Pre-Qualification of Medicines Programme¹² was launched in 2001 for guiding United Nations agencies with respect to the quality of medicines for treatment of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), tuberculosis and malaria. In 2013, the programme was merged with the WHO Pre-Qualification of Diagnostics Programme and Vaccines, to create the WHO Prequalification Team. The team provides a variety of services, including: assessment of quality control laboratories; training, advice and clarifications within the framework of its guidelines for national medicines regulatory authorities; and assessment of active pharmaceutical ingredients and finished pharmaceutical products for HIV/AIDS, malaria, tuberculosis, hepatitis, diarrhoea, influenza, reproductive health and neglected tropical diseases. The team’s role in assessing medicines consists of an in-depth, transparent assessment of all technical files of the product and inspection of manufacturing sites and contract research organizations.¹³ After awarding prequalification, the team ensures the ongoing quality of prequalified products by monitoring variations, periodical re-
qualifications, reinspection of manufacturing sites and field quality surveys. WHO’s prequalification programme has raised awareness of the importance of quality assurance: a system by which quality is built into a product at every step of development, production and distribution.\textsuperscript{1,3}

The findings of structured medicines quality surveys\textsuperscript{14–16} have demonstrated that WHO prequalification has had a major impact in assuring the quality of HIV/AIDS, malaria and tuberculosis medicines used in low- and middle-income countries and in reducing the likelihood that scarce resources are spent on products of unknown quality.\textsuperscript{17} The list of prequalified medicines by therapeutic area is available publicly\textsuperscript{18} and is an important tool for purchasers of medicines. As of 2014, WHO had prequalified 85–90\% of antiretroviral, antimalarial and tuberculosis medicines, procured by or with funds from the Global Fund, United Nations Children’s Fund and Unitaid.\textsuperscript{17} The prequalified products lists are also used by nongovernmental organizations (NGOs) and other stakeholders, such as national procurement agencies. It is hoped that the positive experience with HIV/AIDS, malaria and tuberculosis medicines will be replicated in the other areas covered by the WHO Prequalification Team, such as hepatitis, diarrhoea, influenza, reproductive health and neglected tropical disease. Currently, in early 2020 however, relatively few essential medicines are covered by WHO prequalification. In addition, there are not yet prequalified products for some medicines in therapeutic areas under its the team’s scope;\textsuperscript{19} for others, only one product has so far been prequalified.

Here, we aimed to gain an understanding of the perceptions of some small- and medium-sized organizations towards the WHO prequalification and to ascertain organizations’ unmet needs. We combined these responses with the reflections of our researchers to formulate recommendations on the activities of the WHO Prequalification Team.

Methods

We conducted an exploratory, qualitative study between 10 September and 15 October 2018 among representatives and focal points of Belgian and non-Belgian organizations that are members of Be-Cause Health or QUAMED. Be-Cause Health is a Belgian network that facilitates exchange and capitalization of knowledge about international health and development cooperation, and hosts a medicines working group for members interested or involved in the management of medicines procured for and used in low- and middle-income countries.\textsuperscript{20} QUAMED is an independent not-for-profit
organization that brings together NGOs and public or not-for-profit procurement centres, to improve access to quality medicines by raising awareness of and strengthening the quality assurance systems of its partners.\textsuperscript{21,22}

We invited participation from all representatives of organizations that are members of the Be-Cause Health Medicines Working Group and procure medicines, and from all focal points of organizations that are members of QUAMED. All potential respondents already knew the researchers through their shared membership of the two platforms. We contacted participants by email, provided them with information about the study and, if they agreed to participate, made an appointment for an interview. The study was approved by the institutional review board of the Institute of Tropical Medicine, Antwerp, Belgium (ref. 1247/18). All respondents provided written consent for participation.

