WHO RPQ impact assessment: Regulation and prequalification activities

External assessment report on programmes in the Department of Regulation and Prequalification

Executive summary

March 2023

Disclaimer

The contents of this document reflect a consolidation of views gathered through numerous interviews with various stakeholders; they are not the official view of World Health Organization (WHO).

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A Executive summary

A.1 CONTEXT AND OBJECTIVES

An effective regulatory system plays a critical role in ensuring the quality of health products, spanning from their development in the laboratory to their administration in health facilities. This system serves as a cornerstone for achieving high-quality prevention, diagnosis, and treatment and is an indispensable element of the World Health Organization's (WHO) drive towards universal health coverage (UHC). Moreover, it is a significant contributor to WHO's objective of reaching the "triple billion" target, which seeks to expand the number of people benefiting from universal health coverage, enhance protection against health emergencies, and promote improved health and well-being for one billion people each.

As of December 2022, there are over 1,580 products – medicines, vaccines, In Vitro Diagnostics (IVDs), vector control, and immunization devices – that are prequalified and have improved public health in low- and middle-income countries (LMICs). Furthermore, there are 13 National Regulatory Authorities (NRAs) that have achieved stable and well-functioning regulatory systems commensurate with maturity level 3 or 4 for at least one product type. The WHO department that is driving the aforementioned impact is the Regulation and Prequalification (RPQ) department whose broader mandate is to "*help Member States strengthen regulatory systems through a variety of approaches*" and to "*ensure medicines, vaccines and other health products for supply to low-income countries are quality-assured, safe, effective and accessible to all populations*" [1]. The structure of the RPQ department has been included in Appendix 1.

In 2018, an independent impact assessment report of this department was commissioned with three specific objectives:

- Create a fact-based understanding of the value that the PQ and system-supporting activities have created in the global health ecosystem, with a 360-degree view across all stakeholders
- Generate both qualitative and quantitative assessments of the value created by PQ and system-supporting activities
- Create insights that can feed directly into the team's strategic plan to create greater impact at a country level, driving towards the triple-billion targets laid out in WHO's 13th General Program of Work (GPW13)

This impact assessment has been one of the inputs that informed the elaboration of WHO's five-year plan (2019-23)[2] to help build effective and efficient regulatory systems. This strategic plan sets out four strategic priorities for the RPQ department:

- Strengthen country and regional regulatory systems
- Improve regulatory preparedness for public health emergencies
- Reinforce and expand WHO prequalification and product risk-benefit assessment
- Increase the impact of WHO regulatory support activities

At this five-year juncture of the plan considering (a) the value generated by the 2018 assessment report, (b) the shifts that have occurred since its publication in 2019, both in the global health ecosystem (e.g., due to the COVID-19 pandemic) and (c) the changes within the RPQ department - a new independent impact assessment of the scope[3]

[1] https://www.who.int/teams/regulation-prequalification/about (Link verified on March 31, 2023)

[2] https://www.who.int/publications/i/item/WHO-MVP-RHT-2019.01 (Link verified on March 31, 2023)

[3] Except prequalification of medical devices and vector control products

of the RPQ department has been commissioned[4]. In addition to the RPQ department activities, the activities and impact of the work done by the Health Product Policy and Standards (HPS) department on the topic of norms and standards are also within scope of this assessment considering their close connection to the mandate and activities of the RPQ department.

This new assessment has focused on the last five years (2018-22) and has four specific objectives:

- Generate both qualitative and quantitative assessments of the value created by the RPQ department for its main stakeholders with a focus on country impact in line with the four strategic priorities of the RPQ department
- Create an understanding of the value that the RPQ department activities have created in the global health ecosystem, with a 360-degree view across all stakeholders
- Identify and analyze the main developments since the publication of the previous assessment in 2018
- Develop insights and recommendations that enable both operational quick wins (i.e., allowing for efficiency gains) and long-term improvement

A.2 SUMMARY OF METHODOLOGY

To create a fact-based understanding of the value that the RPQ department has created across all stakeholders, three main sources of insight were taken into consideration. First, desk research and data analysis provided an objective and fact-based overview of the current ecosystem, case examples, and economic benefits. Second, a total of 28 interviews with WHO stakeholders and 44 interviews with external stakeholders (60 minutes each) provided a more nuanced perspective that is directly linked to the needs and interests of the various stakeholder groups. The external stakeholder interviews covered 9 NRAs (including 2 Stringent Regulatory Authorities (SRAs)), 18 manufacturers (4 Rx, 7 Vx, and 7 Dx), 14 procurers/donors, 2 industry associations, and 1 civil society organization. Finally, a survey was shared with 179 NRAs to collect their perspectives on the relevant WHO activities. A total of 39 NRAs completed the survey.

