The lack of quality-assured sources of medicines on the global market: a survey to explore the priority needs of purchasers in the Belgian humanitarian sector

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Table of acronyms

DGD	Belgian Directorate-General for Development Cooperation & Humanitarian Aid
GMP	Good Manufacturing Practices
ITM	Institute of Tropical Medicine
LMIC	Low and Middle-Income Countries
NGO	Non-governmental Organizations
NMRA	National Medicines Regulatory Authorities
NCDs	Non-communicable Diseases
NTDs	Neglected Tropical Diseases
PHC	Primary Health Care
PMS	Post-marketing Surveillance
PQ(P)	Pre-Qualification (Programme)
PV	Pharmacovigilance
QA	Quality Assurance
QUAMED	Quality Medicines for All
SF	Substandard and Falsified (medical products)
SRA	Stringent Regulatory Authority
WHA	World Health Assembly
WHO	World Health Organization

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1. Background and rationale

Substandard and Falsified Medicines: a public health threat

Access to quality-assured medicines is crucial for access to health. The Sustainable Development Goal 3.8 aims at universal health coverage, including "quality and affordable essential medicines and vaccines for all". But the increasing globalization of pharmaceutical production, coupled to the lack of resources of National Medicines Regulatory Authorities (NMRA) in most low and middle-income countries (LMICs), makes it difficult to thoroughly assess the quality of medicines circulating in the global market (Caudron 2008). In particular, most NMRAs in LMICs lack adequate human and financial resources to assess the efficacy, safety and quality of medical products that are submitted for marketing authorization in their country, and to maintain adequate post-marketing surveillance (WHO 2008). Consequently, poor quality medicines, including *substandard medicines* (legitimate medicines that do not comply with adequate quality standards) as well as *falsified medicines*, are especially prevalent in LMICs, where they often go undetected, and result in avoidable morbidity, mortality and drug resistance (Newton et al 2011, Ravinetto et al 2016).

The World Health Organization (WHO) underlines the growing importance of this problem, as well as its deleterious effects for public health and for health systems. In 2017, the World Health Assembly (WHA) formally agreed on new definitions of "substandard and falsified" (SF) medical products, by explicitly requiring compliance with both national and international quality standards; by removing the confusion around the issue of 'counterfeit' medicines, which have been increasingly associated with intellectual property issues; and by clarifying that both substandard and falsified medicines must be tackled from a public health perspective[1]. Also in 2017, the WHO published a report based on data gathered by its Global Surveillance and Monitoring System. The report outlines the dangers that SF medical products present to individuals, communities and countries, and it includes estimates that about 10% of all medicines available in LMICs are substandard or falsified (WHO 2017).

The challenges of the global pharmaceutical market

The WHO launched in 2001 the Pre-Qualification (PQ) Programme for medicines, in response to the HIV/AIDS pandemic. The WHO PQ initially aimed at guiding the agencies of the United Nations and some other international organizations with respect to the quality of antiretroviral medicines for supply to low-income countries. Today, its services cover assessment of finished pharmaceutical products in some selected therapeutic areas (i.e., HIV, malaria, tuberculosis, hepatitis, diarrhea, influenza, reproductive health and neglected tropical diseases), as well as assessment of the corresponding active pharmaceutical ingredients, and of quality control laboratories. The WHO PQ Team also provides technical assistance and training activities[2]. The PQ process for medicines consists of a transparent and scientifically sound assessment, which includes the *product dossier review*, i.e. the in-depth assessment of all technical files of a new product, and *site visits to manufacturers*[3]. The lists of prequalified products per therapeutic area are publicly available[4] and they represent a practical, useful guidance for all those who purchase medicines in/for LMICs.

[1] http://www.who.int/mediacentre/news/releases/2017/dementia-immunization-refuguees/en/

[2] https://extranet.who.int/prequal/content/overview-history-mission

[3] http://www.who.int/topics/prequalification/en/

[4] https://extranet.who.int/prequal/content/prequalified-lists/medicines

Overall, the WHO PQ had a major positive impact for assuring the quality of HIV/AIDS, malaria and tuberculosis medicines in LMICs ('t Hoen et al 2014), and it is hoped that the same will happen for the therapeutic fields that were included more recently under its mandate. Unfortunately, not all essential medicines are covered by the WHO PQ. In addition, to date there are not yet pre-qualified sources for several medicines in therapeutic areas under the WHO PQ scope (either because there are no candidate products, or because the candidate products did not fulfil the adequate quality requirements). This is the case, for instance, of benzathine penicillin (Nurse-Findlay S et al, 2017). For some others, there is only one pre-qualified source.

The term 'Stringent Regulatory Authority' (SRA) had been developed to promote reliance and guide procurement decisions. To date, medicines are considered as fully quality-assured if they are either pre-qualified by the WHO, or if they have been given a marketing authorization by a SRA, such as the NMRAs in Europe, the United States and Japan[5]. The WHO is currently working at a *Global Benchmarking of Regulatory Systems*, so as evaluate regulatory systems through a more comprehensive and systematic benchmarking, based on 4 *maturity levels*. Under the new framework, the term SRA will be replaced by *WHO-Listed Authority*, where current SRA will be regarded as WHO-Listed, while the designation of additional NRAs will be based on WHO Global Benchmarking Tool + completion of confidence-building process[6].

