



NAVIGATING COMPLEXITY TO IMPROVE GLOBAL ACCESS:

SUPPORTING A MORE EFFICIENT AND EFFECTIVE
WORLD HEALTH ORGANIZATION
PREQUALIFICATION PROGRAM

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NAVIGATING COMPLEXITY TO IMPROVE GLOBAL ACCESS: Supporting a More Efficient and Effective World Health Organization Prequalification Program

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Key Terms

AMA – African Medicines Agency

API – Active pharmaceutical ingredient

CRP – Collaborative registration procedure

CSA – Coordinated Scientific Advice

EDL – Essential Diagnostics List

EML – Essential Medicines List

EOI – Expression of interest

FPP – Finished pharmaceutical product

HIC – High-income country

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IVD – In vitro diagnostic

LMIC – Low- or middle-income country

NRA – National regulatory authority

PQ – Prequalification

SRA – Stringent regulatory authority

WHO – World Health Organization

WLA – World Health Organization Listed Authority

EXECUTIVE SUMMARY

Since the late 1980s, the World Health Organization (WHO) has provided a safety, quality, and efficacy assurance assessment process now known as “prequalification” (PQ) to ensure products supplied by procurement agencies meet acceptable standards and to facilitate the regulatory review and uptake of health products in low-resource settings. Prequalification has enabled the creation of a US\$3.5 billion market for prequalified products in low- and middle-income countries (LMICs), spurred the development of products that would not otherwise have been developed for LMIC settings, raised manufacturing standards in LMICs, and enabled access to significant procurement tenders from various aid agencies.¹ Situated within the Access to Medicines and Health Products Division within WHO, the PQ program also works together with teams focused on national regulatory strengthening and local production and assistance to facilitate access to health products.

While the importance of the PQ function is broadly recognized, the activities remain complex with different processes, pathways, and requirements for eligible products. Despite recent efforts by WHO to develop a more streamlined and transparent process, these reforms have not yielded sufficient clarity and common understanding, and many external stakeholders still struggle to navigate the various PQ pathways and structures.

In order to identify opportunities to strengthen the PQ program and its role in a larger, evolving regulatory ecosystem, the Global Health Technologies Coalition and the Duke Global Health Innovation Center at Duke University analyzed the timelines and regulatory pathways of more than two dozen prequalified health products, conducted a literature review of public PQ materials, and interviewed more than 20 related independent experts. In this report, we document key findings about the PQ structure and process, offer analyses of activities and timelines on specific prequalified products, illuminate both key pain points and improvements made by WHO that were raised by stakeholders, and offer actionable recommendations to WHO to continue to improve the program.

KEY FINDINGS AND CHALLENGES

Prequalification Mission and Scope

- Prequalification is an assessment of a product’s safety, quality, and efficacy, primarily for use in LMICs, to guide procurement by international, regional and national procurement and funding agencies and member states. This information is not always clear to the broader product development community.
- PQ is not an isolated process, but one that works in tandem with national regulatory strengthening and local production and assistance units at WHO to serve as a resource for accelerating access to health products in LMICs.
- Prequalification is limited to certain products for specific health topics and is available to both generic (multisource) and novel (innovator) products.

Prequalification Process

- In order for a product to receive a prequalification listing, it must first be included in WHO guidelines (clinical practice or public health policy recommendations made by the agency). However, our analysis shows variability on the timing of guidelines publication and that this historically has taken place before or after a PQ listing. Guidelines teams function outside of the PQ program in their respective health or therapeutic areas, and the interface between guidelines and prequalification processes is not well understood by outside stakeholders. Novel

products seeking PQ may present a complication, since they may not have the body of evidence required to generate a guideline.

- The complex PQ process for each specific product stream (medicines, vaccines, vector control, and in vitro diagnostics) can be generalized into a four-step process for all products: 1) assessment of eligibility to apply to PQ; 2) dossier submission; 3) dossier assessment, including site inspections and lab evaluations; and 4) prequalification listing.
- Challenges in the PQ process for manufacturers include significant effort required to address the high data and evidence standards, knowing how to produce a complete dossier for submission, and interacting with PQ's consultants who may not be as familiar with certain product stream processes.
- Key performance indicators on the PQ process were developed by the PQ program in 2017, though data has not been publicly reported, leaving a gap in understanding of PQ timeline expectations.

Prequalification Resources

- The PQ program has a small team of permanent staff and is heavily reliant on external consultants to perform essential work—a situation partially resulting from broader WHO staffing policies and human resource capacity controlled by WHO Member State policies.
- Communication efforts, such as website updates and release of information to the public, have progressively improved, though continued enhancements are necessary and have been recommended in previous PQ impact assessments.
- PQ staff must manage essential work while facing increasing numbers of applications during the COVID-19 pandemic, managing large numbers of small grants that add a heavy administrative burden, and maintain important functions such as external communication.
- During the COVID-19 pandemic, PQ assessment fee revenue decreased due to reduced sales and exemption of products used in public health emergencies, leading to potential budget shortfalls, though public data on actual revenues for 2021 and 2022 is not yet available.

Prequalification and the Regulatory Ecosystem

- Duplicative national regulatory and PQ dossier requirements, such as the need to carry out multiple bioequivalence studies, as well as limited data sharing, can result in inefficiencies for PQ and product manufacturers.
- PQ coordinates with certain stringent regulatory authorities, primarily high-income country regulatory agencies, and occasionally with LMIC regulators, to conduct joint dossier reviews to accelerate a product's assessment.
- WHO-led initiatives, such as the Collaborative Registration Procedure (CRP) and the Coordinated Scientific Advice (CSA) procedure, are strengthening and accelerating product access in LMICs in alignment with PQ.

RECOMMENDATIONS

Based on these findings and challenges, we have identified certain areas where our understanding of PQ could be strengthened and how PQ might be made more efficient and effective. **As such, we offer the following near-term recommendations to the prequalification program and Access to Medicines and Health Products Division:**

- 1. Continue to improve communications for Access to Medicines and prequalification to generate greater clarity and awareness for external stakeholders.**

- a. Publicly report on key performance indicators for the prequalification program, including those developed and updated since 2017. Performance indicators will likely be heavily influenced by staffing capacity as addressed in item 4 below, so this should be included in reporting.
 - b. Continue website improvements, including improvements to navigation and access to documents, and launch a robust database of product information for greater transparency for all prequalified products.
 - i. If not included in the database, ensure that WHO Public Assessment Reports (PARs) of prequalified products contain the same information across product streams; current PARs in some product streams do not appear to contain dossier submission dates according to our review.
 - c. Develop a resource guide or FAQ document, including a visual aid that outlines the specific steps and communication milestones, that provides greater transparency and guidance for external stakeholders on the interactions and process between guidelines and prequalification.
 - d. Disseminate biennial report-outs on general health of the Access to Medicines Division, inclusive of feedback from stakeholders.
- 2. Support and advise on the expansion of interim or “living” guidelines, similar to those issued recently for COVID-19 therapeutics and treatments for drug-resistant tuberculosis, for other innovator or novel products to expedite opportunities to address real-time needs.**
- 3. Provide greater opportunities for external stakeholder feedback into processes and strategy.**
- a. Develop a platform for ongoing, macro-level discussions, beyond annual manufacturers meetings, to include a wider audience and more holistic topics, such as the future state of the PQ program, how it can best serve the shifting needs of global procurement agencies and Member States, and how its work will evolve as a result of (and collaborate with) new efforts to strengthen national regulatory bodies (e.g., through WHO Listed Authorities, a framework for evaluating and publicly designating regulatory authorities) and the launch of regional regulatory bodies like the African Medicines Agency.
 - b. Create more robust consultation processes to inform the updated *Roadmap for Access to Medicines, Vaccines, and Other Health Products*, a strategy that informs PQ’s operational priorities, and provide feedback mechanisms to gather technical input on the linkages as well as strengthened coordination between guidelines and prequalification, including the use of product pipeline forecasting.
 - c. Work with external stakeholders to improve product developer and country participation in two WHO-led processes intended to facilitate and expedite access to health products: the Collaborative Registration Procedure (CRP) for expediting national product registration for vaccines, medicines, and soon in vitro diagnostics, and the Coordinated Scientific Advice (CSA) procedure for aligning health product research and development data with WHO PQ requirements.

Finally, we offer an additional near-term recommendation to WHO leadership and Member States to strengthen support for the prequalification program:

4. Advocate for **WHO Member States to adopt a new policy to enable WHO to have greater flexibility in its human resource structure** to allow for the hiring of additional permanent staff, some of which could support the needs of the prequalification team. For institutional sustainability and effectiveness, it would benefit WHO to create permanent positions to compensate for what appears to currently be an overreliance on long-term consultants.

Overall, this research has unearthed the advances that WHO has made, and continues to make, to enable greater access to critical health products in LMICs through prequalification and other regulatory strengthening activities, but has also unearthed several ongoing pain points and challenges. We encourage WHO to continue to strengthen these important activities as well as engagement and communication across diverse stakeholder communities. Our organizations will continue to monitor the progress and execution of these recommendations and will reassess progress at the World Health Assembly meetings in 2023.

INTRODUCTION

Since the late 1980s, the World Health Organization (WHO) has provided a safety, quality, and efficacy assurance assessment process, now known as “prequalification” (PQ), to ensure vaccines, medicines, in vitro diagnostics (IVDs), and vector control products supplied by procurement agencies meet acceptable standards and to facilitate the regulatory review and uptake of health products in low-resource settings. Prequalification has enabled the creation of a US\$3.5 billion market for prequalified products in low- and middle-income countries (LMICs), spurred the development of products that would not otherwise have been developed for LMIC settings, raised manufacturing standards in LMICs, and enabled access to significant procurement tenders from various aid agencies.ⁱⁱ Situated within the Access to Medicines and Health Products Division within WHO, the PQ program also works together with teams focused on national regulatory strengthening and local production and assistance to facilitate access to health products.

While the importance of the PQ function is broadly recognized, the program remains complex with different processes, pathways, and requirements for eligible products. Despite recent efforts by WHO to develop a more streamlined and transparent process, many external stakeholders still struggle to navigate the various PQ pathways and structures. A 2019 impact assessment recommended improvements to communication, clarity on processes, accelerating request response times, and several other important enhancements to PQ and related departments.ⁱⁱⁱ In this paper, a number of our recommendations continue to encourage WHO to address some of these earlier suggestions.

In order to identify opportunities to strengthen the PQ program and its role in a larger, evolving regulatory ecosystem, the Global Health Technologies Coalition and the Duke Global Health Innovation Center at Duke University analyzed the timelines and regulatory pathways of more than two dozen prequalified health products, conducted a literature review of public PQ materials, and interviewed more than 20 related independent experts. In this report, we document key findings about the PQ structure and process, offer analyses of activities and timelines on specific prequalified products, illuminate both key pain points and improvements made by WHO that were raised by stakeholders, and offer actionable recommendations to WHO to continue to improve the program.

