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Regulatory work package

Feedback from global and in-country assessment

Summary of insights from interview with global regulatory experts on SRA pathway (1/2)

Takeaway

- The preferred regulatory pathway should be evaluated based on the **Quality Assurance policy of global procurement, as well as the in-country procurement requirements** in target countries where there is a significant domestic procurement.
- This is **not a comprehensive regulatory strategy**. What we provide in this deck are high level insights from stakeholder interviews. A detailed strategy is still required.

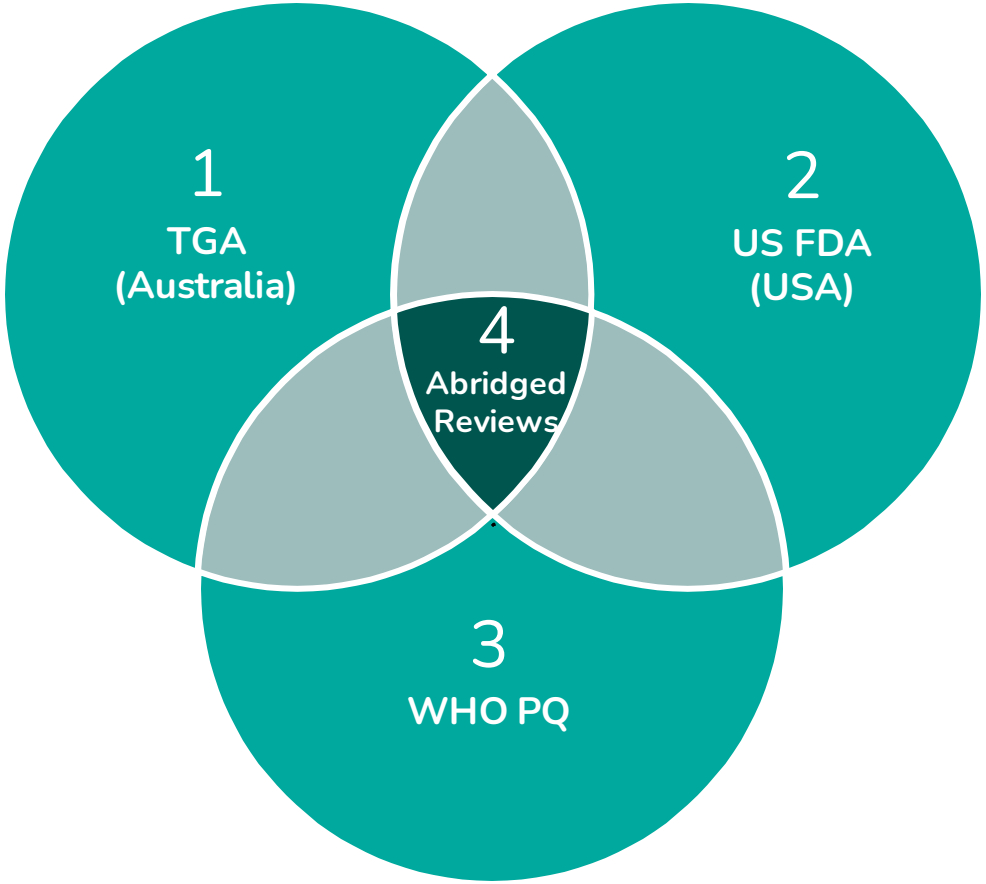
CATEGORY	INSIGHTS
Product Classification 	• GHDF countries will classify NAATOS as a Class C product • For Africa, the classification may be Class C or D product. It will depend on the country's interpretation of the IMDRF classification.
Design input 	• The rapid test format is typically prone to mistakes. It is important to reduce the amount of design features where humans need to make decisions. The current design of test looks simple, but it still requires a number of design features to make it look simpler – Dropping 6 drops of samples from the buffer tube increases chances of error. Consider inserting a line on the buffer tube to check that enough sample is collected. This is important as there have been issues in the past around evaporation and egress of samples from soft plastic – Limited space on the cassette to write patient ID number. This is important for use in a real-world setting – Traceability of sample to patient result will be critical. Think about how to expand the utility of the QR code for improving traceability, perhaps by the introduction of a reader – Visual reading prone to mistakes. Having a reader may also be beneficial – Material of cassette: Think of the green agenda and how this might be incorporated into the choice of material for the product