If, for a given medicine, there are no sources pre-qualified by the WHO, and no sources approved by a SRA (and unfortunately, products of little/limited interest in affluent countries, are unlikely to be submitted to SRAs) there is no full assurance of the quality of the available sources. This implies that purchasers must take a marge of risk when making the purchasing decision. This is not a theoretical case. For example, penicillins are still used in significant quantities in LMICs, but production has been progressively abandoned in affluent countries in favor of more recent antibiotics such as cephalosporins, quinolones, and macrolides. When MSF and UNICEF audited 11 production sites for injectable penicillins, they found that only two where adequately implementing Good Manufacturing Practices (GMP). Noteworthy, the remaining nine had important market shares in Asia and Africa (Caudron 2008).

In addition, if only one quality-assured product exists (either pre-qualified by the WHO or registered by a SRA), other problems may arise, e.g. lack of sufficient stock to address all needs or, especially for products only approved by a SRA in an affluent country, high prices unaffordable to purchasers in LMICs.

Procurement and quality assurance in humanitarian and development medical programs

Fully ensuring the quality of medicines is always a moral imperative, given that failure to do so may result in therapeutic failure or direct toxicity, contribute to the emergence of resistances (e.g. to antimalarials, anti-TB medicines, and potentially to antibiotics), and weaken the health systems. This moral imperative becomes even stronger when medicines are bought and provided in the frame of humanitarian and/or development programs, and/or when public money is used to purchase medicines for medical programs overseas. There should be no double standard (WHO 2011), and all possible efforts should be done to avoid differences in the level of quality assurance (QA) (and thus, of protection) for patients in the "donor" country, where medicines are always

[5] A stringent regulatory authority is a regulatory authority which is a member or an observer of the International Conference of Harmonization (ICH), or is associated with an ICH member through a legally-binding mutual recognition agreement. The definition originated from the Global Fund and it is reflected in the quality assurance policies of most major international organizations involved in procuring medicines (WHO Expert Committee 2017).

[6] http://www.who.int/medicines/regulation/benchmarking_tool/en/

approved by a SRA, and for patients in the "beneficiary" country, with no SRA (Ravinetto 2018). This moral responsibility is high on the agenda of Belgian stakeholders, as illustrated below.

First, Be-cause Health, i.e. an informal and pluralistic Belgian platform that provides a place for exchange and capitalization of technical knowledge and scientific evidence on international health and development cooperation, hosts since more than 10 years a *Medicines Working Group*, bringing together individuals and organizations involved in the management of medicines in the context of international health and development cooperation. In 2008, representatives of these organizations signed a *Charter for the Quality Assurance of Medicines*. This aspirational document expressed the concerns of these organizations about the North-South gap in access to quality-assured medicines, as well as a commitment to strive to correct it[7,8].

Second, the QUAMED Network was created in 2010 under the Framework Agreement 3-II between the Belgian Directorate-General for Development Cooperation & Humanitarian Aid (DGD) and the ITM, for contributing to "improving access to quality medicines, by raising awareness among the key players involved in the pharmaceutical supply system and by reinforcing the quality assurance systems and supply procedures of its partners". The members of QUAMED, i.e. NGOs and public/not-for-profit procurement centers, pool resources and information for improving the quality of medicines they supply in LMICs. In 2017, QUAMED evolved into an independent not-for-profit organization, with the same core activities, and retaining an ongoing research collaboration with the ITM (Nebot 2017; Van Assche 2018).

Third and importantly, a process led by the DGD resulted in the *Commitment to Quality Assurance for Pharmaceutical Products*, signed on 25th October 2017 in Brussels by the Belgian Deputy Prime Minister and Minister for Development Cooperation Alexander De Croo, and by 19 Belgian implementers, i.e. NGOs, the Belgian development agency, academia, and the Belgian investment company for developing countries (Commitment 2017, Ravinetto 2018). A key-role was played in this process by Be-cause Health. The Belgian *Commitment* is accompanied by proactive advocacy and support toward the WHO PQ Programme.

The rationale for this study

Within the frame of the Belgian support toward the WHO PQ, it has been agreed that the DGD in collaboration with the Belgian implementers would provide a field-based feedback on what medicines should be prioritized by the WHO PQ (either within or outside its current scope), to address unanswered needs. The feedback should be based on the real-life challenges met by the concerned actors when making purchase decisions for medicines to be used in LMICs. The current survey is a result thereof and is designed to address the question concerning the prioritization of medicines urgently needing quality-assured sources. Given that the lack of full quality assurance corresponds to a risk for the final user, the prioritization exercise should be triggered by the concepts of "patient-centeredness", and of "risk" for users/patients. The volumes of medicines purchased by the humanitarian actors was not taken into account, because this could lead to neglecting the needs related to diseases with small burden yet high morbidity and mortality.

2. Objective

The objective of this study was to conduct an exploratory assessment of the unmet needs of humanitarian/development organizations, either Belgian or involved in Belgian consortia, that purchase medicines for humanitarian, development or public programs in LMICs; and this, in order to identify those essential medicines for which, to the best of their knowledge, no quality-assured sources are currently available in the market.

[7] https://www.be-causehealth.be/en/bch-news/seminar-on-access-to-quality-assured-medicines/

[8] https://www.becausehealth.be/en/bchgroups/access-to-quality-medicines/.