We collected the data by means of semi-structured interviews, to obtain an in-depth understanding of participants’ perspectives and perceptions of the WHO prequalification process and of the organization’s unmet needs. Interviews were conducted by telephone or in person, mostly in English and some in French\textsuperscript{4} or Spanish.\textsuperscript{1} The interview guide is available in our institutional website.\textsuperscript{23} The primary scope of the interviews was: to identify those essential medicines for which, to the best of the respondents’ and researchers’ knowledge, no quality-assured finished pharmaceutical products are currently available in the market; and to formulate recommendations about possible expansion of the activities of the WHO Prequalification Team. The interviewers first addressed the general challenges related to procurement and purchase of medicines for field medical programmes, and gradually moved to the core issues of the survey, that is, which medicines are not available as prequalified products.

Handwritten notes were taken. The researchers who conducted the interviews analysed the data manually from the notes, using thematic content analysis which focused on examining themes or patterns of themes from information collected during the interviews. After the systematic data analysis, we identified and listed the main themes, discussed them among our research team and, when needed, cross-checked them with the WHO prequalified products list.\textsuperscript{18} We also analysed whether specific patterns emerged related to the types or categories of organizations or respondents.

Results

Participants
We contacted potential respondents in 22 organizations; 19 people agreed to participate and 17 participants from 15 organizations attended the appointment for an interview. Our final sample included 17 representatives of 14 small- and medium-sized medical NGOs and one African procurement centre. Most interviewees were pharmacists (10 participants), followed by medical doctors or nurses (four participants). Eight participants had worked in the organization for 4 years or less, and six participants for 10 or more years. The majority had previous relevant experience in procurement of medicines and all participants had some degree of responsibility for quality assurance of purchased medicines. All the organizations purchased medical products for programmes in low- and middle-income countries, with different scopes and target populations, ranging from well-established primary health-care or hospital programmes to vertical programmes and emergency interventions.

Programme scope
Most respondents expressed a wish that the WHO Prequalification Team would provide guidance in more critical fields than are currently covered. Most respondents agreed on expanding prequalification to essential antibiotics, such as penicillin, particularly for paediatric formulations. Similarly, medicines for noncommunicable diseases were viewed as an important area. Insulin, antihypertensives and medicines for treating different forms of cancers were specifically mentioned. Few respondents (one to three per item) also mentioned that WHO prequalification should assess large-volume intravenous infusion solutions, such as glucose infusions, which are easy to manufacture but are harmful if substandard (for example, if they do not comply with sterility specifications); disinfectants and antiseptics; various medical devices; ribavirin, lidocaine, diazepam and opioid analgesics. A few respondents observed that their organization’s needs remained unmet even in therapeutic areas within the scope of the WHO prequalification system. For example, the WHO-prequalified list of medicines for neglected tropical diseases contained few finished pharmaceutical products; and there were at the time of the study no prequalified finished pharmaceutical products for certain medicines for multidrug-resistant tuberculosis.

Procurement
While our main question revolved around essential medicines for which no quality-assured finished pharmaceutical products were yet available, the interviews uncovered some other issues indirectly linked to prequalification that are necessary if WHO-prequalified medicines are to reach all those in need. Many participants observed that the procurement of WHO-prequalified finished pharmaceutical products was not always straightforward. For instance,
a low volume of purchase can make an organization unattractive for suppliers: its orders are less likely to be accepted or prioritized, and price negotiation is more difficult. Several respondents noted that WHO-prequalified finished pharmaceutical products were not always readily available on the international, regional or local markets. In addition, prices may vary considerably between suppliers. Some respondents, especially those in small organizations, expressed the view that WHO-prequalified products were more expensive than non-prequalified ones, limiting their capacity to procure quality-assured medicines. The difficulty was more pronounced in the case of dependency on a single supplier, when variability in pricing of WHO-prequalified finished pharmaceutical products was observed and when information about authorized distributors of prequalified products was not easily available. On a broader note, some representatives of small and medium-sized NGOs reminded us that they mainly purchased from wholesalers and distributors, rather than from manufacturers on a product-by-product basis. Participants observed that access to public, easy-to-access information about distributors of WHO-prequalified products, possibly by geographical region, and including transparent pricing information, would be helpful.