RESEARCH METHODS AND LIMITATIONS

We applied a combination of quantitative and qualitative research methods to better understand regulatory and WHO prequalification processes and identify opportunities to strengthen PQ. Our analysis reviewed four out of five PQ product streams: vaccines, medicines (both finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs)), IVDs and medical devices, and vector control products. We conducted extensive desk research on regulatory and prequalification milestone activities for 26 prequalified health products (7 vaccines, 4 in vitro diagnostics, 10 medicines, and 5 vector control products) to measure the timespans to achieve PQ and to gain a deeper understanding of PQ processes, nuances, and complementary ecosystem interactions. We reviewed publicly available documentation, including information on the WHO website, and grey and peer-reviewed literature, as well as reached out to product developers and WHO to collect additional or missing information. The team also conducted semi-structured interviews with 24 key stakeholders representing product developers, product development partners, general global regulatory experts, regulatory experts in LMICs, and WHO prequalification and regulatory systems experts. Findings from our quantitative and qualitative analyses were combined to describe PQ and related ecosystem interactions and are described in this paper. See Appendix 1 for additional detail on our methods. Source data is available upon request.

We recognize that this research has limitations, primarily small sample sizes for both the interventions studied and the individuals interviewed. While we do not have sufficient data to conduct statistical analysis, our data provides trends and descriptive statistics. Despite the smaller number of experts interviewed, we were able to interview senior regulatory leaders with extensive expertise on prequalification and national regulatory processes. We did not interview specific PQ product stream leaders but interviewed members of the WHO PQ leadership team.

KEY FINDINGS

WHO’s prequalification program is part of a broader ecosystem of regulatory actors, including product developers and manufacturers, national and stringent regulatory agencies (NRAs and SRAs), procurement agencies, and internal WHO entities, such as those that publish guidelines supporting global access to health products. These actors and processes, generally depicted in Figure 1, all play a significant role in facilitating access to certain health products in low-resource settings.

I. PREQUALIFICATION MISSION AND SCOPE

The work of the PQ program is organized into five product streams: 1) vaccines, 2) medicines (both FPPs and APIs), 3) IVDs and medical devices, 4) vector control products, and 5) immunization devices.

Inspection services is an additional team within PQ that serves all product streams by evaluating the compliance of manufacturers, research organizations and laboratories with international standards of quality, safety, and efficacy.^{iv} The specific product types and health areas assessed for prequalification in the four areas of our research focus are described in Figure 2. The pipeline of products eligible for assessment by the PQ program emerges from programmatic, Member State, and procurement agency needs and is limited in scope.

Prequalification is available for both generic (multisource) and novel (innovator) products, although interviews yielded considerable variation in perception of how, and to what extent, PQ assesses these two categories of products. Many interviewees highlighted the success of the PQ program in the prequalification of generic products (primarily medicines) and vaccines; one interviewee stated that “PQ is generally used for generics or existing products with new indications, not for new chemical entities entirely.” On the other hand, as a WHO PQ staff member noted, it is “not 100% accurate to say that PQ only handles generic products,” citing vaccines as an example of WHO PQ capacity to review novel products.

According to our analysis of the four product streams studied, WHO has prequalified 1,125 generic and novel medicines, in vitro diagnostics, vaccines, and vector control products since the assessments began in 1987 through April 2022 (Figure 3), with an acceleration of prequalifications in the late 2000s.^{v,vi,vii,viii,ix}

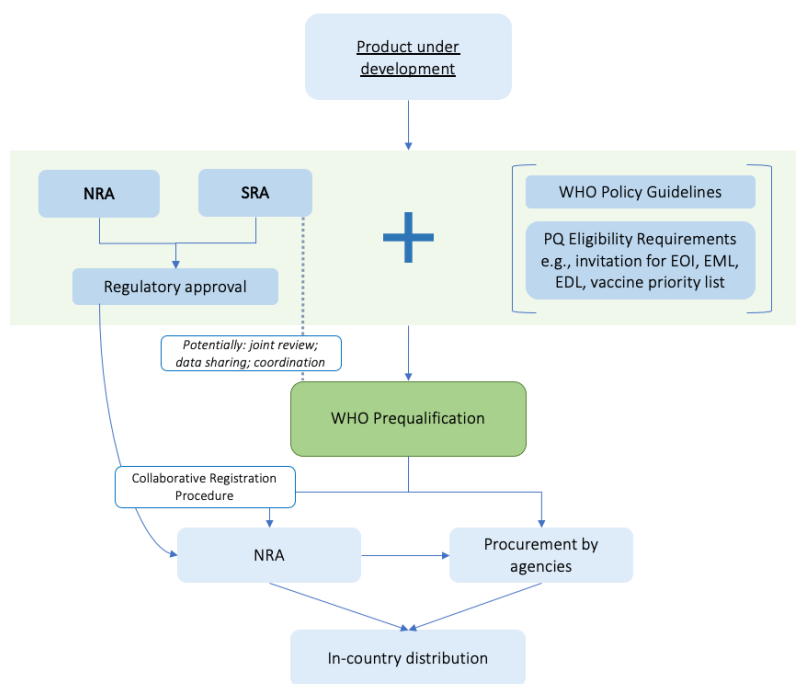


Figure 1. WHO prequalification and the regulatory ecosystem it sits within.

Medicines	Vaccines	IVDs	Vector Control
<ul style="list-style-type: none"> • HIV/AIDS, malaria, TB, reproductive health, hepatitis, diarrheal diseases, and select neglected tropical diseases • NEW: biotherapeutic products for certain cancers; insulin for diabetes 	<ul style="list-style-type: none"> • Routine immunization (24 priority diseases) • Equipment for national vaccine programs 	<ul style="list-style-type: none"> • Diagnostics and devices for endemic and epidemic diseases 	<ul style="list-style-type: none"> • Prevention of vector-borne disease • Bed nets, sprays, larvicides

Figure 2. Product types and health topics assessed by WHO prequalification in the four product streams specific to our research.

Since 2010, our analysis indicates an average of 47 medicines, 12 vaccines, and 8 in vitro diagnostics have been prequalified each year. Given the transition of vector control product approvals from the original WHO Pesticide Evaluation Scheme to prequalification status in 2017 and 2018, the average prequalifications per year for vector control products cannot be accurately calculated at this time.

It is also unclear how many applications are submitted and reviewed each year. During the COVID-19 pandemic, according to a WHO source, nearly 200 COVID-19 diagnostic dossiers were submitted under the WHO’s Emergency Use Listing procedure (expediting availability during a public health emergency), which is supported by the PQ team; 95 of these dossiers were assessed, and 30 COVID-19 diagnostics have been listed for emergency use as of June 2022, a significant increase from the annual average number (8) of prequalified in vitro diagnostics.^x

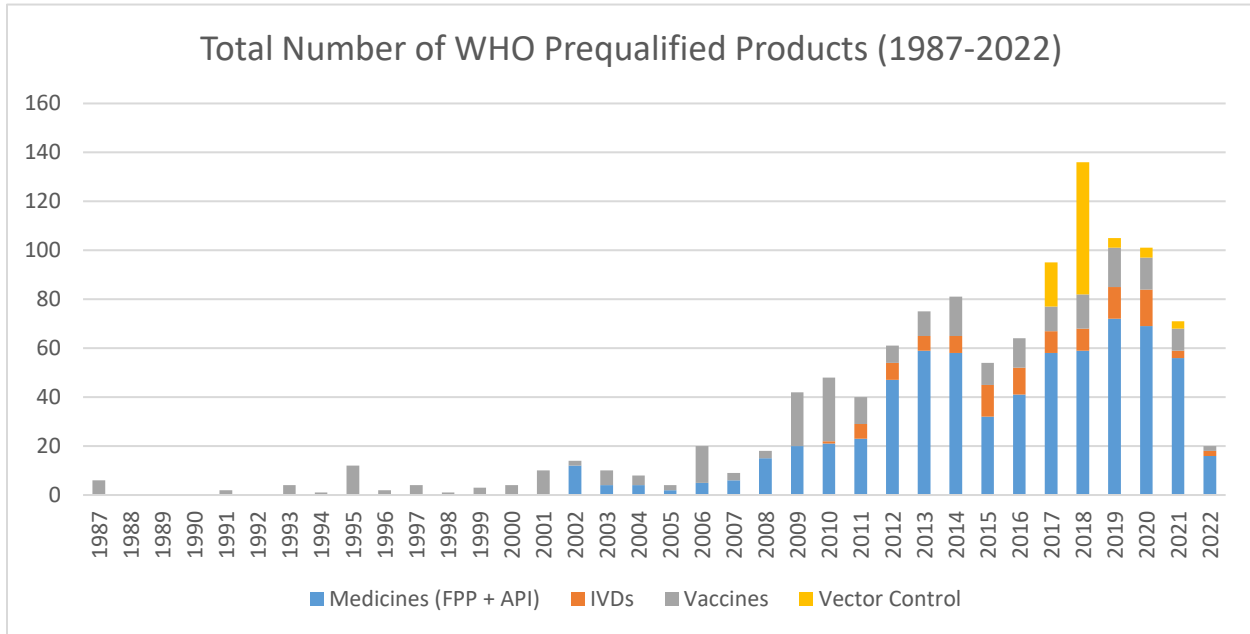


Figure 3. Analysis of prequalified medicines, IVDs, vaccines, and vector control products (1987-April 2022).

Overall, there is strong consensus regarding the success of PQ in facilitating access to health products in LMICs, as is evident from the number of products prequalified. Based on interviews with several product development partners, there appears, however, to be inconsistent interpretations and understanding of the scope, types of assessments, and reviews that WHO PQ undertakes. It was also noted by a WHO

source that there is a lack of understanding of what it means to regulate for a global market—the remit of PQ. This global market regulation refers to the stringent evidence and process WHO sets to ensure safety, quality, and efficacy of products for LMIC settings. As noted by a WHO source and PQ expert, this is significant considering that many new products are being produced for an LMIC market, which may have differing regulatory expectations and requirements to those in a high-income country (HIC) market, such as inability to maintain cold chain or simplified packaging.

II. PREQUALIFICATION PROCESS

The prequalification process itself varies by product stream, with differing assessment pathways, criteria for eligibility to participate in the PQ process, and sequences of steps leading up to PQ and listing. Specific prequalification process charts for each product stream are included in Appendix 2. Despite the variation in specific PQ processes, all four product streams studied (medicines, vaccines, in vitro diagnostics, and vector control products) have several foundational steps in common that are described in detail below and depicted in Figure 4.