11 impact themes were assessed with detailed assessment metrics for each:

1. Strengthening regulatory systems (including three quantitative assessment metrics, one perception assessment metric, and one case study)
2. Improving the management of Substandard and Falsified (SF) medical products and incidents (2 quantitative metrics and 2 case studies)
3. Increasing compliance of laboratories with required standards in LMICs (2 quantitative metrics and 1 case study)
4. Strengthening pharmacovigilance (4 quantitative metrics and 1 perception)
5. Enabling faster access to prequalified, SRA-approved and Emergency Use Listed products (5 quantitative metrics and 1 perception)
6. Improving regulatory preparedness for public health emergencies (2 quantitative metrics and 1 case study)
7. Improving access to donor-funded procurement markets (1 quantitative metric and 1 case study)
8. Supporting Member States to build the ecosystem and capacities for high-quality and sustainable local production (3 quantitative metrics, 1 perception metric and 1 case study)
9. Assessing the economic return on investment (RoI) savings generated by PQ (1 quantitative metric)

[4] This new impact assessment is an update of the 2018 assessment.

10. Contributing to saving lives (2 quantitative metrics)
11. Increasing adoption of WHO guidelines and technical standards (1 quantitative metric and 2 perception metrics)

Five limitations of this report should be considered. First, the insights are by no means exhaustive, given that the interviews focus on stakeholder groups that have the highest direct exposure to WHO and have a general understanding of the impact of their activities. Also, no additional stakeholders (e.g., patients or regional regulatory bodies) were interviewed. Second, comprehensive data was not available in some instances (either it was not collected at present or because the information was not publicly available (when related to data for other stakeholders outside of the RPQ department). Third, the scope of this report is limited to specific activities, which is why it does not give an exhaustive review of all RPQ department activities or all the teams within and related to the RPQ. Fourth, the evaluation focuses on the key strategic issues of the RPQ rather than providing a detailed assessment of each activity. Last, there are many projects that the RPQ department has under implementation (e.g., implementation of a new Quality Management System and the electronic PreQualification IT system (ePQS) that have the potential to impact some of the recommendations made in the report. However, since these have not yet been fully rolled out as of December 2022, their impact is not considered within the scope of this assessment.

A.3 SUMMARY OF ASSESSMENT

Based on the combination of quantitative analysis and the insights from the stakeholder interviews across the different metrics, the RPQ department has had meaningful impact. Across all activities, some areas for improvement have been identified that could enhance the impact of the RPQ department.

Overall, the seven key findings of this assessment are:

1. **The RPQ department has had significant impact in terms of enabling access to critical health products for the global population:**
    a. Increased responsiveness in a global pandemic – The RPQ department has listed 11 COVID-19 vaccines and 42 COVID-19 diagnostic products for emergency use and prequalified 17 COVID-19 related medicines. WHO Emergency Use Listings (EULs) approvals were relied on by more than 170+ Member States and Territories to approve COVID-19 medical products for entry into their markets following facilitation by the WHO through its Regional and Country Offices.
    b. Contributed to averting more than five million deaths during the COVID-19 pandemic – Between 5.1 million and 7.6 million deaths have been averted in LMICs in 2021 thanks to COVID-19 vaccinations[5]. The RPQ department contributed to this positive impact by listing 10 COVID-19 vaccines for emergency use between December 2020 and December 2021. As the large majority of LMICs rely on WHO EULs, the responsiveness of the RPQ department to list COVID-19 vaccines enabled the delivery of hundreds of millions of doses in 2021 (e.g., COVAX delivered over 842 million doses of COVID-19 vaccines in LMICs in 2021; these doses could not have been delivered without an EUL).
    c. Continued progress on improving access to health products: Even with the increased workloads and disruptions to processes (e.g., in-person site inspections) due to COVID-19 overall, the number of prequalified products has increased by 13%[6] in the last 5-year period (2018-22) compared to the previous 5-year period (2013-17), while the number of products EUL-listed has increased by 325%[7].

