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NAATOS TB: REGULATORY ASSESSMENT AND STRATEGY - EXECUTIVE SUMMARY

GHL is developing a LAMP platform with a lateral flow immunoassay read-out for commercialization in Low- and Middle-Income Countries (LMIC). The first test developed on this platform is for the molecular detection of *Mycobacterium tuberculosis* (MTB) DNA. The purpose of the regulatory assessment and strategy is to assess the NAATOS LAMP platform from a global regulatory perspective and provide a regulatory plan with guidance to reach as many target jurisdictions in the most efficient and cost-effective manner as possible.

REGULATORY ASSESSMENT

The device assessment identified multiple options for the commercialization of parts of the NAATOS system including two individual instruments, one of which could be commercialized as a stand-alone instrument (Sample Preparation Module), pathogen-specific kits and two different systems: the NAATOS TB System (Sample Preparation Module, TB Assay Kit, Power Module) and a Sample Preparation System (Sample Preparation Module and a generic Bead Beating Kit).

Intended use statements suitable for regulatory purposes, aligned with WHO terminology as much as possible, were generated for the NAATOS TB System including:

- as an Aid in Diagnosis for pulmonary TB
- as a Systematic Screening (Active Case Finding) test, and
- as a generalized screening test.

Intended use statements for the Sample Preparation devices were also generated, and suggestions on selection of study sites in at least two WHO regions to generate a comprehensive picture of device performance in multiple LMICs was provided which could reduce the requirement for individual country pre-market studies and forms a comprehensive dataset that would be acceptable to WHO if a device using dorsal tongue swabs becomes eligible for WHO assessment.

The impact of Reference Standards on the NAATOS TB System was assessed. There are two areas where the regulatory pathway for the NAATOS TB System is not straightforward. The first is the use of dorsal tongue swabs instead of sputum as the specimen type, and the second is the desire to expand testing to atypical intended use populations including children, the elderly and sub-clinical (asymptomatic) individuals who cannot (easily) produce sputum.

- In the first case, Composite Reference Standards exist for pulmonary TB using sputum as the specimen type, but they vary by regulatory authority (WHO vs US FDA). A regulatory submission using dorsal tongue swabs must be certain to use the appropriate Composite Reference Standard that complies with the requirements of the regulatory jurisdiction being applied to. Performance data of the NAATOS TB System must be compared to the Composite Reference Standard as published (i.e. paired study specimens must be obtained; sputum for testing the reference standard component tests, and dorsal tongue swabs used for NAATOS testing). A substantial amount of

high-quality data will be required to support the use of a novel specimen type such as dorsal tongue swabs and it is recommended to obtain guidance from the regulatory bodies of interest to ensure alignment on performance expectations, reference standards and data analysis techniques including discordant resolution prior to performance study initiation.

- For the evaluation of TB infection in specific sub-populations of interest, both the lack of a defined Reference Standard and study size considerations will impact the ability to move forward to obtain these device claims. First, there is no consensus on a Reference Standard for individuals who cannot produce sputum (including children, the elderly, and asymptomatic individuals) as there is not sufficient clinical evidence of acceptable performance of diagnostics in these populations. Secondly, the study sizes required for generation of suitable data sets to assess sub-clinical infections, especially for the general screening claim, will be much larger than for an Aid in Diagnosis claim on symptomatic individuals, which can make it challenging for manufacturers to carry out well-designed studies that reach statistical significance.

With these considerations in mind, ACT-IVD has proposed to move forward with studies for the claims with the lowest barrier to market entry, specifically the Aid in Diagnosis claim. Once the device has achieved one regulatory approval, focus could move to addressing the challenges needed for claim expansion into the desired sub-populations as time and money permit. In addition, once the device has entered a specific market with demonstrated good performance, there may be government or other funded opportunities that become available to explore claim expansion driven for example by an individual country's Ministry of Health or an organisationlike FIND or PATH dedicated to improving access to novel devices in LMICs.