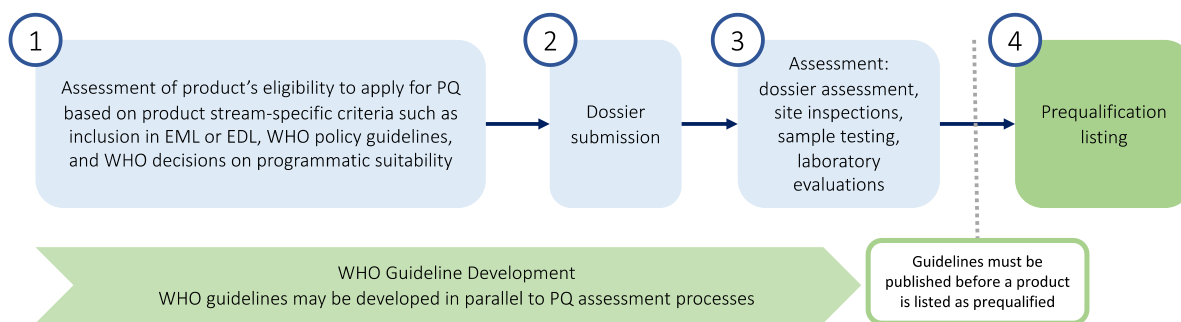


Figure 4. General WHO prequalification process.

1 ASSESSMENT OF ELIGIBILITY TO APPLY FOR PQ: For a product to start the PQ process, it first has to be deemed eligible. Eligibility for PQ varies by product stream and therapeutic area, influenced by a broader ecosystem of factors. According to a former PQ staff member and a PQ expert, while each product stream maintains its own criteria for eligibility, it is generally impacted by whether there is enough data and evidence to make a determination on the safety and quality of a product. Announcements of eligibility are released by the PQ product stream teams in various forms; for example, expressions of interest (EOIs), inviting manufacturers to indicate their intent to submit a dossier for PQ, are published for medicines, and eligible vaccines are included on the Vaccine Prequalification Priority List. Once products are deemed eligible to proceed through the process, each product stream has an established procedure for how product developers announce their intent to submit a dossier, whether through pre-dossier submission meetings or other request procedures.

2 DOSSIER SUBMISSION: After indicating their intent to proceed, product developers submit a dossier with required product information and data to the relevant PQ product stream. Overall, each dossier contains evidence of quality, safety, and efficacy. Expected evidence for each of these three characteristics differs depending on product stream and type.

Many interviewees reflected on the substantial data and rigorous evidence requirements included in the dossier. The norms and standards expected for PQ are perceived as a strength and generally regarded as a stringent assessment.^{xi} PQ's rigorous standards ensure that LMICs are receiving the same quality product as HICs, particularly in cases where manufacturers submit different dossiers for products intended for LMICs as opposed to those for HICs. PQ is also assessing for specific LMIC market standards and making sure "outputs can be applied globally". On the other hand, the high standards were also cited by many interviewees as a barrier to PQ given the level of effort involved, and possible redundancies in the process, for products with generally low profit margins. Additionally, one interviewee remarked that WHO's "gold standard" syndrome of not being able to prequalify a product until it achieves the highest of standards is limiting innovation and novel product development.

Several interviewees mentioned that less experienced manufacturers may also find the process cumbersome and therefore may submit inadequate applications to PQ. Incomplete dossiers will not be accepted. The PQ team works with developers to ensure that dossiers are complete and include all relevant and required product data. Some interviewees lauded this technical assistance from PQ, particularly for LMIC-based manufacturers, in an effort to support regionally distributed manufacturing capacity strengthening, an activity that SRAs may not support.



DOSSIER ASSESSMENT: The PQ product stream team assesses the dossier and carries out any other required activities, including manufacturing site inspections, laboratory tests, and field tests. Questions for the manufacturer, and subsequent responses, are also important activities in this part of the process. According to WHO sources, eligible product dossiers are typically prioritized for review in the order in which they were submitted—first come, first served—with exceptions for products needed for public health emergencies like the COVID-19 pandemic or polio resurgence. Product areas that have not had a prior prequalified product are also prioritized. The PQ team may also prioritize the review of a product whose manufacturer responds quickly to questions to be able to reduce the queue of products under review.

For all product streams, dossiers are assessed for safety, quality, and efficacy. Interviews with a former WHO PQ staff member and a PQ expert noted that some novel products may not yet have the same level of evidence as generics to assess safety, quality, and/or efficacy for PQ. Additionally, some interviewees noted that WHO PQ teams may not have the capacity to assess novel products and require review by SRAs and personnel with the appropriate technical backgrounds.



Medicines or diagnostics that have already received regulatory approval from an SRA, or vaccines with marketing authorization from an eligible, functional NRA, may be eligible to proceed through a faster or abridged prequalification process, wherein the SRA and WHO may conduct joint dossier reviews or share information with WHO PQ to accelerate review. Additional information on the interaction with SRAs is included in the discussion to follow regarding PQ interaction with the regulatory ecosystem.

As shown in Figure 5, our research shows that these alternate pathways (e.g., abridged assessments, abbreviated assessments, streamlined procedures) may be working as intended, producing shorter prequalification timelines from dossier submission to PQ listing, particularly for medicines. Vaccine dossier submission dates were not publicly available at the time of the research, thus limiting our analysis.

Products that proceeded down alternate pathways were prequalified faster, on average, than were products going through full assessment pathways. For example, Coartem Dispersible, which was assessed through the abbreviated assessment pathway for products that have received SRA approval (on the basis of an approval from Swissmedic), was prequalified in just four and a half months. The average time between dossier submission and PQ was about 6 months for products that went through alternate pathways, compared to an average of about 17 months for products that went through full assessment pathways. It is important to note that these time intervals include not only the time taken by the WHO PQ teams to assess product dossiers, but also the time for manufacturers (the applicants) to respond to questions from the PQ team and submit additional data as needed.

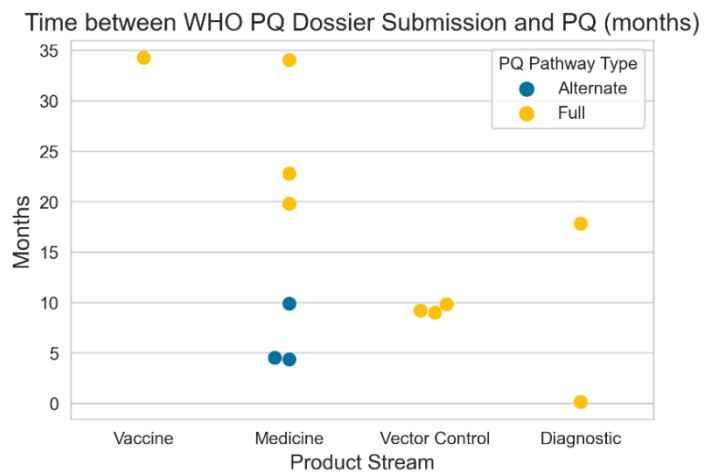


Figure 5. Timespan between dossier submission and prequalification for products following alternate or full assessment pathways.

Several interviewees also noted a lack of public key performance indicators (KPIs) for measuring expected timelines for dossier review by PQ teams. As one product developer noted, without timelines it is difficult to plan. A WHO PQ staff member also highlighted the importance of KPIs for setting up priorities and timelines to be more predictable. The PQ program developed KPIs in 2017 (see Appendix 3), which include the target time it takes for PQ from acceptance for assessment to prequalification, but no data on how the PQ program is performing in relation to the KPIs has been publicly released. The PQ website provides some detail on the estimated WHO-specific timelines for completing the review process for vaccines and IVDs but is lacking information on medicines and vector control products. These estimates also do not include the time it takes for manufacturers to respond to questions and participate in other aspects of the review process.

4

PREQUALIFICATION LISTING*: If the dossier review is successful, a product is prequalified and is included on WHO’s lists of prequalified products.



*PREREQUISITE TO PREQUALIFICATION LISTING:

The existence of WHO clinical or policy guidelines for a product, or guidelines under development, are one of the criteria that WHO uses to determine eligibility for PQ, but a published guideline is not required for a product to proceed with the PQ process after eligibility has been determined. However, a product cannot be included in the prequalified products list without a published guideline that includes the product. For the purpose of this report, a WHO guideline is “any information product developed by WHO that contains recommendations for clinical practice or public health policy.”^{xii}

The guideline development process is triggered by early or interim product data and spearheaded by the Guidelines Review Committee outside of PQ. According to our sources, guidelines cannot be publicly

released until the original data, upon which the guideline is based, is also published in peer-reviewed literature or another respected source. It was observed, however, that the "pathways between guidelines, technical teams, and the PQ process" is not clear to outside stakeholders, and thus how and when these processes interact and influence one another is unclear.

According to our analysis, for nearly half of the interventions studied (42%), WHO guidelines have been released after PQ, indicating historic variability in this pledge to release guidelines prior to prequalification (Figure 6). Several interviewees also noted that a "green light" must be received from the guidelines teams in order for a product to be assessed by the PQ team, though we understand that this may happen in parallel to the PQ assessment as is currently being piloted for COVID-19 therapeutics.^{xiii}

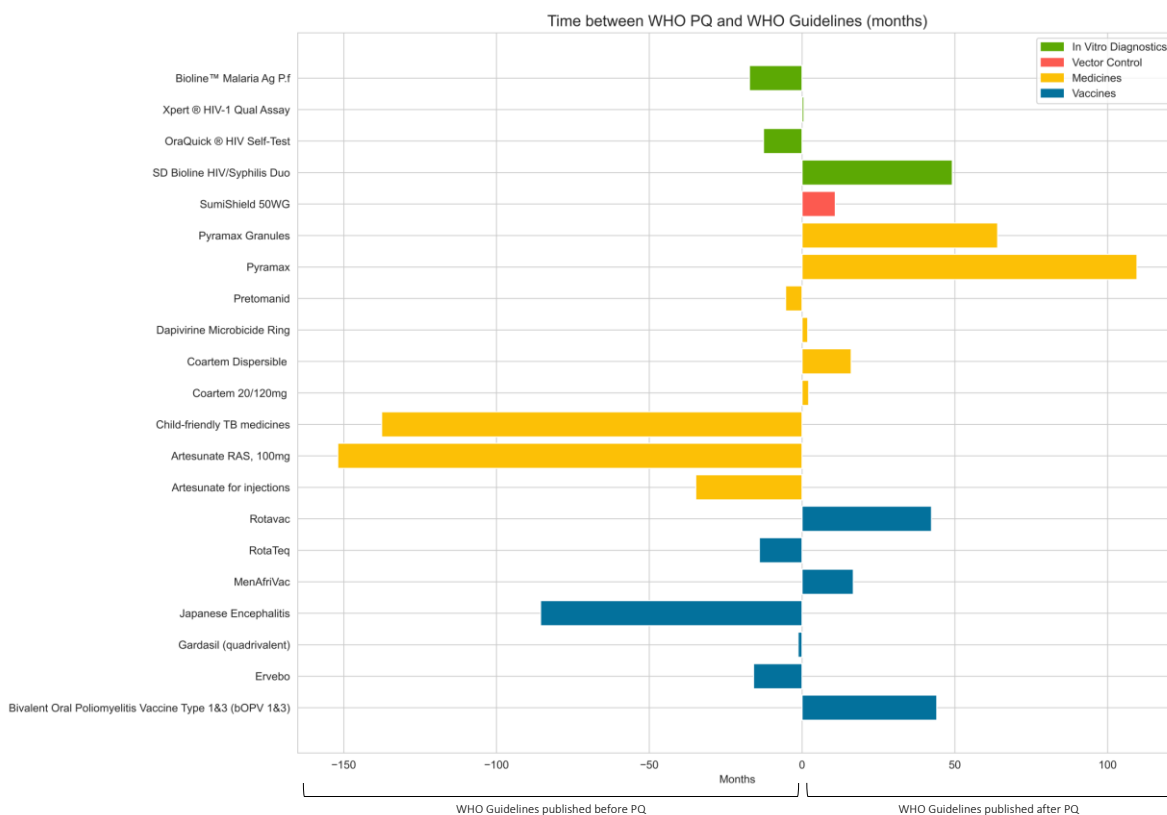


Figure 6. Time, in months, between WHO PQ and the release of WHO guidelines for the 26 interventions studied.