[5] Source: Global impact of the first year of COVID-19 vaccination: a mathematical modelling study, The Lancet (2022)

[6] From 422 to 439 prequalified. It is worth noting that the number of submissions has decreased by 24% between 2013-17 and 2018-22.

[7] From 12 to 51 products EUL-listed. It is worth noting that the number of submissions has increased by 313% between 2013-017 and 2018-022.

2. **The RPQ department played a direct and significant role in strengthening regulatory systems globally: between 2018 and 2022, NRAs from 12 Member States** (which represent ~30% of the world's population) have been supported to reach one of the four Maturity Level 3 (ML3)[8] or Maturity Level 4 (ML4)[9] categories, which brings the total number of countries that achieved ML3 or ML4 for at least one medical product type from 1 in 2017 to 13 in 2022 (representing ~50% of the world's population). Many more have been supported in the strengthening of their regulatory functions, e.g., vigilance systems and marketing authorization during public health emergencies (even though there may not have been an increase in the overall maturity level of the NRA).

3. **The RPQ department has expanded the scope of its activities to support Member States, manufacturers, and other stakeholders more comprehensively, some examples include:**

   d. Increase in the therapeutic areas within scope for prequalification (five therapeutic areas added for medicines[10], three for vaccines[11] and four for diagnostics[12])

   e. Development, implementation, and promotion of the concept of reliance, including through the publication of the WHO Good Reliance Practices (GreIP) in 2021 and organization of training sessions and webinars around reliance.

   f. Development and launch of the Coalition of Interested Parties (CIP), a WHO Network on regulatory systems strengthening aimed at coordinating efforts by partners contributing to regulatory strengthening and convergence activities at national, regional, and global levels.

   g. Expansion of the Collaborative Registration Procedure (CRP) to enable market entry and national marketing authorizations for PQ products:

      › Number of Member States that have signed CRP agreements for medicines has increased from 35 to 59 (70% increase), for vaccines from 20 to 49 (150% increase) and for diagnostics, since the launch of the CRP process in 2019, 26 countries have signed CRP agreements

      › Number of Member States that have completed product registrations under the CRP agreements has increased by 20% and 25% respectively, for medicines and vaccines. For diagnostics, since the launch of the CRP in 2019, 25% of them have registered products through this pathway.

4. **In addition to expanding the scope of its existing activities, the RPQ department has been piloting and testing new processes and support mechanisms to respond to the changing needs of its stakeholders, including but not limited to:**

   a. *Pursuant to NRA feedback to replace the previous concept of Stringent Regulatory Authorities (SRA)*: Launch of the first pilots for performance evaluation (currently under way as of December 2022) under the new WHO Listed Authorities (WLA) framework [13]which was developed in response to tremendous feedback from NRAs for a transparent and evidence-based pathway for regulatory authorities operating at an advanced level of performance to be globally recognized, thereby replacing the previous concept of SRAs.

   b. *Pursuant to the strategic objectives of the department's 2019-23 strategy:* Development of new approaches to directly support Member States in strengthening their national strategies and capabilities

[8] ML3 confirms that a stable, well-functioning and integrated regulatory system is in place

[9] ML 4 (which is the highest level of maturity) is achieved by a regulatory system operating at an advanced level of performance and continuous improvement

[10] Infections in newborns and young infants and childhood pneumonia; Insulins and insulin analogues (BTPs); Certain cancers (BTPs); COVID-19 (BTPs and small molecules); Ebola Virus Disease (BTPs)