Summary of insights from interview with global regulatory experts on SRA pathway (2/2)

CATEGORY	INSIGHTS
Performance specifications	• As there is nothing else in its class, GH Labs will need to build the evidence that the product has clinical and economic utility even if it hasn't met the exquisite sensitivity threshold of a near point of care molecular lab test – Risk-benefit analysis: The argument would need to be made to regulators that while it may not have the exquisite sensitivity of a molecular lab test (e.g., Cepheid GeneXpert) and you might miss a small percentage of patients, it provides superior clinical and economic value because it is much cheaper and is able to pick up X more cases (in absolute numbers) as a decentralizable point of care test – Decreased sensitivity would not necessarily be an issue if we could demonstrate the clinical benefit. If it ends up missing too many cases, it may never pass regulatory approval – The case to be made will be similar to what was done for HIV self-tests. Once this evidence is available and the argument can be made to the WHO Guideline Development Group, it will become an acceptable class because it will actually be fitting an unmet clinical need
Regulating a platform technology	• Each device will be reviewed and registered separately but the clinical and verification study underpinning each submission will be the same – The lysis instrument and amplification devices will be Class A instruments which in most jurisdictions only need to be self-declared – The TB assay will likely be reviewed as a Class C device • The actual TB assay will be registered separately and will need full pre-market assessment and approval, but the evidence generated will be using all three devices together. The clinical and verification evidence will need to demonstrate that the lysis instrument and amplification devices do exactly what they claim to do when used as one unit • You could try to submit one dossier for all devices but the risk is that if something goes wrong with one device, you will need to recall the entire submission

The recommended stringent regulatory approval options based on the stakeholder interviews

GIVEN CHALLENGES WITH THE NEW EU IVDR REGULATIONS, WE HAVE EXCLUDED CE MARK AS A VIABLE SHORT TO MEDIUM TERM OPTION



1

- ✓ Earlier access to countries around Australia have high TB burden and recognize TGA. Examples are Indonesia, Papua New Guinea
- ✓ Not as expensive as US FDA
- ✓ Known by most jurisdictions and often accepted for abridged reviews
- ✓ Gives fast-track PQ approval
- ✗ Requires MDSAP (or ISO certificate from a notified body)

2

- ✓ ISO certification required. They have not transitioned to MDSAP which is a harder and more expensive QMS route to follow
- ✓ Known by most jurisdictions and often accepted for abridged reviews
- ✓ Gives fast track PQ approval
- ✗ Expensive
- ✗ If there is nothing else in class, it may go through a de novo classification request which makes it more expensive and significantly lengthens timelines

3

- ✓ Recognized and held in highest esteem by Ministries of Health in African countries. LATAM and Southeast Asian countries rely less on PQ
- ✓ Not as expensive as US FDA
- ✓ Qualifies for the WHO Collaborative Registration Procedure (CRP)
- ✗ PQ registration only would not be sufficient for an importation license in the markets with mature NRAs (e.g. India, Kenya, South Africa, Ghana)

4

- ✓ Qualifies for abridged reviews in the target countries using WHO PQ and SRA approvals. This allows for shorter NRA reviews
- ✓ The independent evaluation study results can be used for both WHO and SRA submissions simultaneously

The regulatory pathway will be determined by quality assurance policies of the buyer and/or importation policy of the recipient countries