One example of parallel guideline development and prequalification assessment pilot occurred with nirmatrelvir and ritonavir (brand name: Paxlovid), an antiviral therapeutic for COVID-19. Sufficient evidence was assessed by the WHO PQ team to release an EOI, inviting manufacturers to indicate their intent to submit a dossier for PQ.^{xiv} Pfizer submitted its dossier for Paxlovid, though no guidelines on the product had yet been published. Paxlovid was prequalified on the same day that the COVID-19 therapeutics "living guidelines" were updated to include a recommendation for Paxlovid—indicating that guideline development and PQ assessment took place in parallel.

III. PREQUALIFICATION RESOURCES

Human Resources

Under the WHO governance structure, Member States determine policies and the budget. In recent years, the policies defined by the Member States have limited the total number of permanent staff at headquarters, which has caused a resource strain on the PQ program. As a result, there is a mismatch between the expectations for the PQ program and the available resources to deliver on those expectations.

Several interviewees noted the heavy use of consultants, in lieu of permanent staff, to assist with review steps within the PQ process. Roughly one-quarter of interviewees noted that reliance on consultants may result in inconsistent approaches to the review of dossiers due to their lack of familiarity with PQ processes; WHO sources indicate there are mitigation measures in place to improve this concern, including peer review of all activities and quality assurance of all outputs and communications by PQ staff. It is also important to note that external consultants and experts may be inevitable, as it would not be feasible to have a permanent workforce with the combination of technical and regulatory expertise for every health product type and stream. Several interviewees highlighted that this became a risk during the COVID-19 pandemic, however, as the pool of experts that WHO would normally use dwindled as a result of competing priorities for COVID-19 product review in their respective countries.

Communications

Despite already being short-staffed, the PQ team is also responsible for many communications activities, like website maintenance and other functions. WHO stakeholders noted that this places additional strain on their teams, as they are often not equipped to assume key functions that communications professionals generally handle. A quarter of interviewees observed that although the PQ website was significantly improved during the last update, it can still be difficult to navigate, and broken links permeate the site. However, one positive response highlighted the particular transparency in relation to COVID-19 products, and another that the website contained a diversity of information from public documents and templates. Some stakeholders noted that they would like to see this level of transparency mirrored for other health areas.

Despite the staffing constraints, teams from the various PQ product streams are thought to be generally responsive and available to share information with manufacturers. However, outreach is often more ad hoc and driven either by external organizations or based on existing personal relationships to WHO PQ staff. As a result, multiple interviewees highlighted communication challenges stemming from staff and consultant turnovers within the WHO PQ team and stakeholder organizations. Product development stakeholders noted that communications from PQ decreased during COVID-19, though they acknowledge this was likely due to a significant increase in workload during the pandemic.

Budget

The PQ program is funded through the collection of fees from manufacturers engaging the PQ process, assessed contributions by WHO Member States, as well as voluntary contributions and grants. For context, the Access to Medicines program has a US\$306.6 million budget for 2022–2023—an 80% increase since 2016-2017.^{xv} According to our sources, the increase in this budget is primarily due to an increase in voluntary contributions, many of which are grants earmarked for specific activities. Approximately one-quarter, or nearly US\$70 million, of the budget for the Access to Medicines program

is allocated to prequalification activities.^{xvi} Some interviewees reflected concerns that the PQ program in particular was managing a high number of smaller value grants, which puts a significant administrative burden on the program.

Since 2017, WHO PQ has received fees from manufacturers to perform screenings of applications, assessment reviews, site inspections, to apply changes to product assessments, and annual fees to maintain prequalification status. Fees may be reduced or waived for products with low profit margin; fees were also waived for COVID-19 products during the pandemic. The fees by product stream are available in Appendix 4. During the COVID-19 pandemic, sources indicate that fewer manufacturers were producing and submitting products for assessment, therefore reducing the fee revenues for PQ in 2021 and likely 2022, though public data on actual revenues is not yet available. We calculated that prequalification fee revenues make up 12–14% of the annual budget for the Access to Medicines program.^{xvii}

At the recent World Health Assembly meetings in May 2022, the World Health Assembly agreed to gradually increase the Member States' assessed contributions to represent up to 50% of WHO's core budget over the next ten years; in 2020-2021 these contributions represented only 16% of the budget.^{viii} While we understand that the PQ program does not currently receive assessed contributions, this increase in funding over time to the core budget may provide an opportunity to better fund prequalification and decrease the reliance on voluntary contributions and the corresponding agendas of the contributors that may not always align with WHO's most pressing needs and priorities. On the other hand, PQ is one of few WHO programs that generates revenue, so some interviewees questioned whether, or how much, the program would or should be the beneficiary of increased core funding by Member States.

IV. WHO PREQUALIFICATION AND THE BROADER REGULATORY ECOSYSTEM

In addition to looking at the specific process and timelines for PQ, our analysis looked at a broader set of regulatory, policy, and product introduction milestones that occur along the journey of product access, including timelines for SRA approval, NRA approval, and country launch dates. Our analysis indicates some variability in the order in which specific regulatory and PQ activities take place, illustrating some of the nuance in the steps described above. Figure 7 indicates that the vaccines studied follow a fairly consistent sequence of steps, with NRA/SRA approval occurring first, then launch in a specific LMIC, followed by WHO guidelines and then PQ. This commonality reflects the PQ eligibility criteria for the vaccines product stream, which require marketing authorization from the NRA of the country of manufacture of the vaccine. We found more variability in the other product streams in the sequence of events leading to and following WHO PQ. Additional definitions on the milestones studied can be found in Appendix 1.

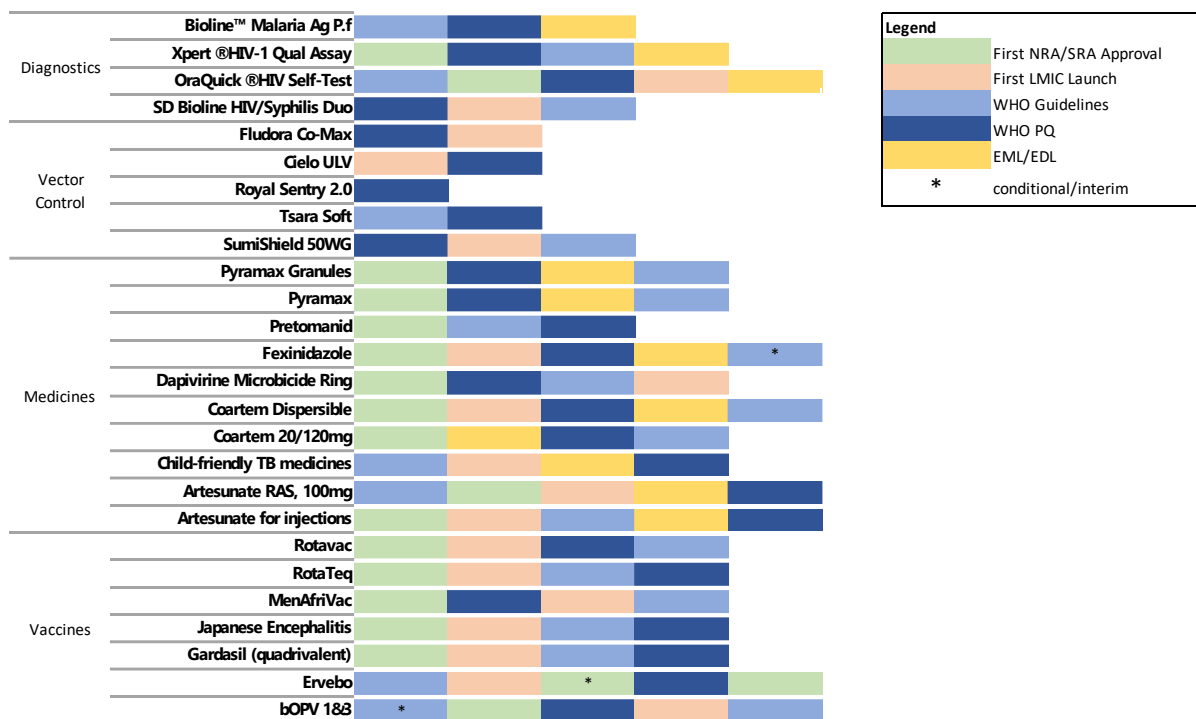


Figure 7. Chronological order of milestones by product.

Regardless of the order of these activities, prequalification cannot be isolated from other processes that facilitate access to health products in LMICs, including national regulatory approvals. Some of these activities occur prior to or in parallel with the PQ process (upstream) and some take place after PQ (downstream), as shown in Figure 8.

