End-to-end diagnostics implementation: Advocating for innovative solutions

24 February 2022, 15:00-17:00 (UTC+1), held virtually

Background

Syndromic management based on clinical diagnosis with empiric treatment has been the mainstay of healthcare (except for HIV and malaria rapid diagnostic testing) in low- and middle-income countries. Slowly, appreciation for the clinical value of diagnostics is changing, but it remains suboptimal.

The rapid development of tests for COVID-19 has taught us that sufficient political will, funding and resources can lead to success in a short time. There is much research and development on innovative technologies for in vitro diagnostics (IVDs). However, "valleys of death" exist along the path to commercialization, distribution (especially at the global level) and programmatic implementation due to a lack of funding and the complexity of processes to successfully commercialize diagnostics for the global market.

Additionally, market push-and-pull incentives do not result in investments that can meet public health needs, especially in low- and middle-income countries. For diagnostics, in comparison with pharma, the profit margin is lower, the path to market access is longer, and attention and/or financing is lower. Even when funding from public or philanthropic sources supports product development, it is seldom, if ever, available for commercialization. Complex regulatory approval processes further hinder product development; thus, the potential for success is low.

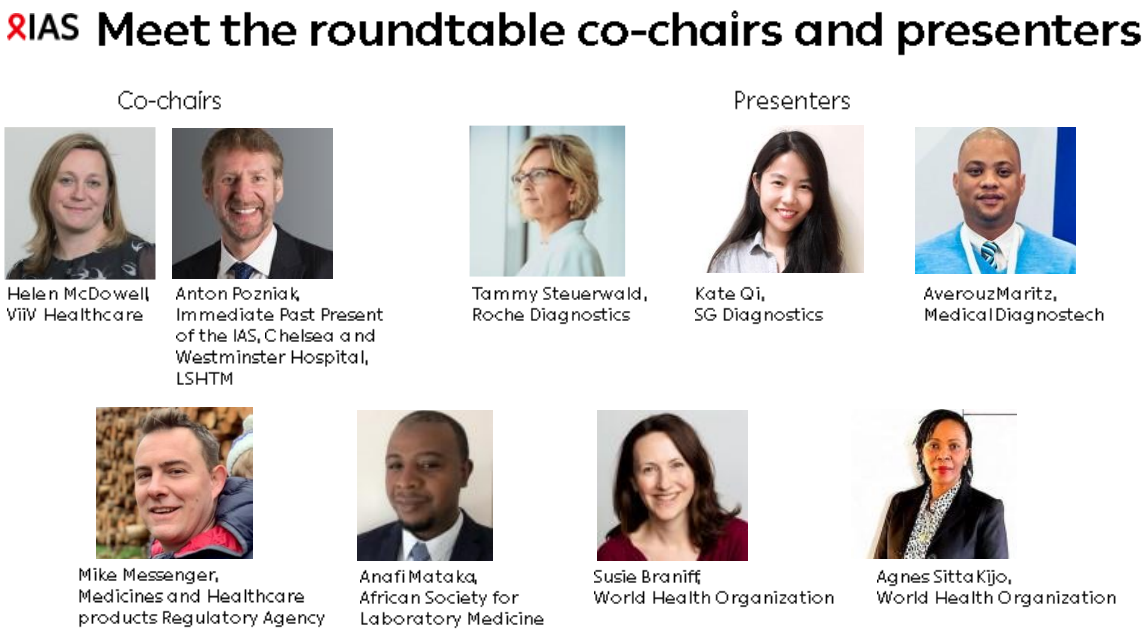
To address some of these issues, the World Health Organization (WHO) developed the Collaborative Registration Procedure for the accelerated registration of prequalified IVDs based on its experience with similar procedures for prequalified medicines and vaccines. This procedure was successfully piloted in 2019 and is now being rolled out. In June 2021, WHO published further guidance to support the use of the registration procedure in the WHO Technical Report Series (TRS) 1030, 2021 (Annex 4). In addition, the COVID-19 pandemic taught us critical lessons that, if shared and adopted, can help us be better prepared for the next pandemic.