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Essential Conditional

Buyer Archetype	Examples	Quality requirements for procurement or importation
A Global donor agencies and their implementing partners	• Global Fund, Stop TB Partnership, Unitaid, and their implementing partners	1 Prequalification by the World Health Organization Prequalification Programme (WHO PQ)*** 2 SRA approved for use by one of the regulatory authorities of the founding members of the Global Harmonization Task Force (e.g., EU, USA, Canada, Australia, and Japan)*** 3 Be recommended by the Expert Review Panel for Diagnostics (ERPD) for a time-limited period
B In-country buyers	• Governments tenders • Local NGOs • Private sector	4 The importation requirements of the National Regulatory Authority (NRA) in the respective countries takes precedence. This could be full marketing authorization or waiver for importation
C Programs of international organizations NOT funded by the global donors	• Philanthropic organizations e.g., Gates Foundation • International NGOs (e.g., KNVC, Aurum Institute, MSF etc.)	4 The importation requirements of the National Regulatory Authority (NRA) in the respective countries takes precedence. This could be full marketing authorization or waiver for importation 5 The procurement and quality assurance policy of the organization may take precedence in special cases, e.g., when an MoU exists between government and sender – An example is the MSF Host Country Agreement between MSF and governments

****Some countries will still require local marketing authorization despite having WHO PQ and/or SRA approval. These include South Africa, Brazil, India etc****

While WHO PQ pathway is well recognized by many low- and middle-income countries, it does not eliminate the need for in-country registration in countries with mature regulatory processes

Strengths

- ✓ Product becomes **eligible for procurement from UN agencies and large donors** (e.g., Global Fund and GDF). Without WHO PQ, the only other pathway is Expert Review Process which offers time-limited approval, and contingent on product being in PQ process
- ✓ Access to the **WHO Collaborative Registration Procedure (CRP)**
  - Faster NRA regulatory approval time. Average review time is 90 days
  - Streamlined NRA dossier development and submission process. The WHO PQ assessment and inspection reports are shared with NRA for abridged reviews. This reduces need for duplicative documentation.
  - Particularly useful for approval in countries that lack formal IVD regulatory processes

Weaknesses

- × In most countries, a **PQ product almost always needs to be registered by the NRA** in each country where it will be used
- × The PQ timelines are often longer than 365 days (**expect ~18months)**
- × The implementation of **CRP process for IVD is relatively untested**. Implementation is currently limited, and while it claims to have over 60 NRAs participating in the CRP process for finished pharmaceutical products, it is unclear how many of these countries are part of the IVD process since many countries do not have formal processes for IVD regulation.
- × **Individual NRA fees still apply** if CRP process pursued
- × The **CRP process only starts once WHO PQ is obtained**. They cannot run in parallel

Requirements and timelines

1. Full pre-qualification process

- Full dossier review + performance evaluation + manufacturing site inspection
- Timelines: 270 – 350 days (depends on performance evaluation pathway)
- Cost: US$17,000

2. Abridged pre-qualification process

Applicable if product has been reviewed and approved by a recognized SRA

- Abridged dossier review + performance evaluation + manufacturing site inspection
- Timelines: 100 – 180 days (depends on performance evaluation pathway)
- Cost: US$8,000

The ERPD process offers an interim procurement pathway while WHO PQ or SRA approval is underway, but it is accepted only by Global Fund and Unitaid

ERPD is an independent review of potential risks and benefits associated with procurement and use of diagnostic products that may have a high public health impact but have not yet undergone a stringent regulatory assessment

Strengths

- ✓ ERPD approval allows for **time-limited procurement for early product introduction activities** such as implementation or demonstration studies. Approved products are listed on the Global Fund catalogue and available for procurement through WAMBO
- ✓ The process is **free and quick** (3-months from submission to decision if all data requirements have been met)
- ✓ ERPD approval granted for 12months or until product is WHO PQ or SRA-approved. This means **12-month timeline can often be extended**
- ✓ In countries with no formal IVD and medical device regulatory process, an import waiver may be permitted for products with ERPD approval

Weaknesses

- × ERPD accepted **only by Global Fund and Unitaid**. The US government and other implementing partners do not consider ERPD as an acceptable regulatory standard
- × In countries with established IVD and medical device regulatory processes, **NRA approval required for importation of ERPD-approved products**

Requirements and timelines

Eligibility requirements

- The diagnostic product has a dossier already under review by the WHO PQ one of the founding members of the Global Harmonization Task Force (GHTF). If product not submitted to PQ or SRA body, the manufacturer can **provide a letter of commitment** to submit to WHO PQ or an SRA body after successful ERPD review