3. Methods

Data were collected by means of semi-structured interviews. The reason for choosing semi-structured interviews instead of a self-administered questionnaire, was pragmatic. Different organizations have different capacities to monitor the pre-selection, supply and management of medicines[9], and the eligible respondents have varying profiles and expertise. The semi-structured interviews allow the interviewer to guide and orient the less specialized respondents, so as to ensure that collected information is accurate, reliable and especially comparable across different respondents. The semi-structured interviews also allow a more in-depth understanding of how purchasing decisions are made, and of how dilemmas are faced.

Interviews were carried out by the two researchers with pharmacy expertise (RR and ANG), either by phone/Skype or in person, and using an interview guide (Annex I).

Identification and recruitment of respondents

Potential respondents were all the representatives/ focal points of organizations members of the Be-Cause Health Medicines Working or of QUAMED. As such, all were already regularly in touch with the two researchers. The Be-cause Health members were, in addition, already aware of this particular study, since it had been presented at their meeting on 4th June 2018. Inclusion criteria were as follows:

- Representatives of organizations that are members of the Be-cause Health Medicines Working Group and procure medicines for medical programs overseas, **AND/OR**
- Focal points of organizations that are members of QUAMED, **AND**
- Agree in written to participate in the study.

Each potential participant was individually contacted by email by RR or ANG, and provided with the information about the study, as detailed in the informed consent documents. If they agreed to participate, an appointment was done for the interview. If the interview was in person, the respondent indicated the most adequate location (i.e. at office, or at a conference venue).

Data collection, analysis and storage

The interviews were conducted in (mainly) English, or French, between 10 September and 15 October 2018. The initial aim to pre-test the interview guide with 2 to 3 members of the Medicines Working Group of Be-cause Health who were not eligible for the study was not possible in practice, because in practice there was no candidate sufficiently representative of the study group, i.e. with comparable experience and expertise in the study topic (aside from the eligible participants, whom were kept in the sample).

Most interviews were conducted by the two primary researchers (RR and ANG) together, after defining the respective role of interviewer and of note-taker. Data were analysed manually by ANG, using content analysis, and findings discussed with RR. MR was available in case of disagreements between the two primary researchers. When needed, responses were cross-checked versus the most recent WHO PQ list[10].

Based on the systematic analysis of all interviews, the "top priority needs" were listed. We tried as much as possible to look at possible correlation to the kind of organizations (e.g. mandate, size, countries/regions of operation) and of responders (e.g. background, role, years of experience), so as to explore if any patterns emerged related to the types/categories of respondents.

[9] E.g., they may or may not have a responsible pharmacist, a QA-pharmacist, an adequate procurement policy, an effective stock management tool….

[10] https://extranet.who.int/prequal/content/prequalified-lists/medicines

Notes, informed consent statements and any other source documents will be kept at the ITM or QUAMED offices, under the responsibility of the primary researchers, for at least 2 years.

4. Results

Descriptive results

Participants were sampled among the representatives of 22 humanitarian/development organizations, either Belgian or involved in a Belgian consortium. To the best of our knowledge, these were all the organizations that fitted the inclusion criteria. Out of all eligible participants, 19 preliminarily accepted to participate in the semi-structured interview, and 17 actually reported at the agreed appointment. Out of 15 interviews, (12) were conducted by the two researchers together, after defining the respective role of interviewer and of note-taker, and (3) were conducted by ANG alone.

4.1.1. Characteristics of the representatives/focal points interviewed

Overall, 17 focal points from 15 organizations were interviewed. The discrepancy is due to the fact that for two organizations, two representatives were identified and interviewed together. The characteristics of the 17 interviewees are summarized in Table I below.

Table I – Main characteristics of the interviewees

Background	
Pharmacists	10
Nurses	1
Medical doctors	3
Social sciences	3
Years in the organization	
≤4 years	8
5-9 years	3
≥ 10 years	6

A vast majority of interviewees were pharmacists (10/17), followed by medical doctors or nurses (4/10). The duration of appointment in the current organization was variable, with 8/17 having worked in it for ≤4 years, and 6/17 for ≥ 10 years. The majority had previous relevant experience in this field.

Even if all have some degree of responsibility in what concern the quality assurance of purchased medicines, we found a great variety of terms and definitions for their current position, reflecting either the characteristics of the organization or the way the position has evolved within it, but making comparisons across organizations quite challenging. These terms and definitions are not listed here, to avoid making individual interviews identifiable. However, we list here below those tasks related to medicines purchase and QA that were mentioned:

- Reviewing and/or validating the national and/or international orders
- Consolidating the list of suppliers/sources to purchase
- Looking for alternatives in case of stock outs
- Looking for potential suppliers/sources in case of unplanned (emergency) purchase
- Consolidating a database with the validated couples manufacturer-product

- Giving technical support to the field teams on pharmaceutical management and planning
- Developing QA systems and/or risk management SOPs
- Promoting and monitoring their implementation
- Promoting and/or leading a pharmacovigilance system

4.1.2. Characteristics of the humanitarian/development organisations

All the organizations represented in this survey purchase medicines and other medical product for humanitarian or development or programs in LMICs, but they have different scopes and different target populations, and they face different challenges and constraints. For instance, well-established primary health care (PHC) programs in stable countries can set up regular supply channels, while emergency interventions require special preparedness and reactivity. Also, some vertical programs (and/or some specific products) can rely on the guidance of the WHO PQ Programme, while this is limited for most PHC or hospital programs. An overview of the characteristics of programs most frequently run by these organizations is given in **Table II** below.