The Industry Liaison Forum, part of the Corporate Partnership Programme of IAS – the International AIDS Society – held a roundtable discussion bringing together representatives of regulatory and normative agencies and the diagnostics and pharmaceutical industry to introduce the collaborative procedure, particularly in low- and middle-income countries. They discussed the lessons learned by IVD manufacturers and regulators from the COVID-19 pandemic and explored the Collaborative Registration Procedure.

Summary

The following speakers addressed the roundtable discussion:

1. **Welcome and introduction** – led by Forum co-chairs, Anton Pozniak, Chelsea and Westminster Hospital and LSHTM, and Helen McDowell, ViiV Healthcare, UK
2. **Challenges and opportunities for IVD manufacturers – COVID-19 lessons learned** – Tammy Steuerwald, Roche Diagnostics, USA
3. **Challenges and opportunities for IVD manufacturers in Southeast Asia (SEA) – COVID-19 lessons learned** – Kate Qi, SG Diagnostics, Singapore
4. **Challenges and opportunities for IVD manufacturers in South Africa – COVID-19 lessons learned** – Averouz Maritz, Medical Diagnostech, South Africa
5. **Generalizable lessons from the UK response to COVID-19** – Mike Messenger, Medicines and Healthcare products Regulatory Agency, UK
6. **Addressing the data gap to facilitate the regulation and uptake of IVD** – Anafi Mataka, African Society for Laboratory Medicine, Lesotho
7. **Overview of the WHO PQ for in vitro diagnostics** – Susie Braniff, In vitro Diagnostics Assessment, Regulation and Prequalification Unit, World Health Organization, Switzerland
8. **WHO Collaborative Registration Procedure: Accelerating national registration of WHO-prequalified in vitro diagnostics** – Agnes Sitta Kijo, Regulation and Prequalification Department (RPQ), World Health Organization, Switzerland



Find the summary of the presentations in Annex 1.

The presentations were followed by a Q&A around the collaborative procedure and a breakout room exercise. The exercise aimed to assess how the adoption of the procedure could be facilitated and which areas require further discussion, including the Industry Liaison Forum's role in facilitating and improving access to diagnostics.

Three prominent themes were raised during the breakout room discussions, and these require further action to facilitate access to diagnostics:

1. **Learning and next steps**: Participants pointed out that we should build on the successes and lessons learned from COVID-19 and start applying those principles beyond emergency situations. Participants also emphasized the importance of South-South collaboration when developing regulatory processes.
2. **Ensuring effective implementation of COVID-19 lessons learned:** There is a need to improve advocacy and awareness of the benefits of reliance and recognition and the WHO Collaborative Registration Procedure. As a key COVID-19 lesson learned, awareness of full recognition between authorities and recognized institutions would significantly improve global access to safe, high-quality life-saving diagnostics. WHO has led international efforts regarding reliance; attendees encouraged WHO to continue leading the charge by partnering with other international organizations, such as the International Medical Device Regulators Forum. Participants also recommended that agencies and WHO ensure flexible processes so recognition can occur based on whichever trusted decision (or inspection) is first available (for example, regulator or WHO). Doing so enables a person-centred mindset that leverages global work to make products available faster while wisely using limited resources.
3. **Frameworks and standards for evaluation of IVDs**: Participants focused on how IVDs are evaluated and what the current challenges are around the evaluation processes. Three sub-themes were raised:
    a. **Collaboration between organizations**: It is important to share assessments between organizations and work within a harmonized IVD-appropriate framework to remove duplication and unnecessary requirements that can delay access without adding to client safety.
    b. **Convergence and harmonization**: There is a need to drive adoption of already existing, internationally accepted standards. When standards do not exist, there is a need to drive toward an internationally recognized standard. Creation of jurisdiction or institution-specific standards adds complexity to the evaluation process and further delays access. Further discussion regarding the benefits and challenges of vertical versus horizontal standards is needed.
    c. **Reduce unnecessary complexities:** Lastly, the roundtable presented ideas to streamline regulatory and WHO processes to expedite access without sacrificing safety or quality. For example, regarding the WHO prequalification process, it was recommended that the programme fully rely on testing already accepted by trusted authorities. It was shared that prequalification testing is not always performed in a resource-limited setting and the product is typically available in other parts of the world (such as the US and EU) before a product makes it through the prequalification programme. If WHO were to further streamline its prequalification programme, it could improve the value of the collaborative procedure.