Throughout the assessment it was clear that a rigorous device risk assessment as per ISO 14971 has not been carried out, which is a requirement for device design and development specified in ISO 13485:2106. To best support the success of this and future projects, GHL should strengthen their QMS to become fully compliant with ISO 13485 Clause 7 (Design and Development) and implement a full risk management system during product design based on ISO 14971:2019. This will not only impact the success of the design with safety and performance features being identified and "built in" at an early stage but will be critical to support a future manufacturing partner as assay developers must meet these international regulatory expectations.

REGULATORY STRATEGY

For the regulatory strategy, the following target markets as provided by GHL were assessed: India, South Africa, Kenya, Uganda, Nigeria, Ghana, and Indonesia. Details on recognition and reliance procedures for these countries and the impact of WHO Pre-qualification on regulatory assessments and procurement are provided.

For the NAATOS TB System, Australia's Therapeutic Goods Administration (TGA) was selected as the initial regulatory authority for submission as it facilitates entry into key target markets, is recognized for procurement opportunities and WHO PQ abridged assessment (if/when available) and does not require studies performed on an Australian population. One option for a sequential submission plan was provided that would represent a multiple year strategy including a combination of parallel and sequential submissions.

For the Sample Preparation System, an application to either the US FDA or Australia's TGA would achieve the same goals for this device.

The regulatory strategy provides an efficient pathway for approval in the desired target markets based on current regulatory requirements. This represents the viewpoint and opinion of ACT-IVD but it is not the only pathway to market and other options may work as well or better for GHL and future partners. The final strategy will also likely require revision based on the choice of a manufacturing partner and their business objectives.

As the NAATOS platform is still in design and development and the final product may not be available for several years, and given the pace of changing device regulation this strategy and its recommendations will need to be revisited at the time of product readiness. It is also recommended that application of risk management principles to this project commence as soon as possible.

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Global Health Labs

NAATOS TB:

Regulatory Assessment and Strategy

DISCLAIMER

Information presented is collated from various websites and documents available for desktop review including regulatory authority websites, published reviews, MedBoard, and regulatory blogs. All attempts have been made to verify this information. However ACT-IVD recommends seeking local assistance when applying for regulatory authorization.

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PURPOSE

PROJECT OBJECTIVE

GHL is developing a LAMP platform with a lateral flow immunoassay read-out for commercialization in Low-and Middle Income Countries (LMIC). The first test developed on this platform is for the molecular detection of *M. tuberculosis* complex DNA.

STRATEGY

Assess the NAATOS LAMP platform from a global regulatory perspective and provide a regulatory plan with guidance to reach as many target jurisdictions in the most efficient and cost-effective manner as possible.

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ABBREVIATIONS

Abbreviation	Definition
DNA/RNA/NA	Deoxyribonucleic acid/ribonucleic acid/nucleic acid
IVD	In vitro diagnostic
GHTF	Global Harmonization Task Force
LAMP	Loop-mediated isothermal amplification
LMIC	Low and Middle Income Country
MTBC	Mycobacterium tuberculosis complex
NRA	National Regulatory Authority
RRA	Reference Regulatory Authority
TB	Tuberculosis
WHO; WHO PQ	World Health Organization; WHO Pre-Qualification Program

REGULATORY ASSESSMENT

In order to inform the regulatory strategy, the NAATOS Point of Care Nucleic Acid Amplification Platform was assessed as follows:

- All NAATOS platform components were evaluated to determine which could be considered as separate devices that may be registered and marketed independently versus as an entire system
- Specific intended use statements based on use cases presented in WHO Target Product Profiles for TB diagnostics were defined for the NAATOS TB System
- A workflow analysis for the NAATOS TB System was carried out to identify potential areas of concern to regulators that should be addressed in platform design and development
- Clinical study design considerations including reference standards to be considered to enable a smooth pathway to multiple regulatory approvals were compiled

DEVICE ASSESSMENT

The NAATOS Point of Care Nucleic Acid Amplification Platform was broken down for consideration to identify which (if any) components could be considered as separate, independent devices based on the regulatory definitions below.