- The product is manufactured at a site that is compliant with the requirements: ISO 13485:2016 or an equivalent quality management system (ISO 13485) recognized by an appropriate body

The ERPD Risk Categories 1 & 2 will permit time-limited procurement by Global Fund and Unitaid. The other two categories offer little to no benefit

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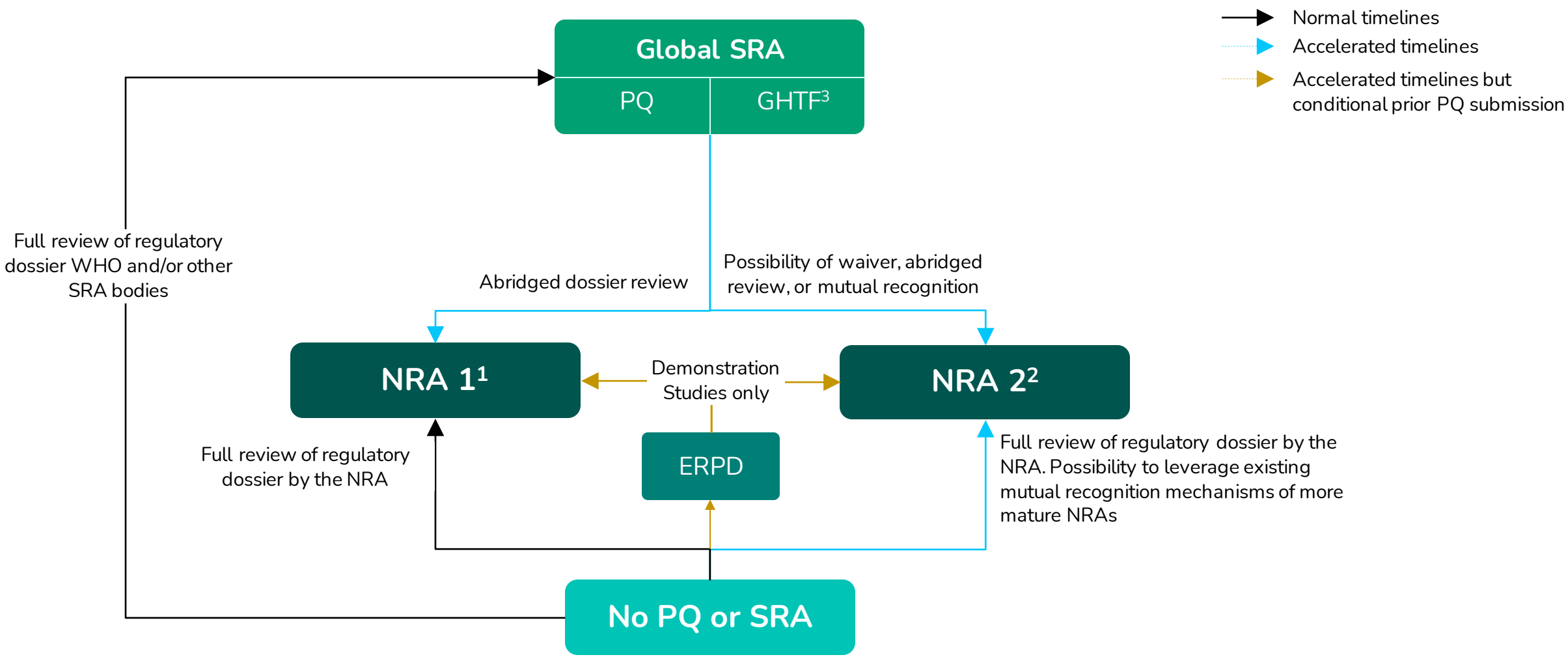
Risk Categories	Characteristics	ERPD advice / implications
1	A. Manufactured at SRA or PQ QMS compliant site (ISO 13485:2003 or equivalent) B. Adequate risk management and manufacturing controls C. Adequate evidence of analytical and clinical performance including data in the intended use settings and utilization of all relevant specimen types D. The submitted data supporting the claimed shelf-life on at least 3 production lots - a minimum of 6-12 months shelf-life can be assigned E. Labelling and instructions for use in line with internationally accepted standards	Product **may be considered for time-limited procurement if no sufficient WHO PQ or SRA-authorized products are available for use** at all levels of Health Care System It **can be listed on Global Fund list** of eligible product for procurement with validity period
2	F. 1a, b & e as above G. Adequate evidence of analytical performance, well controlled but limited clinical performance data in the intended use settings. Additional studies ongoing H. Submitted accelerated stability data on three lots, with acceptable variation. Real-time studies in process, no main concerns, data to support stability of at least 6 months	
3	I. The product is manufactured at SRA or WHO PQ Dx QMS compliant site(s) (ISO 13485:2003 or equivalent), except for some minor nonconformities that are being addressed J. Limited risk-management and control of the manufacturing processes K. Limited performance data available and/or the comparator reference method is not acceptable L. Submitted stability data on one or two batches and the potential for stability issues M. Labelling and instructions for use but insufficient customer support networks in low income countries	Product may be considered for procurement **only if there is no other option** and the risk of not diagnosing or monitoring efficacy of disease treatment is higher than the risk of using the product It will **not be listed on Global Fund list**
4	O. No sufficient evidence product manufactured in SRA and WHO PQ QMS compliant site P. The risk management and control of manufacturing processes are inadequate. Study design and evidence to substantiate clinical performance also inadequate Q. The current stability data is not satisfactory and labelling inadequate	Product **may not be considered for procurement under any circumstances**