Presented with the three sub-themes, members discussed where the Industry Liaison Forum could make the most tangible difference and maximize the efforts of its multi-stakeholder

membership base. Following discussion with Forum members, it was agreed that further harmonization of processes was required to ensure that duplication and redundancies are removed and diagnostics reach the market quicker. It was agreed that another roundtable to tackle this specific issue would take place.

Annex 1: Presentations summary

Challenges and opportunities for IVD manufacturers – COVID-19 lessons learned
Tammy Steuerwald, Roche Diagnostics

COVID-19 has posed challenges in terms of time constraints, divergent emergency pathways from multiple jurisdictions and disparity in regulations within laboratory-developed tests, lab capacities and country-specific clinical trial requirements and in-country testing.

General recommendations:

1. Include COVID-19 lessons learned in normal practice.
2. Develop full reliance on the trusted work of reference authorities and recognized institutions across the total product lifecycle.
3. Ensure convergence of regulatory requirements, which will radically simplify regulatory processes and ensure high quality.
4. Make regulatory processes electronic, including signatures, labelling and even remote inspections.
5. Ensure inter-agency alignment, particularly regarding reporting requirements for positive testing.

COVID-19 lessons learned specific to lower- to middle-income countries:

1. For countries that rely on aid funding to purchase diagnostic products and when funding is contingent on purchasing a WHO prequalified product, it is recommended that aid programmes be allowed to use funding to purchase either WHO prequalified products or products approved by a reference agency (whichever comes first). This will allow countries to secure products as soon as they are approved by a trusted source.
2. WHO will recognize approvals, product changes and inspections from reference authorities, notified bodies or recognized institutions as this will further streamline its progressive programmes.
3. If additional testing is deemed necessary to speed up access, it is recommended that developers be allowed to use non-WHO-approved laboratories as long as they are accredited.
4. WHO will expand the scope of the abridged programme beyond high-risk products because medium-risk products are also highly scrutinized by reference agencies, and expanding the scope would allow tests, like COVID-19, to qualify for the programme.

Key takeaway lessons:

- Have internationally aligned national policies on regulatory reliance and put someone in charge of their implementation.
- Achieve strong alignment on requirements, including standards between WHO and national reference agencies.

Challenges and opportunities for IVD manufacturers in Southeast Asia (SEA) – COVID-19 lessons learned
Kate Qi, SG Diagnostics

Challenges for manufacturers in Southeast Asia
Regulatory bodies responsible for medical device registration in SEA are different in each country, and each regulatory body has its own list of criteria for the registration of medical device products. The lack of a common regional framework and guidelines for SEA makes this process complicated for manufacturers who wish to register a product regionally; registration entails that a product approved in one SEA country undergoes mandatory clinical studies in another country. The complexity in communication dynamics between the manufacturers and various regulatory agencies in the region, as well as the need to satisfy different country-specific criteria for the approval of medical devices, leads to large bureaucratic delays in the commercialization of products on the market in times of need.