Upstream Interactions

In general, many products that are deemed eligible for prequalification will have received regulatory approval from either an NRA in the country of manufacture or SRA, prior to PQ, though this may not be a requirement depending on product stream. Certain SRAs conduct joint dossier reviews, share data, coordinate with WHO to accelerate the PQ process, and have developed specific review procedures particularly for products that are intended for LMIC markets. As many interviewees commented, PQ relies, to

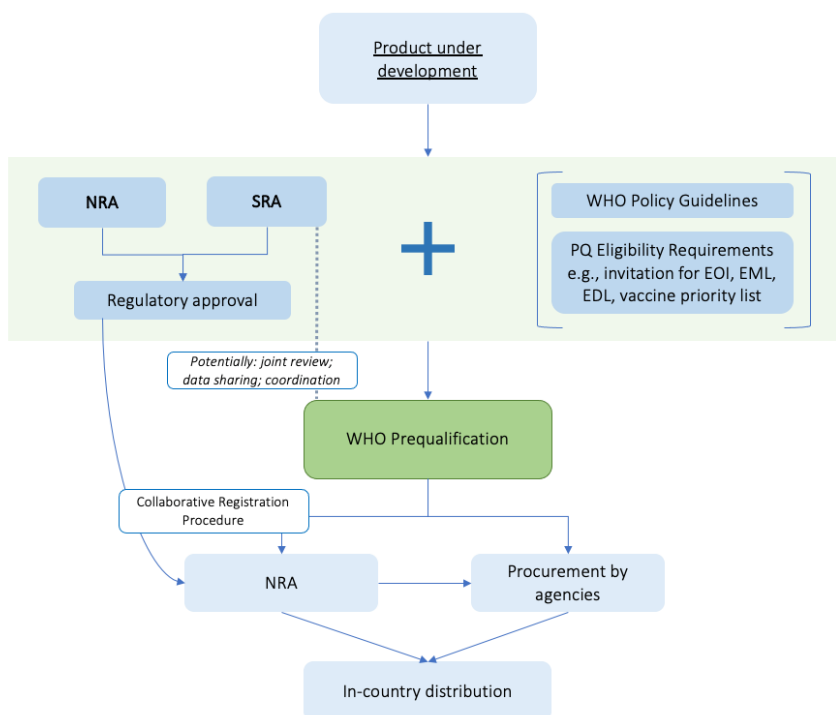


Figure 8. WHO prequalification and the broader regulatory ecosystem it sits within.

some extent, on external partners to provide regulatory review and technical expertise for products. A WHO PQ staff member commented that the emergence of new products developed for disease conditions in LMICs, with no market in HICs, has uncovered a need for new regulatory pathways to expedite access in LMICs, like the European Union’s Medicines for All (EU-M4All) initiative (previously known as the Article 58 procedure) and the Swissmedic Marketing Authorization for Global Health Products procedure, that work together with WHO PQ.^{xviii,xix}

Several interviewees also noted that there is variability in national regulatory and PQ dossier and review requirements, which may necessitate duplicate steps being undertaken to accommodate process requirements, like repeat site inspections. Data-sharing policies between regulatory authorities are also inconsistent, as a few interviewees observed, resulting in duplication of efforts if an original regulatory review cannot provide data upon which PQ can make a decision. Additionally, one product development partner remarked that regulatory processes all operate on their own timelines, so different regulatory reviews may need to take place in sequence rather than in parallel.

Other WHO-specific steps upstream to PQ include activities to ensure product eligibility for PQ and guideline development, as described previously. It is also important to add that a new WHO initiative called the Coordinated Scientific Advice (CSA) procedure, facilitated by the Science Division at WHO in coordination with technical departments and the PQ program, aims to de-risk the WHO policy and PQ pathway for product developers by providing early guidance on development plans and data generation requirements.^{xx} While not a guarantor of PQ, participating in the CSA could enable accelerated timelines and higher-quality PQ submissions. More broadly, several stakeholders noted that WHO should coordinate with both internal and external stakeholders to anticipate products in the development pipeline.

Downstream Interactions

Once a product is included on the prequalified products list, it is eligible to be purchased by UN procurement agencies; prequalification also announces to the world that a specific product is safe, high quality, and efficacious for use in LMICs. Each country that wishes to use the product must subsequently approve the product for use in its population through its regulatory procedures. WHO Member States’ national medicines regulatory authorities may participate in the WHO’s Collaborative Registration Procedure (CRP) that aims to accelerate national regulatory approval for certain products (medicines, vaccines, and in vitro diagnostics specifically) by sharing confidential dossier information from the prequalification process with national regulators and thereby removing duplicative regulatory procedures. Countries commit to approving products within 90 days if they participate in this procedure, though data indicates room for improvement in holding countries accountable to this timeline.^{xxi}

Time between WHO PQ and first NRA approval after PQ (months)

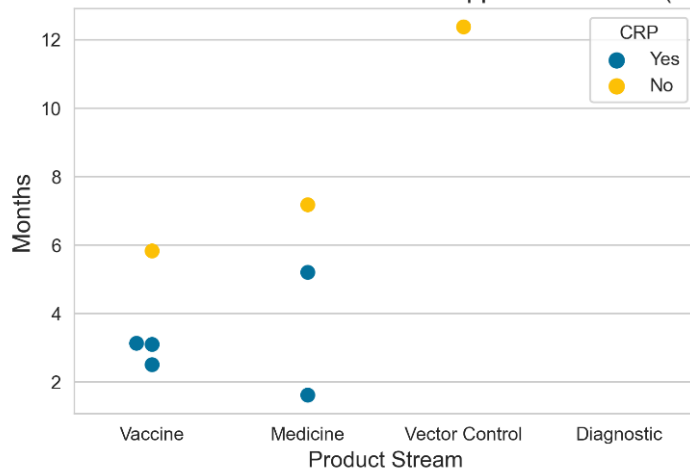


Figure 9. Timespan analysis from date of WHO prequalification to first NRA approval after prequalification.

Our analysis shows that products that were registered in countries participating in the CRP, indicated in blue in Figure 9, received faster NRA approval after PQ than did other products registered in countries that did not engage in the CRP.

Additionally, downstream (post-PQ) NRA approval overall is occurring faster than previously anticipated and was achieved within one year, within an average of about five months. In contrast, the 2019 WHO PQ Impact Assessment Report notes that “prior analysis showed that timelines for downstream NRA approval after PQ could be as long as two years.”

The relatively short interval between PQ and downstream NRA approval highlights the success of the PQ program and related regulatory systems strengthening activities in advancing the goal of increasing access to high-quality, safe, and efficacious health products in LMICs. One related Access to Medicines Division-led regulatory strengthening activity is the establishment of WHO Listed Authorities (WLAs), which intends to remove the binary distinguishing of NRAs and SRAs and instead institute a rating system for all regulatory agencies worldwide. These ratings, known as maturity levels, are measured by the Global Benchmarking Tool; regulatory agencies with an overall maturity level 3 (highest rating = 4) rating will be deemed a WLA.^{xvii} Several interviewees noted that strengthening of WLAs will expand the pool of advanced regulatory authorities that PQ can rely upon as a trusted resource for joint dossier reviews and technical expertise and may help mitigate delays by enabling accelerated PQ review procedures.

On the longer horizon, the establishment of regional regulatory bodies such as the African Medicines Agency (AMA) may also facilitate access at national levels by providing additional opportunities for country regulatory support. Several interviewees highlighted that AMA is anticipated to have good potential for executing on its mission, providing regulatory review of a percentage of products, and providing guidance to smaller African regulatory agencies. Although these interviewees also noted that AMA is still not fully formed or operational and may not be for another decade, entities such as the PQ program and complementary regulatory strengthening teams providing technical assistance will continue to play an important role in health product access for LMICs.

V. PREQUALIFICATION CHALLENGES

While the importance of the PQ function is broadly recognized, its structure, pathways, and processes remain highly complex. Despite recent efforts by WHO to develop a more streamlined and transparent process, these reforms have not yielded sufficient clarity and common understanding, and external stakeholders still struggle to navigate the myriad of PQ pathways and structures. External perceptions vary on the scope of PQ and the extent to which the PQ teams assess both novel and generic products.

Product manufacturers face challenges in navigating PQ—whether facing variability in how dossiers are reviewed by consultants, addressing the high data and evidence standards required for dossier submission, or lacking understanding of the complex processes involved, such as the guideline requirement as a prerequisite to a PQ listing. As one interviewee noted, “The problem is the step before PQ—PQ will not consider anything until it is officially endorsed by the program office or guideline community. This is the biggest obstacle and very frustrating.” The “pathways between guidelines, technical teams, and the PQ process” is not clearly delineated, and, as such, how and when these processes interact and influence one another is unclear. Additionally, KPI data is not publicly reported, leading to a gap in understanding on areas such as expected timelines of PQ activities, making planning ahead difficult. Manufacturers also face challenges around the misalignment and variability between PQ dossiers and the requirements of national regulators, which may necessitate duplicate efforts.

PQ resources, both human and financial, are also mismatched with the expectations and importance of the PQ functions. The PQ program is faced with a limited number of permanent staff as a result of WHO Member State policies. The limited capacity of the staff to perform even essential duties for PQ is exacerbated by increased numbers of dossier submissions during the COVID-19 pandemic, leading to more work, a large quantity of small grants to administratively manage without a grants management team, and continued calls for communication improvements and transparency requiring added effort. While recent improvements to the website have been made, missing data and broken links continue to permeate the site. During the COVID-19 pandemic, PQ assessment fee revenue also decreased, leading to potential budget shortfalls, though public data on actual revenues for 2021 and 2022 is not yet available.

Finally, there are too few opportunities for external input and engagement outside of an annual meeting specific to manufacturers and specific dossier processes. This is particularly the case for assessing the PQ program more holistically and how it relates to broader WHO processes, as well as the shifting regulatory ecosystem. Providing platforms for ongoing dialogue and feedback mechanisms for outside stakeholders, beyond manufacturers, to ensure continued improvement and streamlining of the process, and strengthening alignment with regulatory bodies, is essential.

VI. RECOMMENDATIONS

A 2019 impact assessment of PQ recommended improvements to communication, clarity on processes, accelerating request response times, and several other important enhancements to PQ and related departments.^{xxiii} A number of our following recommendations continue to encourage WHO to address some of these earlier suggestions and to strengthen external understanding of PQ and how PQ might be made more efficient and effective. **As such, we offer the following near-term recommendations to the prequalification program and Access to Medicines and Health Products Division:**

- 1. Continue to improve communications for Access to Medicines and prequalification to generate greater clarity and awareness for external stakeholders.**
 - a. Publicly report on key performance indicators for the prequalification program, including those developed and updated since 2017. Performance indicators will likely be heavily influenced by staffing capacity as addressed in item 4 below, so this should be included in reporting.

- b. Continue website improvements, including improvements to navigation and access to documents, and launch a robust database of product information for greater transparency for all prequalified products.
 - i. If not included in the database, ensure that WHO Public Assessment Reports (PARs) of prequalified products contain the same information across product streams; current PARs in some product streams do not appear to contain dossier submission dates according to our review.
 - c. Develop a resource guide or FAQ document, including a visual aid that outlines the specific steps and communication milestones, that provides greater transparency and guidance for external stakeholders on the interactions and process between guidelines and prequalification.
 - d. Disseminate biennial report-outs on general health of the Access to Medicines Division, inclusive of feedback from stakeholders.
- 2. Support and advise on the expansion of interim or “living” guidelines, similar to those issued recently for COVID-19 therapeutics and treatments for drug-resistant tuberculosis, for other innovator or novel products to expedite opportunities to address real-time needs.**
- 3. Provide greater opportunities for external stakeholder feedback into processes and strategy.**
- a. Develop a platform for ongoing, macro-level discussions, beyond annual manufacturers meetings, to include a wider audience and more holistic topics, such as the future state of the PQ program, how it can best serve the shifting needs of global procurement agencies and Member States, and how its work will evolve as a result of (and collaborate with) new efforts to strengthen national regulatory bodies (e.g., through WLAs, a framework for evaluating and publicly designating regulatory authorities) and the launch of regional regulatory bodies like AMA.
 - b. Create more robust consultation processes to inform the updated *Roadmap for Access to Medicines, Vaccines, and Other Health Products*, a strategy that informs PQ’s operational priorities, and provide feedback mechanisms to gather technical input on the linkages as well as strengthened coordination between guidelines and prequalification, including the use of product pipeline forecasting.
 - c. Work with external stakeholders to improve product developer and country participation in two WHO-led processes intended to facilitate and expedite access to health products: the CRP for expediting national product registration for vaccines, medicines, and soon in vitro diagnostics, and the CSA procedure for aligning health product research and development data with WHO PQ requirements.