Instrument: equipment or apparatus intended by the manufacturer to be used as an IVD medical device. *(GHTF/SG1/N045:2008)*

Kit: A collection of medical products including medical devices, and other products that are packaged together to achieve a stated intended use, being distributed as a single medical device. *(GHTF/AHWG-UDI/N2R3:2011)*

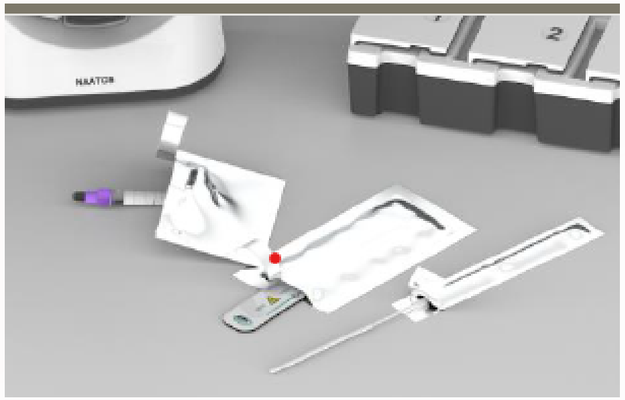
Ancillary Reagents: Reagents that an assay manufacturer specifies in device labelling as "required but not provided" in order to carry out the assay as indicated in its instructions for use; specified by catalogue or product number or other specific designation. *(FDA Class II Special Controls Guideline: MTB NAAT)*

System: A combination of products, either packaged together or not, which are intended to be inter-connected or combined to achieve a specific medical purpose. *(EU MDR Article 2)*

NAATOS SYSTEM

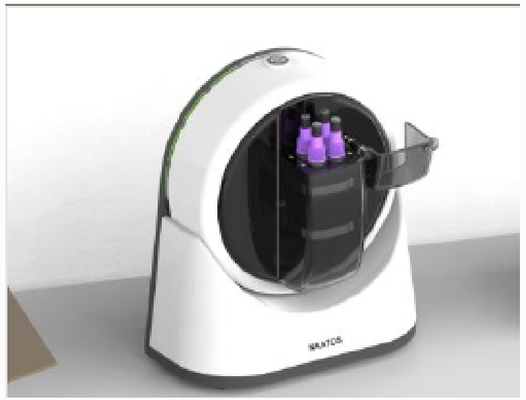
The first configuration is a NAATOS System that includes two (2) instruments (Sample Preparation Module and Power Module) and the pathogen-specific assay Kit

KIT



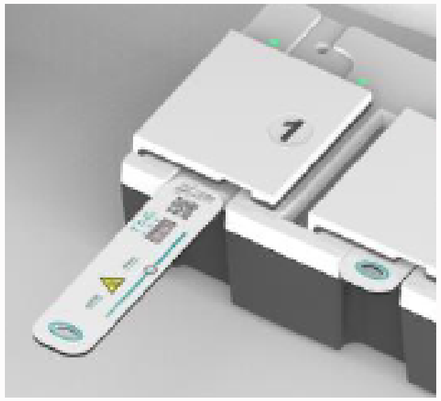
Includes:
Sample Preparation Vial (Bead beating tube with lysis buffer, glass beads, and an Internal Processing Control)
Pathogen-specific Consumable Test Device
Copan FLOQ swab (in sheath)

SAMPLE PREPARATION MODULE



Heated harmonic homogenization device to facilitate bead beating for up to four samples to support microbial cell lysis and nucleic acid extraction

POWER MODULE

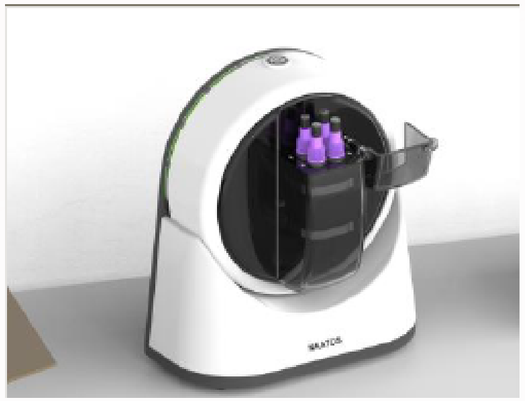


Single test device timer and dual zone heating system to ensure optimal LAMP performance + control reagent flow into nitrocellulose membrane for visual result interpretation

NAATOS INSTRUMENTS

Both the Sample Preparation Module and the Power Module meet the definition of an Instrument. However while the Power Module can only function with pathogen-specific NAATOS cartridges, the Sample Preparation Module could be used to disrupt cells of many different pathogens to generate nucleic acid for any subsequent amplification reaction.