Recommendations:
For manufacturing companies within or outside Southeast Asia, adopt a simplified process for product registration in all SEA countries. Do this by:

1. Establishing harmonized standards and criteria for medical device product registration
2. Increasing effective communication between regulatory bodies in SEA
3. Improving consistency in the quality of medical devices in SEA countries
4. Reducing product registration time without compromising on quality

Challenges and opportunities for IVD manufacturers in South Africa – COVID-19 lessons learnt
Averouz Maritz, Medical Diagnostech

The COVID-19 pandemic in 2020 led to development, regulatory approval and marketing challenges for medical diagnostics companies, especially in Africa:

1. Difficulty in accessing COVID-positive samples due to the lack of ethical clearance procedures and GCP certificates for diagnostic kits, delays in supply chains and lack of funding in South Africa impacted operations and company growth.
2. Challenges in communication between the South African Health Products Regulatory Authority (SAHPRA) and the national reference lab and slow regulatory actions impacted viral spread and late regulatory approvals of diagnostic kits.
3. The swift change of requirements for marketing of in vitro diagnostic devices led to increasing difficulty for local manufacturers to take part in the supply of diagnostic materials.
4. Non-existent import tariffs led to a negative impact on local companies.

As an example of the consequences of these challenges, SAHPRA approved the Medical Diagnostech (Pty) Ltd COVID-19 antigen only in December 2021.

Recommendations:

1. National regulating authorities should re-evaluate the approval process of locally manufactured products to withstand competition with imported ones. WHO prequalification requirements for locally manufactured products could be waived to reduce cost and bureaucracy.
2. Improve public-private dialogue around regulatory processes and national procurement regulations.

Generalizable lessons from the UK response to COVID-19
Mike Messenger, Medicines and Healthcare products Regulatory Agency

A total of 471 million COVID-19 PCR tests and 2.5 million weekly COVID-19 PCR tests were carried out in the UK between August 2020 and January 2022. Testing included a total of 230 million lateral flow tests (assisted and self-testing) and 8.5 million weekly lateral flow tests (as this included self-testing, often not reported, this number is deemed to be much higher). Early in the pandemic, the UK had to introduce parallel regulations to ensure that the quality and safety of the products available on the market were maintained.

Recommendations:

1. Ensure international harmonization and standardization, using the Medical Device Single Audit Program, the single audit framework and Medical Device Safety Reports. In the UK, there is a plan to look at domestic assurance processes whereby regulatory approvals from international partners are fast tracked through UK approvals.
2. Expand regulatory capacity within IVDs across all sectors.
3. Understand better the association between the biomarkers of interest, disease dynamics, populations of interest and clinical indications. This will allow deeper insight at an earlier stage into how different testing modalities change over time, supporting development of effective diagnostic testing strategies.
4. Target product profiles can support the industry in developing technologies.
5. Promote clinical reference standards to guide IVD performance evaluations. This can address the problem of, for example, the lack of clinical reference standards for infectiousness and the consequent difficulty of differentiating between people who are positive for COVID-19 and people who can transmit COVID-19.
6. Ensure early development of reference methods, materials and controls to allow for greater quality control and fast standardization of assays.
7. Support infrastructure for sample collection, sample distribution and platform trials.
8. Increase use of exceptional use authorizations to support the innovation for public benefit.
9. Carry out robust post-market surveillance and post-market performance follow-up plans to mitigate the risk of creating imperfect pre-market evidence. This could provide a model for other regulatory partners, either notified or approved bodies, to take similar approaches in the future.
10. Be transparent and involve the public in decision making to ensure trust and accountability.

11. Ensure global collaboration on IVDs to protect citizens.

Addressing the data gap to facilitate the regulation and uptake of IVD
Anafi Mataka, African Society for Laboratory Medicine (ASLM)

The regulatory and registration approval of diagnostics across Africa is lengthy and complex. Timelines of approval are incompatible with challenges brought by the SARS-CoV-2 pandemic, which compromises access to quality-assured in vitro diagnostics. Operations are also impacted by lack of human resources and lack of uniform registration processes across regions.

To provide the larger population with access to IVDs, countries need to perform an internal validation procedure over several months. In addition, dossiers require approval by programme committees, procurement processes, tender awards and supply chain challenges that might delay availability to end-users. The entire process could take up to 36 months.

Early availability of diagnostics during the Ebola epidemic in Africa could have prevented up to 70% of cases, potentially saving thousands of lives and several billion dollars. This also applies to the COVID-19 pandemic.