Finally, we offer an additional near-term recommendation to WHO leadership and Member States to strengthen support for the prequalification program:

- 4. Advocate for **WHO Member States to adopt a new policy to enable WHO to have greater flexibility in its human resource structure** to allow for the hiring of additional permanent staff, some of which could support the needs of the prequalification team. For institutional sustainability and

effectiveness, it would benefit WHO to create permanent positions to compensate for what appears to currently be an overreliance on long-term consultants.

Overall, this research has unearthed the advances that WHO has made, and continues to make, to enable greater access to critical health products in LMICs through prequalification and other regulatory strengthening activities but has also unearthed several ongoing pain points and challenges. We encourage WHO to continue to strengthen these important activities as well as engagement and communication across diverse stakeholder communities. Our organizations will continue to monitor the progress and execution of these recommendations and will reassess progress at the World Health Assembly meetings in 2023.

APPENDIX 1. RESEARCH METHODS

We applied a combination of quantitative and qualitative research methods to better understand regulatory and WHO prequalification processes that facilitate access to health products in low-resource settings. In the first step of research, the Duke GHIC team developed a data collection template adding milestones based on both internal research and initial background research by the GHIC team. The template is structured in a roughly chronological order, starting with first NRA and/or SRA approval date, first LMIC to introduce the intervention, dates of WHO prequalification, first NRA to grant approval following WHO PQ, and relevant WHO policy dates. Descriptive data is also included about the intervention. Supplementing these dates are the dates associated with application submission, review process, and regulatory pathways taken. Table 1 provides more details.

We conducted extensive desk research on 26 prequalified health products (7 vaccines, 4 in vitro diagnostics, 10 medicines, and 5 vector control products) to identify specific dates of milestone activities in the regulatory and prequalification pathways. We reviewed publicly available documentation and grey and peer-reviewed literature and reached out to product developers and WHO to collect additional information on key milestones. See Table 2 for a list of researched products by product stream. We outreached to approximately 34 key stakeholders representing product developers and product development partners, general global regulatory experts, regulatory experts in LMICs, and WHO prequalification and regulatory systems experts. Stakeholders were selected based on personal connections to contacts with perceived scope and experience in WHO PQ or global health product regulation and desk research. Snowball sampling was used to expand our outreach. We then conducted semi-structured interviews with stakeholders. Interview questions were tailored for each stakeholder depending on their expertise, focusing on their views and experiences of regulatory processes or prequalification. Out of the approximately 34 individuals we outreached to, the team conducted 16 interviews with 24 unique individuals (see Table 3).

The team coded interview notes into common themes using NVivo software. Subsequent analysis of the interview notes allowed us to identify trends in observations and feedback across the different stakeholders. Findings from the analysis were summarized and combined with findings from the grey and peer-reviewed literature to describe PQ and related ecosystem interactions. To support this analysis, the team used Python to calculate time intervals between identified milestones for each of the 26 products researched, analyze these time intervals to look for trends, and create plots of time intervals for key steps in PQ and regulatory processes. Descriptive statistics were calculated after grouping products by various categorical variables (e.g., product stream, PQ pathway, developer type).

We recognize that this research has limitations, primarily small sample sizes for both the interventions studied and the individuals interviewed. While we do not have sufficient data to conduct statistical analysis, our data provides trends and descriptive statistics. Despite the smaller number of experts interviewed, we were able to interview senior regulatory leaders with extensive expertise on prequalification and national regulatory processes. We did not interview specific PQ product stream leaders, but interviewed other WHO PQ leadership. Additionally, while we were able to interview product developers or product development partners with experience in each product stream, our sample size for stakeholders representing each product stream remains low.

Table 1. Quantitative milestone data collected.

Overarching Milestone Categories and Definitions	Specific Milestone Data Collected
<p>National Regulatory Authority (NRA):</p> <p>A national body that regulates medical products for their use in country. Some NRAs are also considered to be SRAs.</p>	<ul style="list-style-type: none"> • Name and country of first NRA to grant approval • Alternate pathway used for NRA, if applicable • Date of application to begin testing • Date of application to NRA • Date of conditional approval • Date of first NRA approval
<p>Stringent Regulatory Authority (SRA):</p> <p>A member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), OR an ICH observer, OR a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement (see: https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs)</p>	<ul style="list-style-type: none"> • Name and country of first SRA to grant approval • Alternate pathway used for SRA, if applicable • Date of application to begin testing • Date of application to SRA • Date of conditional approval • Date of first SRA approval
<p>First LMIC country launch</p>	<ul style="list-style-type: none"> • Date the product was first used in an LMIC country for outside of a research study; also includes name of the country
<p>WHO prequalification process</p>	<ul style="list-style-type: none"> • First formal submission (submissions or communications prior to dossier submission) • Pre-submission requirement (e.g., EOI) • PQ pathway type <ul style="list-style-type: none"> ○ For each product stream, there are options for pathways that differ from the standard PQ pathway, often providing a shortened timeline for receiving prequalification. • Streamlined procedure for vaccines with marketing authorization from eligible NRAs (vaccines): Applied to vaccines that have been licensed by selected NRAs that are eligible and willing to share regulatory information with WHO. The procedure is applied through collaboration and confidentiality arrangements, and with the agreement of the manufacturer of the vaccine to which the streamlined prequalification procedure is being applied. It follows the same process as a full assessment, but the scientific review relies on reports generated by the NRA or the national control laboratory of record. Includes all vaccine applications

	<p>submitted for evaluation under the European Medicines Agency’s Article 58 (now EU-M4All), and intended for immediate prequalification after a positive scientific opinion</p> <ul style="list-style-type: none"> • Fast-track procedure (vaccines): <p>Applicable to licensed vaccines that are used in routine immunization programs, or only during an emergency response. This procedure can be considered for application in the following situations:</p> <ul style="list-style-type: none"> ○ During an acute vaccine shortage that may jeopardize global supplies for routine immunization programs ○ During emergency situations, such as a disease outbreak or epidemic for which no prequalified vaccine is yet available • Assessment of stringently approved multisource (generic) or innovator product (medicines): <p>WHO recognized the scientific evaluation of FPPs (finished pharmaceutical products) that have been conducted by regulatory authorities that apply stringent standards to evaluating quality, safety, and efficacy that are similar to those recommended and applied by WHO when evaluating products for prequalification. WHO bases its decision to prequalify on the basis of the information shared with WHO by the applicant, such as SRA assessment reports and inspection reports.</p> • Abridged assessment (in vitro diagnostics): <p>Abridged assessment involves determination by WHO whether there was prior stringent assessment and approval for the product submitted. The assessment consists of a performance evaluation, manufacturing site inspection of abridged scope, and labelling review.</p> • New intervention pathway (vector control products): <p>The New Intervention Pathway applies only to products not covered under existing WHO policy recommendations. Products become eligible for a prequalification decision once the relevant WHO disease department has established an applicable policy recommendation, at which point the product can proceed on the regulatory prequalification pathway for vector control products.</p> • Dossier submission date • Dates of key WHO inspections/evaluations: site, lab, clinical trial site, field testing
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	<ul style="list-style-type: none"> • Date of prequalification listing
Collaborative registration procedure	<ul style="list-style-type: none"> • If a product was registered in a country using WHO's collaborative registration procedure and, if so, which countries participated
Policy, guidelines, and eligibility criteria	<ul style="list-style-type: none"> • Date when product first appeared on the WHO Essential Medicines List or Essential Diagnostics List • Date of interim policy recommendations or guidelines <ul style="list-style-type: none"> ○ Interim: There are often large time gaps between releases of official guidance, or the advent of new products with promising evidence leads to interim guidelines or recommendations. Interim guidelines have been called out separately from full guidelines • Group that gave interim recommendation <ul style="list-style-type: none"> ○ Vaccines are often given interim SAGE recommendations (Strategic Advisory Group of Experts on Immunization) ○ WHO may issue interim guidance before an official policy release • WHO policy guidelines: date of initial publication, update, and latest guidelines <ul style="list-style-type: none"> ○ For the purposes of this research, the data included for WHO guidelines are those that have been released in an official capacity. Most often, these guidelines are released for specific disease areas and contain recommendations along with level of confidence and evidence.
First post-PQ NRA approval	<ul style="list-style-type: none"> • First NRA to grant approval following prequalification, including relevant regulatory application submission and approval dates
Product characteristics	<ul style="list-style-type: none"> • Scientific and commercial names • Type of intervention and health topics and populations it addresses • Developer

Table 2. List of researched products by product stream.

Product Name	Product Stream	General Health Topic	Specific Health Topic
Bivalent Oral Poliomyelitis Vaccine Type 1&3 (bOPV 1&3)	Vaccines	Infectious disease	Polio
Ervebo	Vaccines	Infectious disease	Ebola
Gardasil (quadrivalent)	Vaccines	Infectious disease	Human papillomavirus (HPV)
Japanese Encephalitis	Vaccines	Infectious disease	Japanese encephalitis
MenAfriVac	Vaccines	Infectious disease	Meningitis Group A
RotaTeq	Vaccines	Maternal, newborn, child health	Rotavirus
Rotavac	Vaccines	Maternal, newborn, child health	Rotavirus
Artesunate for injections	Medicines	Infectious disease	Malaria
Artesunate RAS, 100mg	Medicines	Infectious disease	Malaria
Child-friendly TB medicines	Medicines	Infectious Disease	Tuberculosis
Coartem 20/120mg	Medicines	Infectious disease	Malaria
Coartem Dispersible	Medicines	Infectious disease	Malaria
Dapivirine Microbicide Ring	Medicines	Infectious disease	HIV
Fexinidazole	Medicines	Neglected tropical disease	Human African Trypanosomiasis (HAT)
Pretomanid	Medicines	Infectious disease	Tuberculosis
Pyramax	Medicines	Infectious disease	Malaria
Pyramax Granules	Medicines	Infectious disease	Malaria
SumiShield 50WG	Vector Control Products	Infectious disease	Malaria
Tsara Soft	Vector Control Products	Infectious disease	Malaria
Royal Sentry 2.0	Vector Control Products	Infectious disease	Malaria
Cielo ULV	Vector Control Products	Infectious disease	Malaria
Fludora Co-Max	Vector Control Products	Neglected tropical disease	NTDs
SD Bioline HIV/Syphilis Duo	In-Vitro Diagnostics	Infectious Disease	HIV
OraQuick® HIV Self-Test	In-Vitro Diagnostics	Infectious disease	HIV
Xpert® HIV-1 Qual Assay	In-Vitro Diagnostics	Infectious disease	HIV
Bioline™ Malaria Ag P.f	In-Vitro Diagnostics	Infectious disease	Malaria

Table 3. Key informant categories.