Ideal outcome Not ideal

Schematic diagram of the regulatory pathways in Africa



1. NRAs with established IVD and medical device regulatory processes e.g.. South Africa, Kenya, India
2. NRAs with no formal IVD and medical device regulatory processes e.g., Botswana, Zimbabwe
3. Founding members of Global Harmonization Task Force (e.g., EU, USA, Canada)

Additional tips

1

- If the **performance evaluation study** is undertaken early enough, it may be used for WHO PQ and TGA submissions simultaneously which reduces cost and the need to commission two separate evaluation studies.

2

- Some ML3 NRAs in Africa have MoUs with less mature agencies for **mutual recognition and joint reviews**. For instance, Ghana FDA has MoUs with four NRAs (Rwanda, Senegal, Liberia, and Gambia). Under these agreements, products approved by Ghana receive automatic marketing authorization in the other four countries.
- Additionally, the MoUs enable joint reviews, with Ghana FDA coordinating the review of dossiers alongside other regulators and technical agencies as needed. This has been used for clinical trial reviews. And while this approach is untested for IVDs and medical devices, there is interest in piloting it .

3

- The **ERPD process** is an incredibly valuable mechanism to generate additional real-life evidence and early clinical experience via large-scale demonstration studies.
- There is currently an open expression of interest for TB NAAT-based technologies. **It would be important to get NAATOS on the radar of Unitaid so that they keep the expression of interest open, and they write NAATOS into the schedule of reviews planned for 2024**.

NRA Feedback

Kenya feedback | Perspectives from Kenya Pharmacy and Poison Board (PPB)