Table II – Main characteristics of the programs run by the organizations in the survey

Type of programs	N° of organization reporting them
Primary health care (including hospitals)	10
Sexual and reproductive health	6
Mental health	2
Malnutrition	3
Surgery	1
Nursing	1
Neonatology	1
Emergency interventions	2
Vertical programs for TB, HIV, malaria, NTDs*	8

* NTDs = Neglected Tropical diseases

4.1.3. Main reported challenges

For the purpose of this analysis, we categorized the challenges related to the purchase of medicines for programs in LMICs (whether within the scope of the WHO PQ Programme or not) into three main categories:

- *Type 1: Availability* (we keep the original meaning adopted by respondents, that is any issues related to availability of supply, continuity of supply, shortages and supply delays)
- *Type 2: Quality Assurance* (QA)
- *Type 3: Price*

The three categories are strictly interrelated. For instance, "good availability" will be pointless in absence of QA, and WHO PQ of a given product will not be helpful in absence of adequate supply chains or fair pricing.

Challenges of TYPE 1- Availability

Shortages, either on the national market in the country of intervention or on the international market, have been reported as a major challenge by (8) organizations, as well as **unjustified delays** by the suppliers. The main determinants of such situations were reported as follows:

- ***Depending on one supplier only***. This happens when an organization purchases its medicines and medical products (all, or a part) from one single supplier, which is generally a national or international wholesaler or distributor. The shortage of a given product at this supplier will immediately become a major problem, because of the lack of a (rapidly available) alternative. Such a "dependency" from a single supplier may in turn have different causes: sometimes, the organizational purchase policy is inadequate, while it was reported that in some other cases the reliance on a given supplier comes from a funder's requirement.
- ***The size of the purchasing organization.*** This generally has a very direct impact: low volume of purchase, as compared to other clients, will make an organization un-interesting for many suppliers, so that the orders will not be accepted or prioritized. For instance, some distributors and wholesalers do not prioritize the orders of sub-Saharan African Central Medical Stores, and some International Procurement Agencies show (very) limited interest in supplying NGOs with small field programs. In both cases, the low volume of purchase makes it difficult to find suppliers with adequate quality systems and efficient supply, and can trigger delays and shortages.
- ***Policies forbidding or limiting the importation of (some) medicines*.** These national policies in the countries of intervention can be triggered by legitimate reasons, such as strengthening regulatory supervision on the import of medicines and medical products, and encouraging local production and market. However, they may have the unwanted consequence of preventing the importation of quality-assured medicines, in absence of a quality-assured alternative on the local market. Sometimes, these limitations depend on international rules and regulations, such as in the case of the international restrictions on opioids and controlled substances (Lancet Commission 2017).
- ***Poor stock planning and management*.** Responsibilities are not only on the suppliers' side, and there can be a negative synergy between poor practices at both ends of the supply chain. In particular, poor planning and order calculations will make it difficult, for the supplier, to adequately plan the supply timelines, and to be ready for unplanned orders.
- ***Administrative barriers***. Respondents mentioned that (too) complex contract or payment procedures between the purchaser and the supplier are important drivers of delays.

Challenges of TYPE 2- Quality assurance

Lack of WHO pre-qualified products, or lack of availability of existing WHO pre-qualified sources, have been reported as a major challenge by all respondents. The main determinants of such situations were reported as follows:

- ***Lack of WHO pre-qualified products.*** There was general agreement that the current scope of the WHO PQ often leaves purchasers without guidance in many critical fields. Suggestions were made to expand the WHO PQ scope to new areas, in particular antibiotics and medicines for non-communicable diseases (NCDs diseases), or to new specific products, such as the combi pack of mifepristone and misoprostol.

- ***Single sources of WHO pre-qualified products*.** It was reported that sometimes there is only one WHO pre-qualified source for a given product, or that the pre-qualified sources are not easily available on the international market. One respondent mentioned the case of oral mifepristone and misoprostol (*"(…) They are available and PQ in Europe but the price is much more higher." (I. Yellow))".*

- ***Lack of interest of WHO-prequalified manufacturers for purchasers with low-volume of purchase*.** This is a specific case of what was presented under "Type 1 challenges", i.e. a low volume of purchase makes small clients un-interesting for suppliers, including for some manufacturers of WHO pre-qualified products. A respondent made the example of difficulties in procuring pre-qualified mono-formulated rifampicine. This can preclude access to these quality-assured medicines for communities that are not served by major (vertical) programs.

- ***Lack of QA awareness*** at institutional level. If the organization's top and middle management and/or the field team(s) are not informed, aware and convinced of the risks related to poor-quality medicines, the organizational procurement policies will not prioritize the purchase of WHO pre-qualified medicines, even when available. In such situation, priority will be given to the purchase of cheaper, or easier-to-procure, non-pre-qualified products. Some responders noted that this mentality is often accompanied by a lack of (or a poor) capacity of risk management. Also, it translates into procurement policies that will at best focus on Good Distribution and Storage Practices, with lack of consideration for products' selection and evaluation.