Key Informant Categories	Number Interviewed Within Each Category
Product developers and product development partners	9
Regulatory experts in LMICs	2
Global regulatory experts	5
WHO prequalification and regulatory systems experts	8

APPENDIX 2. PREQUALIFICATION PROCESS CHARTS FOR INDIVIDUAL PRODUCT STREAMS

Prequalification Process for Medicines

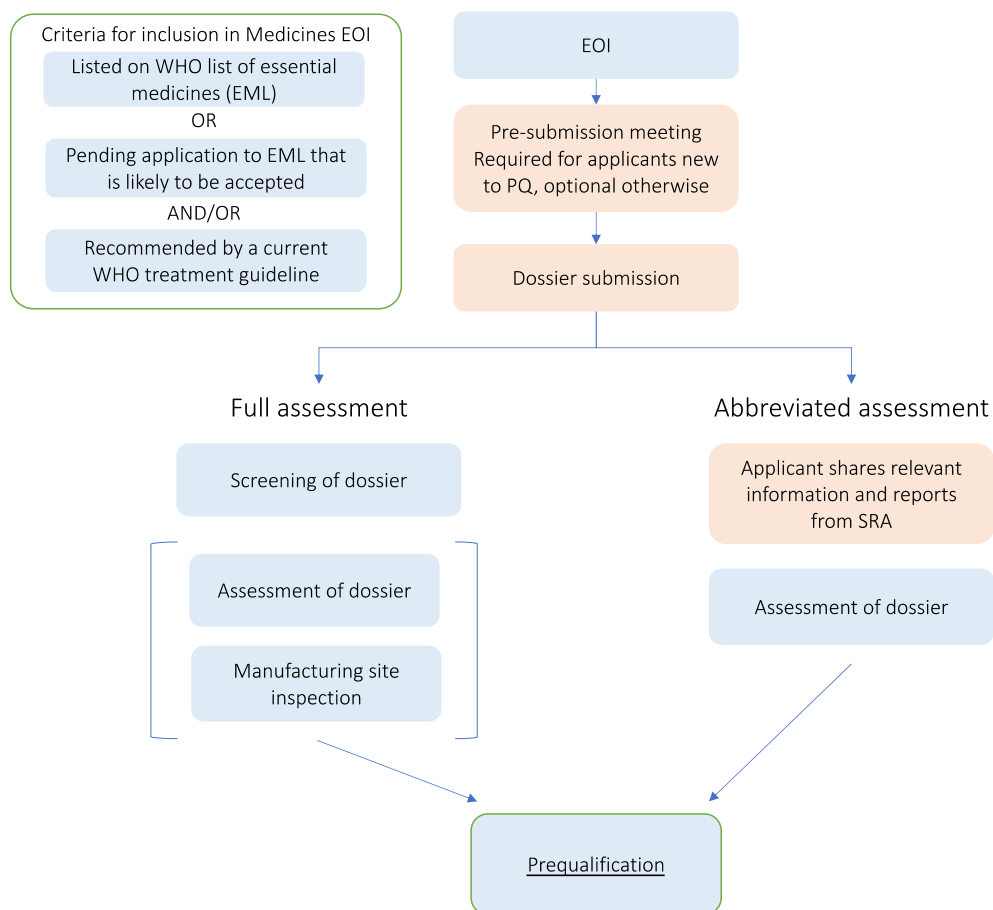


Figure 1. Medicines PQ process.

Medicines going through PQ must first be included in an invitation for EOI, which are published periodically by health topic. Inclusion in an EOI is determined by a set of criteria: the product must be listed on the WHO Essential Medicines List (EML), have a pending application to be included on the EML that is likely to be accepted, or be included in a WHO treatment guideline.^{xxiv} Once a product has met at least one of the criteria, it may be included in an EOI published by the medicines PQ team. Product developers who have not gone through the PQ process before are required to schedule a pre-submission meeting with the PQ team. For developers who are not new to the process, a pre-submission meeting is not required, but is available if desired.^{xxv} Following any pre-submission requirements, developers can then proceed to submit a product dossier to be assessed by the PQ team. Medicines can undergo a full assessment or may proceed through an abbreviated assessment if already approved by an SRA, as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.^{xxvi} In the case of an abbreviated assessment, the applicant shares information and reports from its SRA approval process with the WHO team to facilitate an abbreviated assessment. Manufacturing site inspections are not usually carried out as part of abbreviated assessments but may be requested by the PQ team.^{xxvii}

Prequalification Process for Vaccines

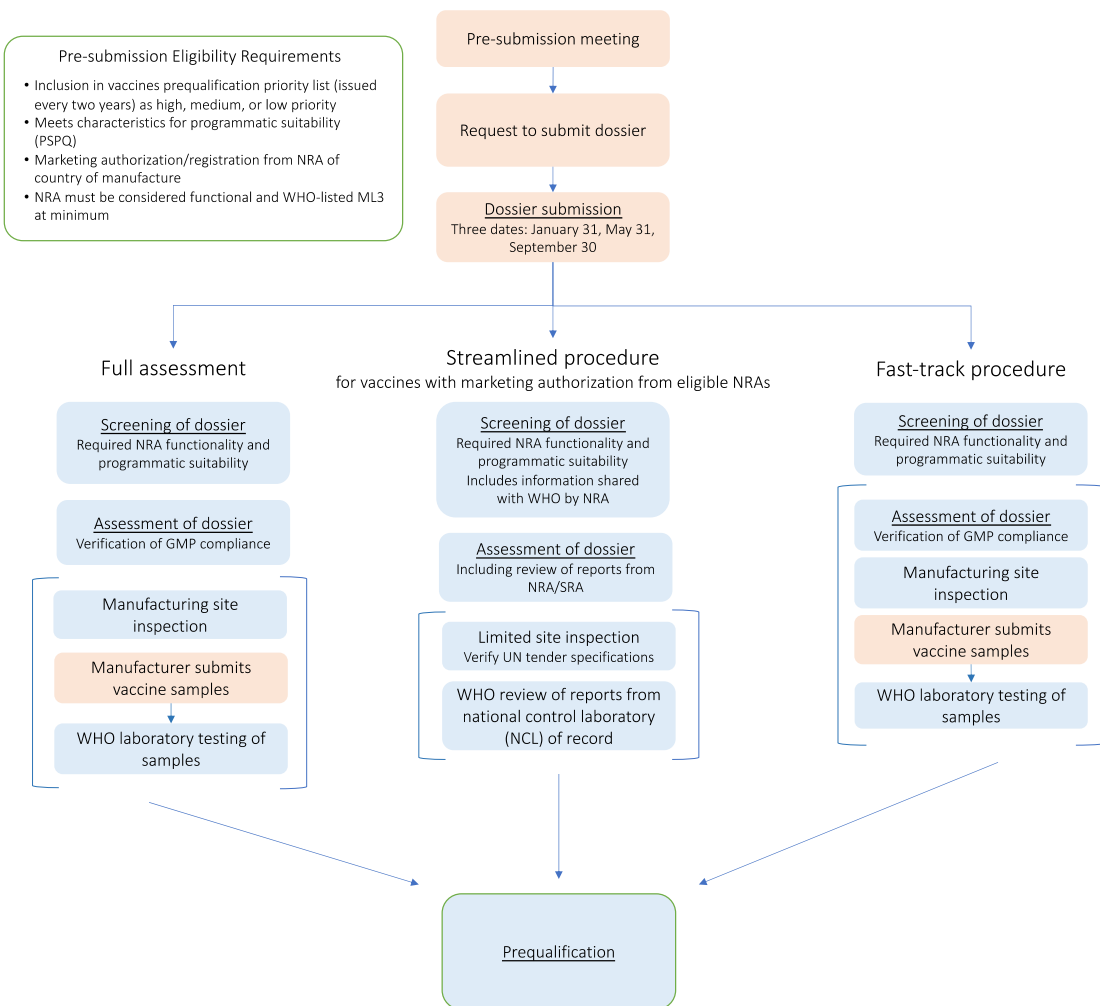


Figure 2. Vaccines PQ process.

To begin the prequalification process for vaccines, a vaccine must first meet pre-submission eligibility requirements: the vaccine must be included in the vaccines prequalification priority list, which is issued by the PQ team every two years, as either high, medium, or low priority; must have received approval and/or marketing authorization from the regulatory authority of the country of manufacture; and this regulatory authority must be considered at least maturity level 3 by WHO.^{xxviii} Once these eligibility requirements are met, developers can schedule a pre-submission meeting with the PQ team if needed, submit a formal request to submit a dossier, and submit a product dossier on one of three pre-determined dates: January 31, May 31, and September 30. Following dossier submission, a vaccine can proceed down one of three assessment pathways: full assessment, streamlined procedure (for vaccines with marketing authorization from eligible NRAs that have agreed to share regulatory information with WHO), or fast-track procedure (for public health emergencies such as epidemics or vaccine shortages). Note that for the fast-track procedure, the established deadlines for dossier submission do not apply. The streamlined procedure leverages data and reports shared by the NRA to carry out assessment procedures, and WHO also carries out a site inspection more limited in scope to streamline the

processes. In the fast-track procedure, dossier review, testing, and site inspection are carried out simultaneously to accelerate timelines appropriately in response to the public health emergency.