STAKEHOLDER PERSPECTIVE ONLY

Questions	Feedback
How would clinical and performance data be assessed?	• The product will fall under **risk classification C or D** (or Class 2B or 3 under US classification). This is because it is uses saliva samples which poses increased risk of contagion from sample extraction • The product will need to be **subjected to performance and validation studies in a Kenyan lab** to determine its sensitivity and specificity and overall robustness to the set standard. The performance validation study will be benchmarked / referenced to the specifications in the WHO technical specification standard for mycobacterium TB molecular detection methods • The sample prep kit is assessed with the other parts in one application
Are there benefits to having WHO PQ?	• The PQ process takes about 2years to get approval and it **does not guarantee automatic marketing authorization approval with NRAs**. In Kenya, you will still need to undertake performance and validation studies through Kenya PPB. This rule typically applies to countries with strong regulatory systems for diagnostics • For countries without formal regulatory processes in place for IVDs and medical devices, the **WHO PQ system is often preferred** • PQ products will go through an **abridged review with shorter timelines (3 – 6months) provided reference document is submitted to PPB**
Are there benefits to having SRA approval?	• Having SRA approval also **does not guarantee automatic marketing authorization**. The kits will still be subjected to in-country performance and validation studies. However, the product will be entitled to an **abridged review (3 – 6months) with shorter timelines provided reference document is available** • Without SRA or WHO PQ approval, **a full review will be warranted which has an approval timeline of up to 24months**
Do you provide registration waivers	• Registration requirements can only be waived in the event that the **product is for research use only, where there is no commercial viability;** or in the event of **emergency use authorization** • Importation for implementation of pilots/studies not eligible for waivers

> *"We have scenario now from the Global Fund for manufacturers of HIV1 & 2 to submit to WHO PQ or an SRA body but there is pushback from regulators in Africa because there is recognition of the need to satisfy the needs of the African regulators who have the mandate to secure the public health of their countries."*

South Africa feedback | Perspectives from South African Health Products Regulatory Authority (SAHPRA)

STAKEHOLDER PERSPECTIVE ONLY

Questions	Feedback
How would clinical and performance data be assessed?	• Covid-19, HIV and TB products are priority products for SAHPRA • The product will fall under **risk classification D**. Generally, classification will depend on the intended use and whether it is a screening or confirmatory test. The risk classification guideline is available here • Clinical evaluation studies will be required for marketing authorization. This should include a **usability study as well as data on humidity and its impact on clinical performance.** Application can be found here • The sample prep and other parts will be reviewed as one application
Are there benefits to having WHO PQ or SRA approval	• A product that has SRA approval from WHO PQ and/or one of the founding members of the Global Harmonization Task Force will go through a **reliance pathway (i.e., abridged or verified review, or recognition)** • If product is US FDA approved, the PMA route will be preferred to 501(K) clearance as it is seen as more stringent
What are the other requirements for Marketing authorization?	• No call up for registration of this class of IVDs • A local representative who is to be a natural person based in South Africa must be appointment in order to secure marketing a uthorization. Timelines are 8 – 24 months from submission to issuing a notification letter • **Validity of license is 5 years**
Do you provide registration waivers	• **Import waiver only available for clinical and validation studies**

> *"We have a scenario now from the Global Fund for manufacturers of HIV1 & 2 to submit to WHO PQ or an SRA body but there is pushback from regulators in Africa because there is no recognition of the need to satisfy the needs of the African regulators who have the mandate to secure the public health of their countries."*

Nigeria feedback | Perspectives from Medical Laboratory Science Council of Nigeria (MLSCN)

STAKEHOLDER PERSPECTIVE ONLY

Questions	Feedback
How would clinical and performance data be assessed?	• The product will fall under **risk classification C.** Draft guidelines can be found here • The product will need to be **subjected to performance studies in the lab.** The requirements can be found here. The cost of the evaluation changes with the different risk classes and peculiarity of the product, complexity of sourcing samples locally etc. • The sample prep kit is assessed as one application
Are there benefits to having WHO PQ or SRA approval	• Products approved by WHO PQ will go through an **abridged review with shorter timelines (90days). A shorter performance evaluation study is still required but the quantity of samples needed is less** (Only 30% of what is required for full review) • Without WHO PQ, a full review will be undertaken. This takes <4months from the date that dossier submission and evidence of payments is provided. The kits submitted for lab study will need to have 6 months shelf-life • **Products approved by SRA bodies go through a full review.** The report from the SRA may help with the submission.
What are the other requirements for Marketing authorization?	• A local representative who is to be a natural person based in Nigeria must be appointment in order to secure marketing authorization.
Do you provide registration waivers	• **No waiver permitted.** Provisional import permit may be requested for validation purposes while product is being reviewed. • Demonstration studies