[11] Ebola, Pneumonia, Malaria

[12] G6PD, Cholera, Syphilis, TB

[13] https://www.who.int/initiatives/who-listed-authority-reg-authorities

around SF products, e.g., (a) supporting Nigeria in procuring handheld devices that have already had tremendous impact in enabling track and trace in the country, (b) collaborating with Tanzania on their national strategy for addressing SF products with the goal of using the lessons learned to develop a handbook for other Member States.

c. *Pursuant to WHO transformation in 2019 and passing of resolution WHA74.6 on strengthening local production of medicines and other health technologies and the 2019 WHO transformation:* Establishing a new WHO initiative "World Local Production Forum" and piloting an ecosystem assessment tool that can support Member States in developing actionable plans to strengthen local production (already piloted in seven countries across AFRO, EMRO, and SEARO).

d. Pursuant to WHO Transformation in 2019, establishing an integrated Pharmacovigilance team in the RPQ department for medicines and vaccines, thereby enabling common tools around reporting and data management across products.

5. **Stakeholders unanimously highlighted the limited resourcing at WHO headquarters as a key constraint across RPQ department's units and teams**. RPQ department resources have remained stable between 2018 and 2022 (from 114 staff members in December 2019 to 115 in December 2022). However, the scope and the workload across all teams have increased substantially in the same time period (some examples discussed above in points 1-4).

6. **One prominent feedback point that has been shared across all categories of stakeholders interviewed is the need for increased communication, and collaboration between the RPQ department and key stakeholders in the public health ecosystem (NRAs, manufacturers, donors and procurers, other WHO departments).** Stakeholders note that strengthening this aspect can enable even greater impact from the RPQ department as it will not only drive more reliance but also enable the RPQ department to identify where they can leverage other stakeholders (instead of their own limited resources) to scale their impact. In particular,

   a. Mature NRAs are keen for the RPQ department to rely on them to drive capacity-building efforts for their regions.

   b. Manufacturers are keen to have more visibility (e.g., on PQ decision timelines and roadmaps for release of technical standards and guidelines) and more collaboration (e.g., on working with the PQ team to prioritize pipelines for their products).

   c. Donors, procurers, and other WHO departments are keen to collaborate with the RPQ department in setting global public health agendas across different therapeutic areas, regions, and stakeholders, for example by participating in the process of developing planned roadmap and scope for PQ teams.

   d. WHO departments (specifically from the Communicable and Non-Communicable Diseases division) are keen to participate and contribute to the RPQ department's strategy and priority setting activities. In addition, they are keen to have visibility on the activities and achievements of the department so that they can identify opportunities for collaboration.

   e. All stakeholders are keen to see the RPQ department have a more central role in the PV ecosystem, coordinating, connecting, and collaborating with stakeholders more proactively

7. **Investing in RPQ remains a sound investment:** every USD 1 invested in running PQ contributes to savings of approximately USD 30-40 while acknowledging that PQ operates in the broader ecosystem of Global Health stakeholders contributing towards these savings as well[14].

[14] ROI analysis from 2018 assessment report has been leveraged as it is believed that the findings are still valid for the period between 2018 and 2022 - these are discussed in greater detail in Section C.9

A.4 SUMMARY OF RECOMMENDATIONS

Based on this impact assessment, there are five major categories of proposed enhancements. It is also noted that several recommendations from the 2018 Assessment continue to be relevant, especially around the topics of cross-departmental collaboration, PQ, PV, and guidelines and standards.

1. **Cross-cutting recommendation on strengthening external and internal coordination and communication efforts**

   a. *Towards both internal and external stakeholders:*

      i. (PQ across all products) Strengthen the consultation process to collect inputs both from internal and external stakeholders prior to determining the prequalification priorities and developing product pipelines. For example: co-develop multi-year roadmaps for scope of products within PQ with stakeholders; develop a "priority" track to be able to designate "priority" medical products based on global health needs (e.g., a global stockout, pandemic)

      ii. Develop a robust[15] communication strategy to articulate the services provided by the RPQ department to each stakeholder type (National Regulatory Authorities (NRAs), manufacturers, donors, etc.) including what is in scope and what is out of scope. This communication strategy will help manage key stakeholders' expectations and create visibility both on the activities conducted by the RPQ department– as several new activities have been launched since 2018 – and on the impact these activities generate in terms of public health outcomes.