SAMPLE PREPARATION MODULE



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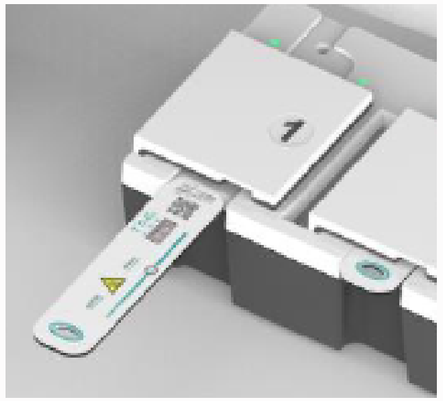


Single test device timer and dual zone heating system to ensure optimal LAMP performance + control reagent flow into nitrocellulose membrane for visual result interpretation

SAMPLE PREPARATION DEVICES

In addition to the Sample Preparation Module standing alone as an IVD Instrument, there are two options for the bead beating consumables:

1) Individual consumables to support bead beating using the Sample Preparation Module could be defined as separate ancillary reagents (i.e. individual part numbers for specific tubes, glass beads, buffer listed in the IFU as “Material Required but Not Provided) to enable other manufacturers to validate their own specific assay methods
OR
2) These consumables could be provided as one “Bead Beating Kit”. Note that in many jurisdictions the “Bead Beating Kit” format would be considered an IVD that would require its own submission or be subject to another grouping as a “Bead Beating System“ with the Sample Preparation Module.

	Sample Preparation Instrument	Bead Beating Consumables	Bead Beating Kit
Function	Heated harmonic laboratory micro-tube homogenizer	General laboratory consumables ordered individually as specified	Specimen homogenization and microbial cell lysis
Components	NAATOS Sample Preparation Module	Ordered individually by specific part number	One SKU that includes microtubes with dropper cap, glass beads and TE buffer
Intended Use	Mechanical disruption of microbial cells to generate nucleic acid suitable for nucleic acid amplification of clinically relevant targets	Not applicable to general laboratory use consumables	Isolation of microbial nucleic acid from clinical samples suitable for nucleic acid amplification of clinically relevant targets

SUMMARY

Multiple options exist for the commercialization of parts of the NAATOS platform as outlined below

Power Module	Sample Preparation Module	Bead Beating Kit (Generic)	Sample Preparation System	Pathogen-specific (here, TB) Assay Kit	NAATOS TB System
Individual instrument	Individual instrument	Generic consumables packaged as one SKU including: 1) microtubes with dropper cap, 2) glass beads, 3) Bottle of TE buffer	1) Sample Preparation Module 2) Bead Beating Kit (Generic)	1) Pathogen- specific microtubes with dropper cap (containing pathogen-IPC), 2) glass beads, 3) Bottle of TE buffer 4) Pathogen-specific NAATOS consumable test device	1) Sample Preparation Module 2) Power Module 3) Pathogen-Specific Assay Kit

Throughout this report options for the commercialization of the different IVD instruments, kits and/or systems will be presented. It is generally more cost effective to submit a registration application for an entire system than individual instruments and components, as the latter requires separate registration and/or conformity assessment fees for each device being registered. However there may be benefits to commercializing instruments and components separately, including the business objectives of a future manufacturing partner.

INTENDED USE

Clear intended use/indication(s) for use statements are needed to support a robust regulatory strategy. Once the various IVDs are identified, the intended use for each must be defined to continue on with the regulatory assessment and strategy development. An intended use statement must include key pieces of information. One device may have indications for use (i.e. multiple claims of performance in different intended use populations). Specifically for the NAATOS TB System, an assessment of the different device Target Product Profiles proposed by WHO is presented with a discussion of key aspects of intended use including intended user, intended use population, and specimen type, as well as a discussion of appropriate Reference Standards.

ALIGNMENT WITH WHO TERMS*

To generate clear intended use statements, the fit of the NAATOS TB System within WHO definitions of device classification was analysed.