- ***Policies forbidding or limiting the importation*****.** This is a specific case of what was presented under "Type 1 challenges", i.e. it is possible that a less quality-assured product must be purchased locally, rather than a fully quality-assured product (either WHO pre-qualified or approved by a Stringent Regulatory Authority), because the latter is not locally available, and cannot be imported.

Challenges of TYPE 3- Price

A high price has been reported as a major challenge to procure quality-assured medicines by (6) organizations. The main determinants of such situations were reported as follows:

- **Single supplier of WHO PQ prequalified sources.** As already mentioned under Type 1 and Type 2 challenges, if there is only one manufacturer (or only one supplier in a given region) of a WHO pre-qualified medicine, the small purchasers can be in a weak position to negotiate fair prices, and some will end up buying non-fully quality-assured products instead. Some respondents suggested that these small purchasers should, instead, organize as groups for collectively negotiating with these suppliers/distributors a fair price, "(…) *in a way can (positively) influence and change the market*"(*I.Red)*.

- **Price variability of WHO PQ prequalified sources.** Various respondents indicated that there may be huge price differences of WHO PQ quality-assured products supplied by different International Procurement Agencies. However, no concrete examples were provided.

- **Easy to access information on suppliers of WHO pre-qualified products.** Corollary to the above, it was noted that it would be helpful to get easy access to public, official information about reliable suppliers/ authorized distributors of WHO pre-qualified products, possibly by geographical region and including transparent pricing information. Noteworthy, almost no respondents seemed to know the Global Fund's procurement tool Wambo (https://www.theglobalfund.org/en/sourcing-management/wambo/), thus they could not give an opinion on whether it addresses this need.

5. Analytical results, reflections & discussion

Our study presents some limitations, mainly linked to the small sample size; the time constraints; the lack of dedicated funding. Nonetheless, this exploratory assessment of the unmet needs of humanitarian/development organizations (either Belgian or involved in Belgian consortia) that purchase medicines for humanitarian, development or public programs in LMICs, allowed us to identify some potential areas of interest.

When we planned the survey, we were mainly thinking of identifying needs for expansion of the current scope of the WHO PQ Programme; but the concerns of respondents go beyond the original objective "to identify those essential medicines for which, to the best of their knowledge, no quality-assured sources are currently available in the market", and beyond the scope itself of the WHO PQ Programme. This is at least partly due to the fact that the WHO PQ is based on the pre-qualification of the couple product-manufacturer. While very relevant for big national and international purchasers, including the major medical-humanitarian NGOs, this approach is less fit to address the needs of small and medium-sized NGOs, and of programmes operating at PHC or hospital level with a panoply of essential medicines and medical products. As we will discuss below, these stakeholders generally do not have the capacity to individually address different manufacturers for each specific product, and they would rather benefit from "pre-qualification" of distributors and procurement agencies.

Other factors that, even if not related to pre-qualification of sources nor to the WHO PQ mandate, can seriously hinder the access to existing WHO pre-qualified products and to other fully quality-assured products, are either internal and external factors (from the perspective of the purchasers).

Internal factors may include poor stock planning, which results in stock-outs and shipment delays and may further cause emergency purchase at unknown suppliers (which inevitably entails an higher quality risk); lack of preparedness for emergency purchases, also resulting in purchase of medicines and medical products of unknown sources/at unknown suppliers; insufficient institutional awareness and commitment to quality; and, at least partly related to the latter, lack of expertise and capacity to prioritize, understand and control quality of medicines, at headquarter and field staff level.

External factors that we already mentioned include the lack of interest for small purchasers by manufacturers and distributors of quality-assured products (resulting in poor availability and/or unfair prices); and the limitations to import, which may prevent the importation of quality-assured products that are non-available in specific countries. Other external factors are:

- The unregulated import of non-registered products (especially those with low volumes of utilization, and some new products)
- Weak pharmacovigilance (PV) programs and post marketing surveillance (PMS) systems, which prevents quality problems from surfacing and being corrected
- Dysfunctional cold chain along the supply chain, leading to the unwanted and unnoticed use of degraded medicines and medical products
- Lack of public information on reliable ("pre-qualified") pharmaceutical *distributors*, both internationally and locally. Small and medium-sized NGOs are mostly purchasing at wholesalers and distributors, rather than (on a product-by-product basis) at manufacturers. Public and reliable information about the quality systems (from selection of sources to good storage and distribution practices, and ongoing monitoring), the pricing policies and the commercial reliability of wholesalers and distributors, would be helpful to guide them to efficient purchase of quality-assured medicines.

Both our planned and unplanned findings may be useful to get a better understanding of the challenges met by non-UN purchasers for making the best use of the WHO PQ guidance, while

dealing with other complex challenges related to pharmaceutical policies and management. Therefore, our further reflections will separately look at:

- The potential areas for expansion of the scope of the WHO PQ Programme.
- The usefulness and user-friendliness of the WHO PQ list, and the challenges to make adequate use of its guidance, for non-UN purchasers in LMICs, depending on the mandate, skills, resources and quality-assurance system of the purchasers, and on the contextual constraints.