      iii. (PQ across all products) Communicate on a frequent basis the status of all health products within WHO EUL/PQ evaluation process on the WHO website (similar to what has been done for COVID-19 vaccines[16]).

   b. *Towards external stakeholders only*

      i. (PQ) Ensure the new ePQS system planned for rollout in May 2023 has the appropriate features and data migration to take action on stakeholder feedback received in the context of this assessment (detailed in Section C.5.6) and of the assessment conducted in 2018[17].

      ii. (Regulatory system benchmarking activities) Increase awareness and understanding of the regulatory system benchmarking process and outcomes for procurers and donors, e.g., through a communication plan that can provide clarity on the purpose of the benchmarking process and tool. This could help address some misperceptions about the purpose of the benchmarking process and tool.

   c. *Towards internal stakeholders only*

      i. (Across all RPQ teams) Ensure synchronization of the future strategic roadmap of the RPQ department with the roadmaps of other WHO departments that are developing policies and recommendations on similar topics / products (e.g., IVB department) to ensure consistency of priorities across all departments.

2. **Cross-cutting recommendation on readjusting strategic priorities or tracking metrics to drive more focused impact on areas of most need for the ecosystem**

   a. (Pharmacovigilance) Consider resetting strategic priorities for pharmacovigilance activities to increase alignment with the biggest needs and gaps in the global pharmacovigilance ecosystem. The strategic

[15] Which includes a clear set of key performance indicators

[16] The status of COVID-19 Vaccines within WHO EUL/PQ evaluation process is available online and is updated at least once a month (link verified on Feb. 9, 2023)

[17] Impact assessment of WHO Prequalification and systems supporting activities (published in June 2019; link verified on Feb. 9, 2023)

priority setting process should include close collaboration with a multi-stakeholder (internal and external) working group.

b. (Local Production and Assistance) Reflect on lessons learned from LPA unit's PQ Technical Assistance (TA) activities and outcomes over the last three years to reconsider: (a) the process/criteria for identifying manufacturers that receive TA and (b) developing the appropriate Key Performance Indicators (KPIs) for measuring impact of TA (current KPI is number of manufacturers supported with TA).

c. (Incidents and Substandard/Falsified Medical Products (ISF)) Incorporate lessons learned from current Member State pilots and initiatives aimed at developing local regulatory capabilities for SF products into a formal strategic plan and priorities for supporting Member States

d. (Norms and standards) Develop tracking process/methodology to monitor the implementation and the adoption of different guidelines, thereby enabling development of a fact base to determine where and on what implementation support is needed the most

3. Cross-cutting recommendation on optimizing RPQ department's capacity (in light of resource constraints at headquarters)

a. *Leverage capacity of NRAs.* Create further opportunities for NRAs to support each other by, for example, strengthening self-sustaining peer learning forums that can be led by mature NRAs in each region (with minimal support from the RPQ department). Based on the findings of this report, some areas where this can be implemented are (a) the self-benchmarking processes and (b) regulatory emergency preparedness.

b. *Create capacity in regional offices*. Staff dedicated RPQ resources (under the supervision and expertise from the RPQ department in HQ) to drive RPQ department activities where local context and presence may be advantageous. Based on the findings of this report, some areas where this can be implemented are:

   i. (ISF) Provide Member States support in developing ISF strategies and responding to incidents

   ii. (Emergency preparedness) Provide support to countries that want to enhance their regulatory systems and requirements to effectively address public health emergencies

   iii. (LPA) Execution of strategy for strengthening local production

   iv. (QCL) Provide support in leading lab inspections to strengthen lab capacity

c. *Optimize allocation of current RPQ department resources in HQ*: Once the new strategic priorities and objectives for the RPQ department have been set, consider an independent assessment of the allocation of human and financial resources across RPQ department activities (both technical and non-technical) to ensure allocation matches strategic priorities. This exercise could add value as the scope of activities of the RPQ department has evolved between 2018 and 2022 while its staff has remained stable.