In Africa, SARS-CoV-2 testing saw quite fast evolution in terms of throughput by shifting from manual PCRs in February 2020 to automated procedures in March, followed by antibody and antigen testing in the second half of 2020. This resulted in the availability of large amounts of data, thus enabling quicker IVD regulatory approvals. However, lack of access to relevant information is still a problem for other diseases, such as HIV, tuberculosis and malaria.

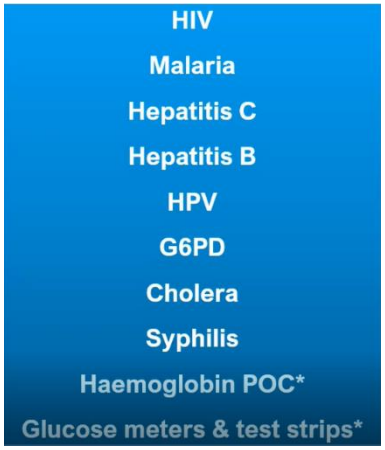
To bridge such a gap, ASLM enabled the creation of a Diagnostic Evidence Lab. This is a knowledge platform that provides national reference laboratories, national regulatory authorities and diagnostics stakeholders with key information from published studies on the technical performance of new in vitro diagnostic products, aiming to shorten the path for in-country validation. Future developments include the development of tools for implementation and scale up of new diagnostics and a better user interface to enable national regulatory authorities to download information.

ASLM noticed that current IVD regulatory process priorities are based on technology performance rather than focusing attention on disease burden. Some tests (TB, HIV and syphilis) might be approved but not offered in the regions where they are needed the most. When new tests are available, systematic data collection on the improvement of clinical and public health and their effectiveness (including cost) in comparison with the known standard of care should be performed. ASLM focuses on bridging such gaps and will continue to work with partners to shape the agenda towards the increased availability and access to context-relevant data on test performance across diseases, disease burden and cost effectiveness of adopted tests for African settings.

Overview of the WHO prequalification for in vitro diagnostics
Susie Braniff, In vitro Diagnostics Assessment, Regulation and Prequalification Unit, World Health Organization

WHO has been assessing and evaluating IVDs for over 30 years. In 2010, WHO introduced a more standardized approach, with the following range of diseases currently within the scope of prequalification (a star indicates diseases that WHO is in the process of developing specifications for):

Fig.1 Diseases within the scope of prequalification



The list is constantly updated, with TB the next to be added.

The aim of prequalification (PQDx) is to promote and facilitate access to safe, appropriate and affordable IVDs that are of good quality, targeting priority diseases and their suitability for use in resource-limited settings. PQDx undertakes a comprehensive assessment of individual IVDs through a standardized procedure aimed at determining if the product meets WHO prequalification requirements, which includes three components:

1. **Review of a product dossier**

   Manufacturers' documents are assessed through:

   a) The analysis of the relevance of the data in the dossier when it comes to claims of quality, safety and performance, and the appropriateness and design of the validation studies

   b) The review of evidence for completeness, accuracy and consistency of data over the IVD lifecycle, from initial product design through validation, manufacture, quality control and release onto the market

   Reviewers check to see that the PQ technical specifications for each particular analyte that is part of the prequalification scope are met. In this process, reviewers also evaluate whether the manufacturer has considered the use of the product in resource-limited settings. This indicates how robust the product performance is under different environmental conditions with different users and how stable the product is over time when environmental conditions are changing.

2. **Performance evaluation**

Performance evaluation is an independent verification of the performance of IVDs submitted for prequalification assessment, where:

a) Assays are challenged with a focus on their use in resource-limited settings and in the context of WHO guidelines.
b) A standard protocol is followed for the evaluation.
c) The dataset obtained complements the verification and validation data submitted by the manufacturer in the product dossier and findings in the site inspection.

Performance evaluation currently takes place in a WHO Collaborating Centre and/or a WHO Performance Evaluating Laboratory.