**Prequalification guidance**

Our interviews revealed that knowledge and use of the WHO-prequalified lists of finished pharmaceutical products as practical tools for guiding procurement choices depended on the characteristics of a respondent’s organization. Only organizations that showed a strong institutional awareness of the need to assure pharmaceutical quality, and that had invested in quality assurance systems, seemed to be in a position to use the prequalified lists adequately and consistently (for example, by checking carefully the product and manufacturing site specifications). Organizations involved in vertical programmes in therapeutic areas covered by WHO prequalification, such as tuberculosis, were more likely to refer to the prequalified products lists on a regular basis. Small organizations, especially those working in primary health care and in hospitals, seldomly referred to the lists. Some respondents mentioned that they would benefit from a type of prequalification of distributors and procurement agencies, both internationally and in the regions and countries of intervention. Finally, the purchasing policies and practices of implementers that depended on external funding were strongly influenced by the funders’ quality assurance policy or lack of it.

**Discussion**

Since we conducted this study, WHO has published as independent external review on the impact assessment of its prequalification and systems supporting activities. The review
provides a perspective of the needs and interests of various stakeholders, including 16 donors or procurers. Nevertheless, we believe that the views revealed through our qualitative assessment are complementary and remain of interest for uncovering some specific views.

Respondents’ desire for expansion of prequalification to essential antibiotics and medicines for noncommunicable diseases is very relevant, given the contribution of poor-quality antibiotics to antimicrobial resistance and the epidemiological shift towards noncommunicable diseases in most low- and middle-income countries. It is noteworthy that in 2019 WHO started a pilot programme to prequalify human insulin. Another pilot programme is ongoing for two anticancer drugs and, in December 2019, the first biosimilar drug (trastuzumab) was prequalified. Respondents’ suggestions for other products outside the scope of the WHO prequalification system illustrate how concern about quality exists across the full range of essential medicines.

Difficulties with negotiating procurement of WHO-prequalified medicines for small- and medium-sized NGOs echo the experiences of some central medical stores in Africa, which in a previous study reported poor transparency and lack of consideration from some suppliers. Our respondents’ concerns about the unavailability of WHO-prequalified finished pharmaceutical products in the market shows that organizations would benefit from access to more accessible information on suppliers or distributors of prequalified medicines, at regional or local level. It is notable that no respondents explicitly referred to the International Medical Products Price Guide as a tool to support negotiations, or to the Global Fund’s procurement tool, Wambo. This finding may indicate that these tools are not known to respondents or that the tools are not easy to use in respondents’ everyday professional life.

Our respondents’ comments about the cost of WHO-prequalified products highlights a possible drawback of quality assurance. Prequalified products may be more expensive than products that are not quality assured or not under the continuous regulatory oversight of a stringent quality assurance mechanism. On the one hand, higher cost can be justified by the harm reduction and the benefit to individual and public health. On the other hand, in many cases, manufacturers who invest in WHO-prequalified products are indirectly rewarded through access to bigger markets, providing them with an opportunity for economies of scale, resulting in lower production costs. This topic would benefit from additional research, to verify whether the prices of prequalified products are always significantly higher than those of non-prequalified competitors. If so, future research should assess whether this
relates to the ex-factory price or to mark-ups along the distribution chain. Understanding whether prices could be better controlled would also be important, and, if so, how: via economies of scale, pooled negotiations and procurement, or enhanced transparency.