4. Cross-cutting recommendation on improving internal operational efficiency for the RPQ department

a. PQ (across all products): Consider a "teardown" exercise of core PQ processes to identify redundancies. E.g., to be able to map time required for administrative/coordination tasks vs. technical tasks and identify where tasks can be automated (e.g., through automated ePQS notifications) or where tasks can be managed by nontechnical resources out of regional offices (e.g., project managers/leads that are focal points for manufacturers for minutes, document uploads, setting meeting agendas)

b. PQ (Vx and IVD): Improve efficiency of post-approval change notification process. Some examples could be:

   i. Enable dedicated pathway: consider evaluating post-change notifications under a separate dedicated pathway (i.e., different pipeline with dedicated resources and special fit-for-purpose processes)

ii. Consider developing a "priority" track for variations that may be a global health priority

iii. Revise process: consider taking a more risk-based assessment approach (i.e., simple changes to label or color of packaging should not require waiting for WHO approval) more similar to how SRAs (e.g., FDA) evaluate post-approval changes

5. Other recommendations – specific improvements to various activities of the RPQ department:

a. (Regulatory Systems Strengthening) Organize focus groups with NRAs currently undergoing benchmarking to understand the root cause of the perception that the tool needs more flexibility. Develop an appropriate action plan based on findings (e.g., better communication materials/plan to dispel misinformation about the tool's purpose and flexibility)

b. (Pharmacovigilance) Communicate the efficiencies to be gained with an integrated pharmacovigilance system that, where possible, uses the same tools and resources for AEFI and ADR reporting and data management

c. CRP (Vx): Consider process improvements that can be made to simplify data sharing between the teams that hold the repository of information on PQ assessments and the teams processing/leading CRP registrations, such that information sharing to enable CRP for vaccines does not require significant capacity from the teams.

d. Reliance: Consider the many different activities being run by the RPQ department on this topic – there is an opportunity for development of clearer strategic priorities, objectives, and KPIs on the impact the department seeks to drive on the topic of reliance

e. (Emergency preparedness) Introduce systematic measurement of the impact of support from the RPQ department on regulatory capacity preparedness for public health emergencies. For example: request countries that received WHO support to re-evaluate the 11 Global Benchmarking Tool (GBT) sub-indicators related to regulatory preparedness for public health emergencies through self-benchmarking

f. (Guidelines, norms, and standards) Strengthen implementation support to NRAs and developing country manufacturers (DCMs) to increase adoption (e.g., through a standardized guideline release protocol that includes introductory workshops, online courses that can be self-paced, toolkit and support documentation)

g. (Guidelines, norms, and standards) Improve accessibility, user friendliness, and transparency to increase adoption (e.g., online, up-to-date, easy-to-navigate platform)

h. (Medicine QCLs) Develop, communicate, and implement clear end-to-end process for PQ of medicines by Quality Control Laboratories to improve efficiency and better manage timelines for the end-to-end PQ process

i. (Laboratories) Streamline support to priority regions and LIC Member States – a targeted focus will be key in building global laboratory capacity, especially keeping in mind resource constraints. For example: considering the unique complexities of LICs, develop a targeted action plan and funding to improve LIC participation in medicines QCL PQ

j. (Pharmacovigilance) Set up incentives for Member States to increase the reporting frequency and quality of adverse events on VigiBase. For example: set up a dashboard of countries reporting performance, enabling peer-to-peer comparison, to foster healthy competition and motivation amongst Member States

k. (LPA) Strengthen implementation support for NRAs and DCMs. For example: evolve the situational analysis tool in a similar direction as the GBT – where there are clear indicators and Institutional Development Plan (IDP) -like roadmaps that can provide concrete guidance to stakeholders, develop clear

metrics/methodology to be able to track the impact of the ecosystem analysis tool (before its launch in 2025)

l. (Guidelines, norms, and standards) Consider alternate pathways (besides working with/relying on the WHO central website/ communications development team) to developing a norms and standards microsite that can have the features that will enable actioning of recommendations from both the 2018 assessment and the current assessment

This section highlights the most prominent measures identified across the assessed metrics. A more detailed list of enhancements is presented at the end of relevant sections and labelled "recommendations". These recommendations are based on both hard facts/data as well as perceptions from stakeholders.

External Assessment Report, March 2023