> *For product brought in by donors and implementing partners, a local marketing authorization is required. MSLCN is mandated to safeguard the lives of Nigeria, and so products coming through all partners will still need to be subjected to performance evaluation studies before it can be imported. That is the Nigerian regulation*

Ghana feedback | Perspectives from Ghana Food and Drug Agency

Questions	Feedback
Under what risk classification would the product fall and what would the costs be?	• The product falls within **the Class II medical device category**. There will be additional documentation that needs to be submitted to validate the use of the device for the intended purpose. • Sample prep module would be assessed with the assay as one application. • Fee for advertisement $600 - $1,800; Fee for registration of the Class II – IV medical device - **evaluation & registration of $2000, and $100 per annum**. All costs are published here. All the required information can be found on the FDA Ghana website under Medical Devices.
How would clinical and performance data be assessed?	• Developer of the product needs to give the product specifications (the type of test, samples, sample prep, software requirements and how results are to be interpreted) for the FDA to verify and validate. The FDA will review and communicate back if there are any gaps or if any additional information is required. • Device platform will be **installed at the FDA appointed testing location** and then FDA will validate the performance on that device. FDA needs to be informed of the location and contact person at the site. **Once the on-sight verification is conducted, the report will be written**. • After additional requirements are met and the report has come out from the Quality Control Department with satisfactory results, then approval can be given
What would the timeline be for approval? What if the product has WHO PQ?	• **Less than 6 months** once all the data from the evaluation and assessment of the documentation is submitted. • **If the product has WHO PQ, it could take about 3 months.** To be submitted as part of the documentation for review, from which they will assess as part of the submission.
Do you provide registration waivers, e.g. research or small-scale demonstration studies?	• Product needs to **undergo in-country validation testing before imported by implementing partners**. No exceptions. • Declare intent to **request waiver for research or small-scale demonstration study** with FDA so that they can assess if this falls within their clinical trial department, which takes a different application process and ethics approval. This will be assessed and approved before a letter can be given to allow the study to be conducted in country

India feedback | Perspectives from WHO India, CHAI India and World Bank India

STAKEHOLDER PERSPECTIVE ONLY

Questions	Feedback
How would clinical and performance data be assessed?	• India's national regulatory body for pharmaceuticals and medical devices is Central Drugs Standard Control Organisation (CDSCO). • All In-vitro diagnostic kits and reagents are regulated under the Medical Device Rules, 2017 (MDR 2017) which are effective as of 01 Jan 2018, and which can be found on the CDSCO website. The product is likely to be classified as **risk classification B or C** under the guidelines. • The developer registers the product on CDSCO's online portal (known as the SUGAM portal) and applies for approvals for performance evaluation studies in India, which are carried out by ICMR • Even if such studies have been done in other settings, CDSCO/ICMR may require them to repeated in India specific settings. • Alternate route could potentially available: Class A and B devices after safety and performance has been established through published safety and performance data or through clinical investigation in the country of origin and a free sale certificate from the country of origin is furnished
Are there benefits to having WHO PQ or SRA approval	• A WHO pre-qualification would be a "good to have" but does not change the evaluation pathway for a new product
What are the other requirements for Marketing authorization?	• The developer needs to appoint **a local "Authorized Agent" from a set of approved bodies that coordinate with CDSCO.** Product registration and evaluation processes are carried by the test developer in partnership by the authorized agent. • Import licence will only be granted where, a free sales certificate has already been issued by the national regulatory authority or other competent authority namely Australia, Canada, Japan, European Union or the Unites States* • Timeline: New Registrations 10 – 12 month
Do you provide registration waivers	• **Not known**

> *"One thing that happened due to the pandemic was that new tests coming into the country are getting evaluated in a fast-tracked manner. The government is not really looking at WHO approvals anymore. First and foremost, they are giving preferences to products developed in India. And every new product has to be validated by ICMR now. "*

*CDSO In-Vitro Diagnostic (IVD) Medical Devices Frequently Asked Questions; Doc No.: CDSCO/IVD/FAQ/03/2022; https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/IVD/FAQs/CDSCO-IVD-FAQ-03-2022-.pdf