Due to the system needing two instruments for device function, NAATOS is best defined as for use in Low Complexity and Near Point-of-Care settings.

The Intended User of the test will be a minimally trained health worker, although in some settings specimens may be collected by community care workers and transported to a health center for processing and test execution.

It is unlikely that test execution will be performed outside of a health center; therefore use of the system by unskilled community care workers is not considered in this report.

	Low Complexity	Near Point-of-Care (POC)	Point-of-Care (POC)
Intended Use Setting	Basic infrastructure (electricity) but no specific laboratory infrastructure. E.g. primary care clinics with or without labs, health posts	Does not require specific infrastructure; can be run in healthcare settings without labs	Does not require specific infrastructure; can be run in healthcare settings without labs
Test Specifications	Instrumented	Instrumented, battery operated	Instrument free
Intended User	Health worker with basic technical skills (basic pipetting, not requiring precision). <1 day training	Health worker with basic technical skills (basic pipetting, not requiring precision). < 1 day training	Unskilled (e.g. care givers or community care workers with minimal training). < 1 day training
NAATOS Fit	Yes	Yes**	No – test requires two instruments

*From "Public Consultation: TPP for a TB Dx Test for Peripheral Settings"
**Option for community swab collection with transportation to Near POC setting to run test

“TRIAGE” TEST

The WHO 2014 TPP and other peer-reviewed literature references a “triage test” to rule out TB if the “triage” test result is negative, and only individuals with a positive result would require confirmatory testing as part of a clinical diagnostic algorithm.

Inspection of the details of the TPP identifies either inconsistencies in the definitions of key parameters, or differences between “minimal” and “optimal” requirements that can be challenging to break down into a simple intended use statement. Key elements are presented to demonstrate the link between the TPP use cases and the intended use statements provided in this report.

Overall, the “Triage Test” includes elements of both the Aid in Dx and Systematic Screening intended use statements as reflected in the accompanying table. Therefore for the rest of the report, we will focus on the Aid in Dx and Systematic Screening claims.

	Triage Test	Aid in Dx	Screening Test	Systematic Screening Test
Intended Use Setting	"Health Facilities” from “community level” to “health posts and primary care clinics or higher levels of the health care system”	Near POC	Near POC	Near POC*
Intended User	“Community health worker and informal providers with a minimum of training” to “Staff trained to the level of auxillary nurses”	Minimally trained operator	Minimally trained operator	Minimally trained operator
Intended Use Population	“Adults and children suspected of having active (pulmonary) TB” and “patients with any symptoms or risk factors for active (pulmonary) TB”	Individuals 15 yoa or older with signs and symptoms of pulmonary TB	Asymptomatic individuals 15 yoa or older, or those with signs and symptoms not compatible with TB	Symptomatic or asymptomatic individuals of any age at high risk for TB disease
Sample Type	Sputum or non-sputum (preferred)	Dorsal tongue swab	Dorsal tongue swab	Dorsal tongue swab

*Option for community swab collection with transportation to Near POC setting to run test

DETERMINING INTENDED USE – USE CASE 1

Indications for use for the NAATOS TB System relevant for LMIC were generated with reference to the published WHO TPP for TB, records of requested public consultation for amendment of the TPP, and the WHO Consolidated Guidelines on TB Module 2.

Diagnostic Test/Aid in Diagnosis

The starting point for most tests/ test systems is as an ***Aid in Diagnosis*** for individuals with signs and symptoms of the specific condition of interest, as outlined below.

The NAATOS TB test, performed on the NAATOS System, is a visually read Loop-Mediated Isothermal Amplification (LAMP) nucleic acid amplification test intended for the rapid, in vitro qualitative detection of Mycobacterium tuberculosis complex (MTBC) DNA in dorsal tongue swab specimens. The NAATOS TB test is intended for use with specimens from patients 15 years of age or older with signs and symptoms of pulmonary tuberculosis. This test is intended to be performed by minimally trained operators in near point-of-care settings as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings. A positive result is suggestive of TB but not conclusive. The NAATOS TB Test does not differentiate between active or treated MTB infection and a diagnosis of TB requires confirmation by other tests or procedures.*

Required if sputum will be used instead of dorsal tongue swabs: *When used with sputum, the NAATOS TB test should only be performed in laboratories that follow safety practices in accordance with the WHO Tuberculosis laboratory biosafety manual and applicable state or local regulations.*

*Note that the definition of “adult” as being individuals 15 years of age or older has been applied based on the WHO Consolidated Guidelines for Tuberculosis (Modules 2 and 3).