Prequalification Process for Vector Control

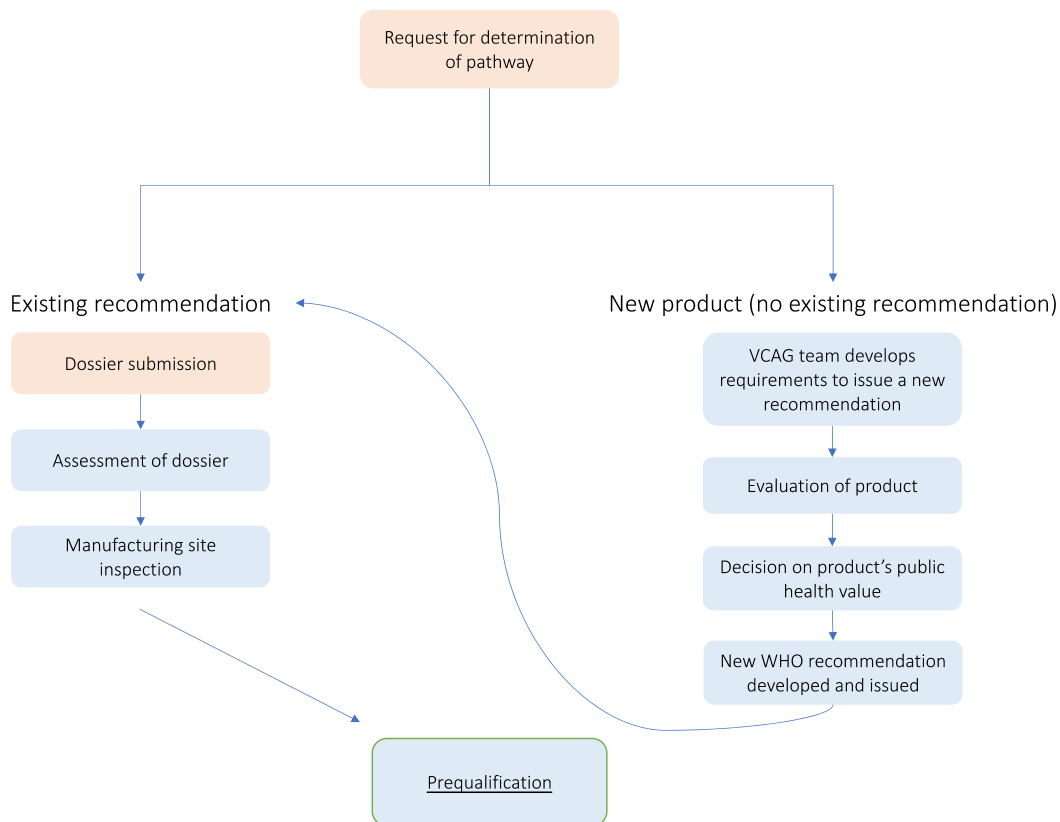


Figure 3. Vector control products PQ process.

The PQ process for the vector control product stream begins with the product developer submitting a request for determination of pathway. This serves a similar purpose to the pre-submission criteria and EOIs for medicines and vaccines: the PQ team determines if there is an existing WHO recommendation for the product, and if there is an existing recommendation, the developer can proceed to submit a dossier. If there is no existing recommendation, the product is instead assessed on its public health value and considered for inclusion in a new WHO recommendation. If a new product, without an existing recommendation, is evaluated positively and determined to be of public health value, a new WHO recommendation will be developed and issued. Once a recommendation exists for a product, the developer can proceed with dossier submission. The WHO PQ team reviews the data included in the dossier, carries out manufacturing site inspections, and may flag pending data from field-testing to be submitted once available. Following dossier assessment, the vector control product may be included on prequalification lists.

Prequalification Process for In Vitro Diagnostics

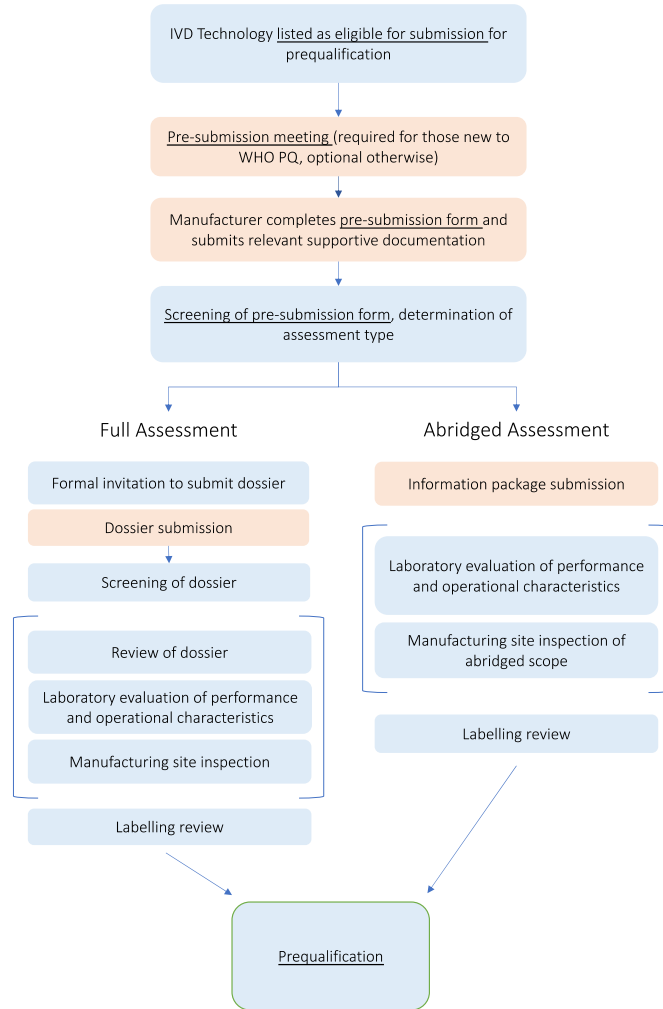


Figure 4. Diagnostics PQ process.

The IVDs PQ team considers for prequalification those IVD technologies that have been determined eligible for submission for prequalification and listed as such by WHO. Product developers may begin the PQ process for those diagnostics included in this list. Pre-submission meetings with the PQ team are required for all product developers new to the PQ process and are offered as an option to all developers. Developers must complete and submit pre-submission forms, which are then screened by the PQ team to confirm that the product is eligible for prequalification and to determine the appropriate assessment pathway. IVDs may undergo a full assessment or an abridged assessment, in which the developer submits an information package in lieu of a dossier and the manufacturing site inspection conducted is of abridged scope. A product may go through the abridged assessment process if a) it has received SRA approval or b) if the version that has been submitted for PQ is non-stringently assessed but there exists a stringently assessed version that is not substantially different. Dossier assessment, site inspection and performance evaluation are performed in parallel steps. For both the full and abridged assessment, the performance and operational characteristics are assessed by a WHO-listed laboratory and a labelling review is conducted before a product is prequalified.

APPENDIX 3. PREQUALIFICATION TIMELINE KEY PERFORMANCE INDICATORS

Source: WHO. Delivering Quality-Assured Medical Products for All (2019-2023).

<https://www.who.int/publications/i/item/WHO-MVP-RHT-2019.01>

KPIs for PQ TIMELINE			
APPLICATION-BASED PERFORMANCE INDICATORS			
#	Indicator	% Target	Target time
Annual PQ cohort (products prequalified in a calendar year)			

Products prequalified (i.e. the annual PQ cohort)

- applicable for product applications accepted after 1 January 2015; for API, after 1 January 2016

100	Number of products prequalified	-	-
101	Median number of dossier review cycles	-	-
102	% of products prequalified for which the number of dossier review cycles is at or below target	70%	Target number of dossier review cycles: 3

Time to prequalification (from acceptance for assessment to prequalification)

- applicable for product applications accepted after 1 January 2015; for API, after 1 January 2016

110	Median WHO PQ time	-	N/A
111	Median manufacturer PQ time	-	N/A
112	Median total PQ time	-	N/A
KPI 1	% of products prequalified at or below target WHO PQ time	70% (30% for APIs)	Full assessment: 270 calendar days 350 calendar days for IVDs prequalified without the alternative laboratory mechanism Abridged assessment: 100 calendar days 180 calendar days for IVDs prequalified without the alternative laboratory mechanism

#	Indicator	% Target	Target time
Submission cohort (PQ applications submitted for PQ assessment in a calendar year)			
PQ applications submitted for PQ assessment (i.e. the submission cohort)			
200	Number of PQ applications submitted for PQ assessment	-	-
Time to screening first action			
210	Number of screening first actions	-	-
KPI 2	% of screening first actions taken at or below-target time	80%	30 calendar days

Assessment cohort (PQ applications accepted for PQ assessment in a calendar year)			
PQ applications acceptor for PQ assessment (i.e. the assessment cohort)			
300	Number of PQ applications accepted for PQ assessment	-	-
Time to dossier first action			
310	Number of dossier first actions	-	-
KPI 3.1	% of dossier first actions taken at or below-target time	80%	90 calendar days 120 calendar days for FPPs & APIs (due to fixed assessment sessions)
Time to inspection first action			
320	Number of inspection first actions	-	-
KPI 3.2	% of inspection first actions taken at or below-target time	80%	210 calendar days

Time to laboratory first action			
330	Number of laboratory first actions	-	-
KPI 3.3	% of laboratory first actions taken at or below-target time	80%	180 calendar days

Products prequalified			
340	Number of products prequalified	-	-
341	Median number of dossier review cycles	-	-
342	% of products prequalified for which the number of dossier review cycles is at or below target	70%	Target number of dossier review cycles: 3

#	Indicator	% Target	Target time
Change assessment cohort (post-PQ change applications accepted for change assessment in a calendar year)			

Post-PQ change applications accepted for change assessment (i.e. the change assessment cohort)

400	Number of post-PQ change applications accepted for post-PQ change assessment	-	-
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Time to post-PQ change first action

410	Number of post-PQ change first actions	-	-
KPI 4	% of post-PQ change first actions taken at or below-target time	80%	APIMF major amendment: 90 days APIMF minor amendment: 60 days APIMF immediate notification: 45 days FPP major variation: 90 days FPP minor variation: 60 days FPP immediate notification: 45 days IVD reportable change: 90 days Vx major variation, type A: 90 days

PQ list cohort (all prequalified products on the PQ lists at the beginning of a calendar year)			
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Prequalified products on the PQ lists (i.e. PQ list cohort)

500	Number of products on PQ list	-	-
501	Number of products withdrawn after prequalification	-	-
KPI	Not Applicable		

APPENDIX 4. PREQUALIFICATION FEES

Table 1. WHO PQ fees by product stream, as of April 2022.

	Screening Fee (US\$)	Reduced Assessment Fee (US\$)	Assessment Fee (US\$)	Site Inspection Fee (US\$)	Change Fees (US\$)	Annual Fees (US\$)
Vaccines: Simple / traditional	2,500	25,000*	100,000	30,000		4,800-140,000***
Vaccines: Combination / novel	5,000	66,000*	232,750	30,000		8,400-250,000***
In vitro diagnostics	5,000	8,000**	12,000		3,000	4,000
Medicines: Finished pharmaceutical product (FPP)		6,000**	25,000		3,000	5,000** 20,000 (full)
Medicines: Active pharmaceutical ingredient (API)		10,000**	20,000			4,000** 8,000 (full)
Vector control	No fees currently					

*For vaccines with urgent public health need but no/small commercial market | **For abridged assessments (versus 'full' assessment) | ***Tiered annual fee structure

Table Sources: World Health Organization Prequalification Fees. Accessed May 3, 2022.

Vaccines: <https://extranet.who.int/pqweb/vaccines/fees-prequalification>

Medicines: <https://extranet.who.int/pqweb/medicines/prequalification-procedures-and-fees>

In vitro Diagnostics: <https://extranet.who.int/pqweb/vitro-diagnostics/procedures-and-fees-prequalification>

Vector Control: <https://extranet.who.int/pqweb/vector-control-products/prequalification-procedures-and-fees-vector-control-products>

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