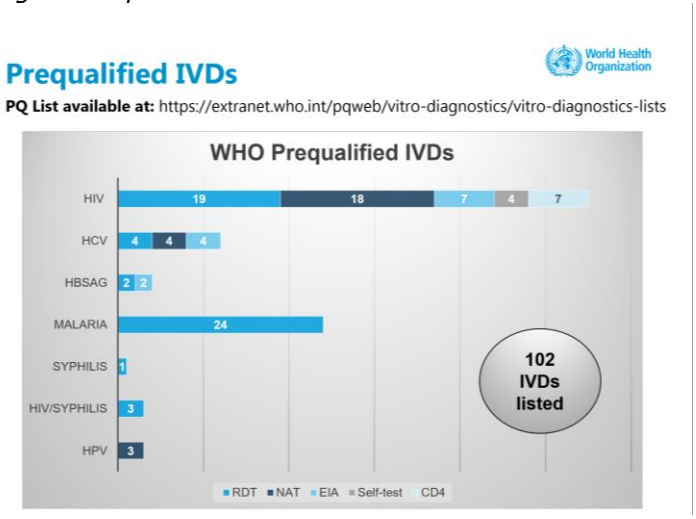
3. Manufacturing site inspection

Site inspectors will:

a) Look for evidence of a fully implemented quality management system based on international standards (IVD design and manufacture meeting ISO 13485 requirements and risk management meeting ISO 14971 requirements). Technical experts advise inspectors on particular areas that they should be focusing on when they are on site.
b) Consider the robustness of the product for WHO's intended settings and users, ensuring that the products undergoing PQ are in routine manufacturing and seeking evidence of sufficient capacity to ensure reliable delivery.

The prequalification decision is based on a successful outcome in all three components of the assessment. A final labelling review is performed and a public report is prepared and posted on the WHO website. At this stage, the product is added to the list of WHO prequalified products and it is eligible for WHO and UN procurement. Currently, 102 different IVDs are listed:

Fig. 2 Prequalified IVDs



Three very detailed reports are produced for each IVD that has been prequalified and are shared using a confidential online platform. The national regulatory authority (NRA) and IVD manufacturer that wishes to use the Collaborative Registration Procedures sign agreements

that allow the sharing of confidential data. Consequently, NRAs have access to the WHO assessment reports supporting the prequalification decision. This will avoid the duplication of effort and accelerate national registration. The goal is to shorten the pathway to national registration for quality-assured IVDs and optimize resources for participating countries.

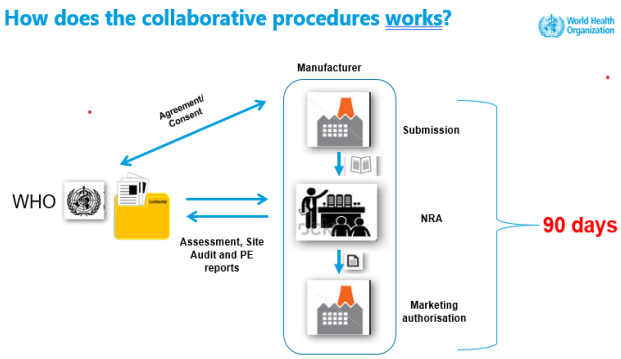
WHO Collaborative Registration Procedure: Accelerating national registration of WHO-prequalified in vitro diagnostics
Agnes Sitta Kijo, Facilitated Product Introduction Team, Regulation and Prequalification Department (RPQ), World Health Organization

NRAs may decide to make regulatory decisions based on their standard process by carrying out their own independent decisions based on their own reviews or may decide to accelerate their decision making by leveraging the work that has already been done by another NRA or trusted institution, such as WHO.