DETERMINING INTENDED USE – USE CASE 2

Systematic Screening Test for TB Disease

The next intended use to be considered is related to the “Triage” test for evaluation of close contacts of confirmed TB-positive individuals; this intended use is related to what is often referred to in the literature as “Active Case Finding”.

The NAATOS TB test, performed on the NAATOS System, is a visually read Loop-Mediated Isothermal Amplification (LAMP) nucleic acid amplification test intended for the rapid, in vitro qualitative detection of Mycobacterium tuberculosis complex (MTBC) DNA in dorsal tongue swab specimens from symptomatic or asymptomatic individuals of any age at high risk for TB disease including: HIV positive individuals; individuals with close contacts to a diagnosed TB case within the last 12 months; and, individuals with a history of completed therapeutic treatment for TB in the last 2 years.This test is intended to be performed by minimally trained operators in near point-of-care settings.
A positive result is suggestive of TB but not conclusive. The NAATOS TB Test does not differentiate between active or treated MTB infection and a diagnosis of TB requires confirmation by other tests or procedures.. This test is suitable for use in appropriate multi-test algorithms.

The challenge for this intended use is the need to evaluate device performance in both asymptomatic (individuals with “subclinical” disease) and symptomatic individuals, which needs careful consideration for study design, as presented in following sections. A screening test will be required to be followed by a confirmatory test to confirm diagnosis prior to initiation of treatment, unless otherwise determined to be acceptable by a Ministry of Health or other public health unit.

DETERMINING INTENDED USE – USE CASE 3

Screening Test

The final intended use to be considered is a general screening test for screening of all members of a community, generally assumed to included asymptomatic (subclinical) presentation of the disease.

The NAATOS TB test, performed on the NAATOS System, is a visually read Loop-Mediated Isothermal Amplification (LAMP) test intended for the rapid, in vitro qualitative detection of Mycobacterium tuberculosis complex (MTBC) DNA in health care provider-collected dorsal tongue swab specimens from individuals 15 years of age or older who are asymptomatic or do not have signs or symptoms compatible with TB. This test is intended to be performed by minimally trained operators in near point-of-care settings. A positive result is suggestive of TB but not conclusive. The NAATOS TB Test does not differentiate between active or treated MTB infection and a diagnosis of TB requires confirmation by other tests or procedures. This test is suitable for use in appropriate multi-test algorithms.

A test having a screening intended use is desirable from a commercialisation aspect, especially as the first test in a multi-test screen-and-confirm algorithm, as it can represent a large number of tests used/sold.
However, similar to the Systematic Screening use case, the challenge for a general screening test is the need to evaluate device performance in asymptomatic (individuals with “subclinical” disease) which needs careful consideration for study design, and often requires very large sample sizes (especially in areas of low prevalence of disease) to determine appropriate test sensitivity.

PRODUCT CLAIMS AND STUDY DESIGNS

Once applicable intended use statements are defined, they can be analyzed to determine the scope and scale of the clinical studies that will be required to achieve each individual intended use claim. ACT-IVD has presented one route for claim determination and claim expansion. We have provided notes on specific study designs to be considered that will impact the final regulatory pathway selected for commercialization.

CLAIM EXPANSION

Each WHO use case and related claims requires a different clinical performance evaluation including different target populations (inclusion criteria) and numbers of participants. If possible studies may be run in parallel and submissions made to regulators once each data set is complete, or they may be run in sequence as funding is available. One path for claim expansion is presented, with considerations for study designs following.