5.1 Areas for expansion of the WHO PQ Programme

The level of knowledge and utilization of the WHO Pre-qualification List as a practical tool for orienting procurement choices, was variable in our sample. The List is better known and used much more frequently by those involved in vertical programs in therapeutic areas covered by the mandate of the WHO PQ, such as TB and malaria; and by organization with a solid QA system. Small organizations, and especially those working at PHC and hospital level, who deal with a great number of essential medicines, tests and devices, know and use it much less frequently, because a large number of the product they need is not covered by the scope of a WHO PQ Program (*"Essential medicines that they use for all the programs and are not in the WHO PQ list"(I. Brown).).*

Another problem concerns products that are included in the WHO PQ Programme, but for which there is only one pre-qualified product, or only one is distributed in a given region. This may create problems at various levels: no (local) alternatives for safe procurement; difficulties or impossibility to procure the prequalified source for small organizations, if the supplier only accepts shipping quantities bigger than the needs; difficulties to negotiate fair prices, due to the lack of commercial competition with other pre-qualified sources. A more detailed list of problems indicated by the interviewees is as follows:

- **Antibiotics**. An expansion of the WHO PQ Programme to essential antibiotics was suggested by most respondents (also, but not exclusively, because of the potential contribution of poor-qualify formulations to antimicrobial resistance). On a more detailed note, it was noted that the need for fully quality-assured sources is especially urgent for **antibiotics' paediatric formulations**. Azithromycin was explicitly mentioned, and also ciprofloxacin, which is on the HIV/AIDS list but from one supplier only. Perhaps, to expand the list WHO PQ list, another way to prioritize among antibiotics would be looking at those in the three categories of the WHO EML List 2017, i.e. ACCESS, WATCH and RESERVE[11].
- **Medicines for Non-communicable disease (NCDs)**. This was the second most suggested area by respondents. It would help addressing the new epidemiological paradigm in LMICs with fully quality-assured medical products. Among these products, insulin and antihypertensive molecules were especially mentioned, as well as medicines to treat different forms of cancer.
- S**exual and reproductive health**. Some respondents expressed the need of WHO pre-qualified sources for a "combi pack of mifepristone and misoprostol"; for "penicillins" (in general); for more source of oxytocin and magnesium sulphate (currently, there are a few, but reportedly often they are not distributed locally).
- **Solutions for parenteral use**. Even if technically easy to manufacture, solutions for parenteral use must comply with adequate specifications, e.g. sterility, and if out-of-specification they can be dangerous for patients' health. Few respondents advocated for WHO pre-qualified products, to help purchasers avoid potentially dangerous products. The related issue of high transports costs was not mentioned.

[11] http://www.who.int/medicines/news/2017/20th_essential_med-list/en/

- **Disinfectants, antiseptics, medical devices.** Some respondents, especially those involved with hospital programmes, noted the interest in having a WHO PQ Programme also for disinfectants and antiseptics, especially those relevant to surgery, and for medical devices (broader than the current PQ programme for In Vitro Diagnostics).
- **Neglected Tropical Diseases (NTDs).** Despite the calls for interest, the WHO PQ list for is still quite short. A respondent expressed the need for pre-qualified sources of medicines specific for leprosy, leishmaniosis, and Buruli ulcer. The issue of how to create a market demand for such pre-qualified sources was not addressed.
- **TB treatment.** The WHO PQ list for looks quite complete, and dynamic. Nonetheless, the need was noted for WHO pre-qualified sources of some specific products, especially those for MDR TB patients, such as clofazimine and gatifloxacine. Also, streptomycin was mentioned as a problematic product, since there is only one pre-qualified source.
- **Others.** When it comes to other medicines, the need for WHO pre-qualified sources was expressed by individual respondents for ribavirin injections, for lidocaine, for oral and injectable diazepam, and for opioids analgesics (especially the oldest one, which do not have a market interest in high-income countries, and thus are not of interest for quality suppliers).
- **Vaccines**. Even if the vaccines WHO PQ was not in the original scope of our work, the need for WHO pre-qualified Lassa fever vaccine was expressed.

5.2 Usefulness and challenges of the WHO PQ guidance

5.2.1 Depending on the organisation's mandate and features

As said in the previous chapter, the **mandate and operational priorities** of small to medium-sized organizations in our sample have a strong impact on the extent and frequency of recourse to the WHO PQ Lists. Those that run vertical programs and/or work in therapeutic areas covered by the mandate of the WHO PQ, such as HIV, TB, Malaria, Sexual and reproductive health, are much likely to know and use the WHO PQ guidance, compared to those working at PHC and hospital level.

However, also across them here are important differences. **Limited human resources** dedicated to pharmaceutical management, and/or lack of pharmaceutical background and time for ongoing professional update, will result in different level of institutional awareness of problems due to poor-quality medicines, and also into variable level of practical knowledge of the WHO PQ Programme and the guidance it can provide for procurement in different therapeutic areas, as well as in supportive domains (for instance, QC laboratories). As a matter of fact, some respondents did not show a practical knowledge of the WHO PQ list, and some organizations may lack the capacity to independently verify if the sources procured via a wholesaler or distributor are actually WHO prequalified. It is important to note here that hiring pharmacists is a necessary pre-requisite for building a pharmaceutical QA system, but they should be in sufficient number depending on the level of activity; and should be empowered to have an impact within the organization. Corollary to this, limited human resources and/or time for pharmaceutical management may also lead to poor stock planning and management and, consequently, shortages and delays of medicines.