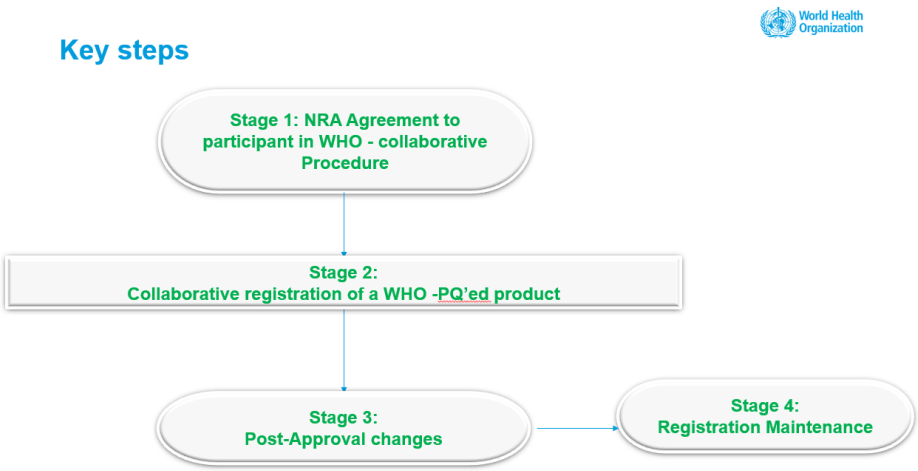
WHO, through the World Health Assembly Resolution 67.20 (2014), has provided flexibilities and opportunities in streamlining national regulatory decision-making processes by introducing specific concepts and advancing various initiatives to promote collaboration and regulatory cooperation framework; this improves the quality of the decision-making process while reducing workloads through joint reviews. WHO has been promoting the use of both the recognition and reliance concepts to assist regulators in executing their responsibilities more efficiently to ensure quick access to the needed tests. Two concepts promoted by WHO regulators use either recognition (acceptance of the final decision of another regulator or trusted institution) or reliance (taking into account the assessment outcome of another regulator or trusted institution in reaching its own decision). WHO has introduced various initiatives to facilitate implementation of the two concepts: Collaborative Registration Procedure (CRP); Stringent Regulatory Authority-Collaborative Registration Procedure (SRA-CRP); and Regional Networks (joint activities and work sharing).

The CRP accelerates national registration of diagnostics that WHO has prequalified. This is achieved through confidential sharing of information between the WHO Prequalification team and participating NRAs at the manufacturer's request. Confidential information that is shared by WHO includes dossiers and audit and performance evaluation outcomes.

CRP for diagnostics, as it is for other categories of products, incorporates elements of capacity building and regulatory harmonization. However, successful application of the procedures is highly dependent on the ability and willingness of manufacturers (the applicants), regulatory authorities and WHO to work together to meet public health goals. In vitro diagnostics that have been prequalified by WHO undergo thorough evaluation (dossier assessment and laboratory performance evaluation) and quality audit of the manufacturing facilities according to international standards to confirm their quality, safety and performance. However, such products must be approved for use by the NRAs of the countries for which market entry is sought. Repeating assessment, performance evaluation and quality audits of those products not only consumes scarce regulatory resources, but also unnecessarily prolongs issuance of market authorization and the time needed to make them available to healthcare clients.



In detail, CRP works as follows. After the manufacturer and the NRA sign and share an agreement and consent form, the manufacturer sends relevant information and the regulatory dossiers to the NRA while taking into consideration national-level requirements for commercialization. The NRA then submits all required regulatory documentation to WHO using confidential SharePoint. Technical file assessment and performance evaluation reports by WHO are then shared with the NRA, which can conduct an additional abbreviated review to confirm the sameness of the product before issuing market authorization. This process can take up to 90 days and should be an attractive framework to accelerate go-to-market approval of IVDs at the national level. WHO and the NRAs manage post-approval product changes and registration maintenance.



The pilot CRP study for IVDs, which was conducted in 2019, proved to be a great innovative mechanism that can accelerate registration of diagnostics and facilitate timely availability of IVDs with the following recorded benefits:

- Shorter regulatory approval times. IVDs can be registered within the accelerated timeline of 90 days.
- Reduced workload for NRA experts due to reduced need for in-country evaluations based on acceptance of WHO PQ reports.