1

AID IN DIAGNOSIS

Symptomatic subjects > 15 yoa
Primary claim for market entry

2

SYSTEMATIC SCREENING TEST

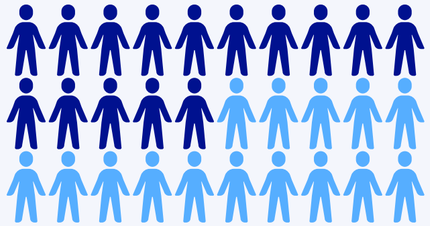
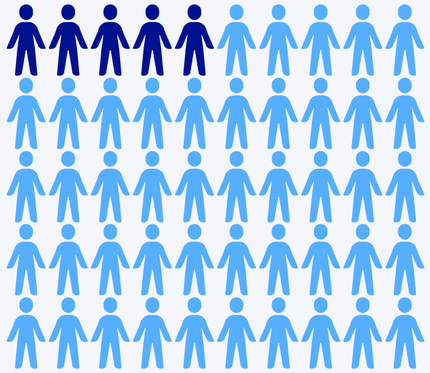
Individuals at high risk of TB (E.g. close contacts of any age)
Will include symptomatic and asymptomatic individuals

3

SCREENING TEST

Large scale community screening
Asymptomatic subjects > 15 yoa
Desirable claim as no POC Molecular TB test has been validated as a screening test to date

STUDY DESIGN CONSIDERATIONS

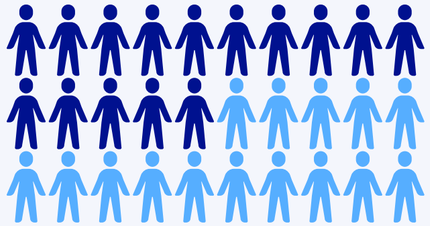
	Study Size	Study Cost	Study Population	Reference Standard	Points to Consider
AID IN DIAGNOSIS		$$$	Symptomatic subjects 15 yoa or older. # Subjects: • TSS-17: minimum 600 subjects (300 Pos/300 Neg) • US FDA: TBD based on power calculations	Sputum Composite reference standard maybe variable by region	• Sputum ***must*** be the reference pulmonary sample, even if tongue swabs are the desired sample type
SYSTEMATIC SCREENING		$$$$	Close contacts of any age. Symptomatic and asymptomatic (subclinical). # Subjects: TBD based on power calculations.	Sputum Composite reference standard may be variable by region	• Sputum ***must*** be the reference pulmonary sample, even if tongue swabs are the desired sample type • How to collect pulmonary samples (sputum) from asymptomatic subjects? • How to collect samples from those who can't generate sputum? • Different reference standard for asymptomatic subjects (e.g. chest radiography) vs symptomatic subjects?
(COMMUNITY) SCREENING		$$$$$$	Asymptomatic (subclinical) subjects. 15 yoa or older. # Subjects: TBD based on power calculations. *NOTE: For STI tests, US FDA historically has required detection of at least 30 new cases in the asymptomatic population.*	Sputum (??) Unclear (composite) reference standard	• Asymptomatic subjects • Will pulmonary sample collection (sputum) be required from asymptomatic subjects and if so, how? • Reference standard has not been defined for asymptomatic subjects/subclinical infection (e.g. chest radiography) and would need careful consideration and discussion with regulators

STUDY PLANNING

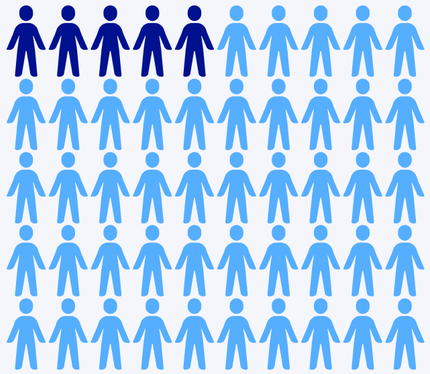
Study Size

AID IN DIAGNOSIS

SYSTEMATIC SCREENING



(COMMUNITY) SCREENING



Study Plans

- ACT-IVD can not estimate the cost of clinical performance studies as these are dependent on the country where testing takes place as well as the chosen clinical research partner or organization.
- It is expected that clinical performance studies are likely to be the major contributor to the cost of any market access activity.
- One way to maximize on the amount of data generated from one clinical study would be to run two studies in parallel at the same study sites. For example, one study could be designed to prospectively enroll symptomatic participants to obtain sample to support the Aid in Diagnosis claim, while a the second study running at the same time could be prospectively enrolling symptomatic and asymptomatic close contacts of known active pulmonary TB patients for the Systematic Screening study.
    - If the study protocols are carefully written, one participant could enroll in both studies (e.g. symptomatic close contact could meet inclusion criteria for both the aid in diagnosis study and the systematic screening study).
    - In this way some data would be obtained on asymptomatic subjects as part of the systematic screening study to inform if device performance is promising enough to investigate use as a (community) screening test before investing in that substantially larger and more expensive study.