Insufficient financial resources may negatively affect the reliance on the WHO Pre-qualification Lists. According to some respondents, while "big" purchasers are in a position to negotiate fair prices with the suppliers of WHO prequalified products, smaller purchasers may lack this negotiating power, and in addition they are not commercially interesting for the supplier. As noted by a respondent, it is *" Difficult to find any medicine because the amount is too low to ask and it does not interest the manufacturer"(I.Green).*

For organizations that depend on external funding**, the funders' QA policy (or the lack of it)** will have a strong influence on the purchase policy, including the quality specifications and the

reference (or non-reference) to the WHO PQ lists, when applicable. For instance, organizations financed by a funder that does not prioritize quality assurance, and does not foresee a budget line for this, will be much more likely to procure medicines and medical products via non (fully) secured channels. Conversely, organizations financed by a funder that prioritizes quality assurance, will be pushed toward including quality specifications in their procurement policies, and will be less likely to use unsecured supply channels.

According to some respondents, **the price** of WHO prequalified products can be higher versus the non-pre-qualified ones, for instance for some TB medicines, and for misoprostol and mifepristone. This topic would deserve ad hoc research, to check if this happen constantly; if it relates to the ex-factory price or takes into account the different additional distribution steps; and to understand which are the factors that can reduce the price, such as economies of scale, pool negotiation, transparency on prices etc.

Overall, it appears that **only organizations with a strong institutional awareness about medicines quality assurance, and having done significant investments in quality assurance systems**, are in the position to use the WHO PQ list adequately and consistently.

5.2.2 Depending on the context where the organisation works

As already mentioned, the **host country policies** have a strong impact on the extent and frequency of recourse to the WHO PQ Lists of the organizations in our sample. It was reported by most respondents that this is in general easier in countries where the importation is allowed, than countries where it is more difficult to import. However, it is important to note that we could not cross-check this qualitative information from the interviews with other important elements, for instance what is the impact of countries being members of the WHO PQ collaborative program with NMRAs? Also, the "easiness to import" may present serious drawbacks, such as the easiness to import also non-quality-assured products.

The capacity to secure quality-assured supply chains will also vary depending on the knowledge of the local pharmaceutical policies and market features (*"In countries were programs have been established for a long time there are some procedures and more reliability of sources, but for the new (countries) ones or the crisis one, there are not clues to buy in a qualified sources. Ex: Early deployment countries." (I. Rose)).*

As already reminded, dysfunctional distribution practices including poor cold chain lead to the unwanted use of degraded medicines and medical products. A respondent noted that it could affect negatively the downstream quality of WHO pre-qualified products, creating risks when they are bought locally. This topic would deserve ad hoc research, to check the effectiveness of cold chain, to identify vulnerabilities, and to support the upgrade of local systems.

5.2.3 Depending on the organisation's procurement policy

We identified two main procurement policies in our sample: policies that prioritize international purchase of medicines and medical products, and policies that prioritize local purchase in the country(ies) of operation. Some organizations adopt a mixed model, with different strategies by country.

Most organisations in the first group pre-select international procurement agencies for their purchase and require (or expect) them to have an adequate QA system in place for pre-selection and monitoring of sources, including reliance on the WHO PQ guidance when applicable. The extent to which they verify the quality system of such suppliers varies a lot in our samples. We suggest that this strongly depends on the human and financial resources dedicated to these activities. Only one organization has its own, stringent policy for pre-selection and monitoring of sources, including reference to the WHO PQ List.

Most organisations in the second group, identify local procurement agencies for their purchase, and should require them to have an adequate quality assurance system in place for pre-selection and monitoring of sources, including reliance on the WHO PQ guidance when applicable. Also in this case, the extent to which they verify the quality system of such suppliers varies a lot, and we suggest that this strongly depends on the human and financial resources that they allocate to these activities. According to some respondent, in addition, it is more difficult to source WHO-prequalified products at national procurement agencies, but this statement could not be double checked with concrete examples.

6. Recommendations

- **The WHO PQ Team could consider,** even if we understand that this would represent a significant undertaking, **expanding its mandate to new areas, in particular antibiotics** (those in the Essential Medicines List, with focus on paediatric formulations) and to medicines for NCDs
- We understand that the pre-qualification of the pharmaceutical wholesalers, distributors and procurement agencies, which would be very helpful for small and medium-sized purchasers, cannot fall under the mandate of the WHO. However, we suggest that **the WHO PQ Team could require from the pre-qualified manufacturers that they make publicly available the list and contact details of their authorized distributors in different regions**, so as to facilitate purchasers who wants to buy pre-qualified products.
- **The WHO PQ Team could consider facilitating a process of harmonization** of quality assurance policies and tools across major donors.
- **The WHO Member States, and the Donors, should increase and sustain the funding of the WHO PQ Programme**, which represents a public good and an essential tool for fulfillment of universal health coverage.

7. References

Caudron JM, Ford N, Henkens M, et al. Substandard medicines in resource-poor settings: a problem that can no longer be ignored. Trop Med Int Health. 2008;13(8):1062–72.

Commitment to quality assurance for pharmaceutical products, between the Belgian Development Cooperation and the actors involved in the implementation of programmes including the purchasing, storage, distribution and/or control of pharmaceutical products. 25/10/2017. https://diplomatie.belgium.be/sites/default/files/downloads/commitment_to_quality_assurance_for_pharmaceutical_products.pdf

Lancet Commission. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the *Lancet* Commission report, 2017

Nebot Giralt A, Schiavetti B, Meessen B et al. Quality assurance of medicines supplied to low income and middle-income countries: poor products in shiny boxes? BMJ Global Health 2017;2:e000172.