Our respondents from small organizations who were not involved in vertical programmes reported that they seldom referred to the WHO-prequalified products lists. The concept of prequalification is based on inspection of manufacturing sites and review of product dossiers; it results in the prequalification of a given finished pharmaceutical product from a given manufacturing site. Such an approach is relevant for big national and international purchasers, including some national procurement centres and major medical humanitarian NGOs. However, the approach seems to be less able to address the needs and capacities of purchasers in small- and medium-sized NGOs, and of implementers working in primary health care or hospitals with a broad range of essential medical products. These small or medium-sized organizations cannot individually address different manufacturers for purchasing on a product-by-product basis (that is, a given product by a given manufacturer), and they would benefit by a prequalification of distributors and suppliers.

We found that the quality assurance policies of funders affected organizations’ purchasing policies and practices. On a positive note, funders are increasingly becoming aware of the need for adequate quality assurance requirements in pharmaceutical procurement, especially when operating in countries where regulation of medicinal products is weak. For instance, some United Nations agencies, the United States Agency for International Development and the Bill and Melinda Gates Foundation are engaged in a process of harmonization of quality assurance policies. Among state funders, Belgium requires that implementers in low- and middle-income countries commit to ensuring the quality of procured medicines. However, when the funder does not prioritize quality assurance, and does not foresee a dedicated budget line, implementers are more likely to choose supply channels that are not fully secured, including medicines that are non-prequalified or not subject to stringent regulation. All funders should understand the relevance of pharmaceutical quality assurance; that they require adequate quality assurance criteria for procurement of medicines in the programmes they fund; and that they make the guidance of the WHO Prequalification Team a mandatory requirement when WHO-prequalified products exist.

Further investigation could look at whether the WHO Prequalification Team could facilitate or oversee a process of upgrade (when needed) and harmonization of quality
assurance policies across all donors. This process could be perhaps by done by building on the experience of the WHO’s Expert Review Panel, which provides guidance for time-limited procurement of much-needed products that are not yet prequalified or approved by a stringent regulatory authority.¹

Our study had some limitations. We did not investigate how organizations make purchasing decisions in the absence of a WHO-prequalified product; thus, some possibly related issues did not emerge. For example, respondents did not mention whether they use the WHO’s Model Quality Assurance System for Procurement Agencies.³⁴ While describing decision-making mechanisms in the absence of WHO prequalification guidance was not the main aim of this research, it would be a relevant subtopic for further research. Also, our findings drew on the views of a relatively small group of representatives of organizations that purchase medical products for public, humanitarian and development programmes for low- and middle-income countries.

**Conclusions**

We have formulated recommendations for how WHO and its Prequalification Team can enhance their capacity to meet procurers’ needs in the field. First, to address current trends in global health, invitations for expression of interest for WHO-prequalified products could be issued for essential antibiotics and medicines for noncommunicable diseases. Second, the WHO Prequalification Team could require manufacturers to make publicly available (in a dedicated website, for example) the lists, contacts and wholesaler prices of their authorized distributors, either acting internationally or regionally. Third, the WHO Prequalification Team could consider facilitating a process of harmonization of quality assurance policies across all donors.

Another recommendation emerged for WHO Member States and funders, given the importance of prequalification for protecting the health of the most vulnerable. In 2013, WHO began charging fees for activities related to medicines prequalification to improve the financial sustainability of the programme. We encourage stakeholders to sustain and increase support for the WHO prequalification programme, as a unique public good that is essential for the fulfilment of universal health coverage.

On another note, unrelated to the scope of the WHO Prequalification Team, we hope that transparent, stringent mechanisms can be put in place for a type of prequalification of wholesalers, distributors and procurement agencies. This could be helpful for small and
medium-sized humanitarian, development and public-sector purchasers in low- and middle-income countries when seeking to procure quality-assured medical products.

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Competing interests:

ANG is the Technical Coordinator of QUAMED, a not-for-profit organization that carries out assessments of local pharmaceutical markets and distributors, with the aim to support humanitarian and development organizations to purchase quality-assured medicines. RR is the Chairperson of the Institutional Review Board of the Institute of Tropical Medicine Antwerp, Belgium, which reviewed and approved the qualitative survey. However, she did not participate in this review, which was coordinated by the vice-chair.

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