Newton, PN, Amin, A, Bird, et al. The primacy of public health considerations in defining poor quality medicines, PLoS Medicine 2011, 8(12): 6-10.

Nurse-Findlay S. Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: An evaluation from multi-country surveys and stakeholder interviews. PLoS Med 14(12):e1002473.

Ravinetto, RM, Dorlo, TPC, Caudron, JM, Prashanth, NS . The global impact of Indian generics on access to health, Ind J Med Ethics 2013; 10(2): 118-120

Ravinetto R, Vandenbergh D, Macé C et al. Fighting poor-quality medicines in low- and middle-income countries: the importance of advocacy and pedagogy. J Pharm Pol Pract 2016; **9**:36

Ravinetto R, Roosen T, Dujardin C. The Belgian commitment to pharmaceutical quality: a model policy to improve quality assurance of medicines available through humanitarian and development programs. J Pharm Pol Pract 2018; 11:12: 1-5

't Hoen, EF, Hogerzeil, HV, Quick, JD, Sillo, HB . A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme'. J Pub Health Policy 2014; 35(2): 137-161

Van Assche K, Nebot Giralt A, Caudron JM et al. Pharmaceutical quality assurance of local private distributors: a secondary analysis in 13 low-and middle-income countries. BMJ Glob Health 2018;3:e000771.

WHO Prequalification Programme, *About the Prequalification Programme*, viewed 1 April 2016, <http://apps.who.int/prequal/>.

WHO Global Surveillance and Monitoring System, 2017. Study on the public health and socioeconomic impact of substandard and falsified medical products. Available at http://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/

8. Annex I

Annex I – Guide for the semi-structured interview

Only start writing down information if the respondent has given formal consent to participate.

Questions do not need be asked in the same order as in the guide; however, please ensure that at the end of the interview, you will have gone through <u>each point</u>, even if you already personally know the respondent and you presume to know in advance what he/she will say.

First, we put some general questions, also useful for the interviewer to check/understand the skills and expertise of the respondent.

Pseudonym: ……

1. Which organization do you represent/in which organization (s) are you currently working? Please note that this information will not appear either in the study reports or publications.
2. How long have you been with the organization? And in other relevant organizations and positions before?
3. What is your current position?
4. What is your background?
5. Do you know about the Charter of 2008 and the Commitment of 2018 for Quality of medicines? Do you know if your organization is a signatory of any of them?
6. Is your organization an active member of the Because Health Medicines Working Group? Or a member of QUAMED. If yes, since when?
7. What is your link to/role in medicines' purchase?

Prompts: are you a purchaser yourself? Do you supervise purchase? If a medical director/coordinator, what are your responsibilities in link with purchase? Do you regularly meet the purchasers/the pharmacist in your organization? …..

Second, put a general question, to move gradually to the specific focus of the survey

1. What types of medicines are procured/purchased in your programs?

Prompts: general programs (primary health care, hospital…..)? Vertical programs (e.g. TB, neglected tropical diseases, diabetes….)?

2. What are the main problems met by your organization related to the procuring medicines?

Prompts: are you aware of any difficulties? Personally, or reported by colleagues? Do you remember any examples in the last year? Would you share details on this? …..

Prompts: high prices? Failure of the supplier to respect commercial agreements? In-country registration? Import permission? (Suspected or confirmed) quality accidents? Cold chain? Lack of pre-qualified supplier? Lack of pre-qualified source?….

Third, move to the core issues of the survey

1. To the best of your knowledge, which are the medicines for which you do not have a fully QA-source/which your organization is obliged to purchase as non-fully-QA assured sources?

Important: for the sake of results completeness, we should collect for each case the International Nonproprietary Name + Dosage form+ Strength. For this reason, the respondent can send complementary information later by mail, and/or interrupt the interview and continue later on after collecting information

Prompts: depending on the skills/role of the respondent, remind the definition of "full QA" (also, if needed: do you know the definition of SRA? Do you know the WHO PQ? Are there other similarly stringent mechanisms?)

Prompts: give examples of non-fully QA sources, depending on the respondent's and organization's features, e.g. "what benzathine penicillin do you buy", "are all medicines for MDR-TB that you use pre-qualified by the WHO" etc.

Prompts: ask explicitly if they have a list of pre-qualified suppliers/sources, and or of problematic products

2. If any products have been listed above: what is missing in terms of full QA for such products? What is in your opinion the related risk?

Prompts: for instance, GMP-compliance of the manufacturer, proof of bio-equivalence…; also in this case, the respondent can send complementary information later by mail, and/or interrupt the interview and continue later on after collecting information

Prompts: for instance, lack of purity/sterility → toxicity for the patient; insufficient efficacy → therapeutic failure… ?

Important: try to understand if the respondent knows it by sure, or if he/she is guessing

3. Is there anything else you would like to add?

Prompts: would you like to share any ideas/opinions about what are the most "urgent" among the cases mentioned above? Or about corrective actions?

4. Would you agree that a list of all the organizations that have participated in the survey is shared with the WHO PQ, without any links to your specific answers (circle the preferred answer):

YES

NO

I DO NOT KNOW (REASK ME LATER)