STUDY SITE CONSIDERATIONS

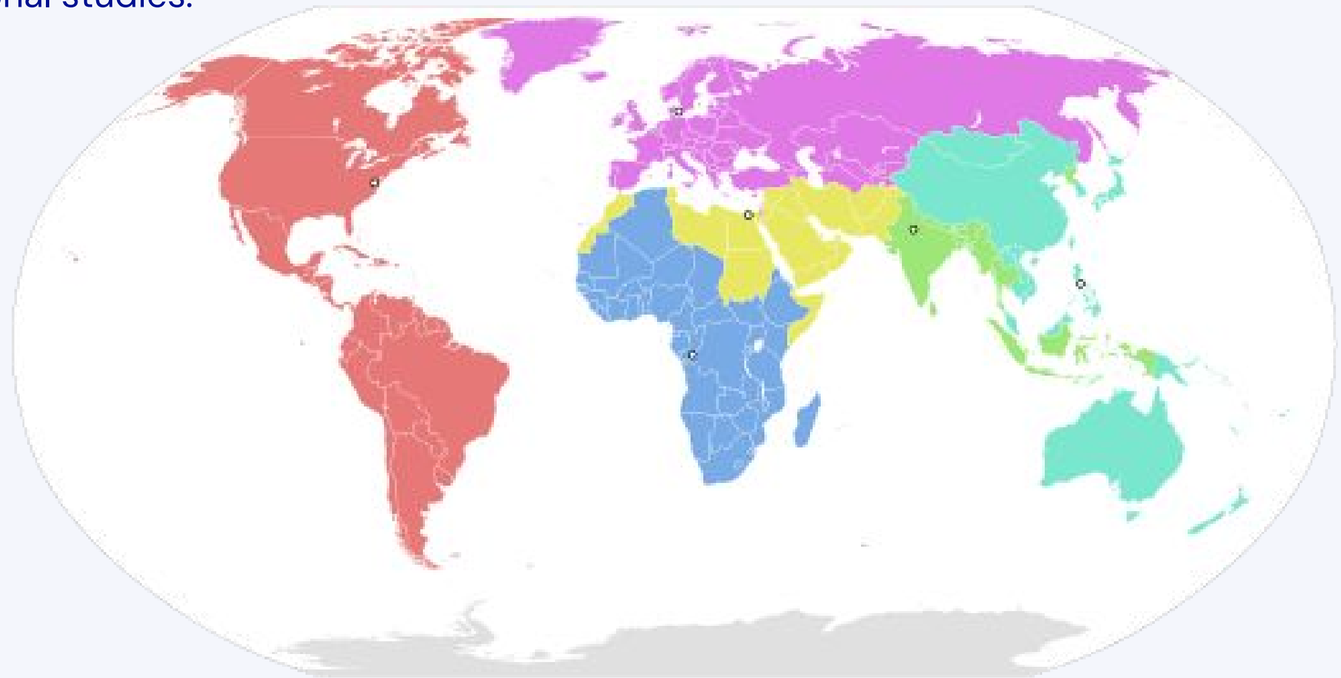
Reference Regulatory Agencies (RRAs) whose market authorisation can be leveraged for market entry in other jurisdictions, generally will want to see study sites selected to include multiple geographically different locations, including both a high prevalence (> 40 TB cases per 100,000 population*) and low prevalence (<20 TB cases per 100,000 % for TB populations*) populations (*WHO 2014 TPP).

For a test that is intended to be commercialized primarily in LMIC, regardless if WHO PQ is available/desired, it is beneficial to choose study sites in more than one LMIC. This will demonstrate device performance in relevant countries with the appropriate intended user and intended use population. Additionally if it is possible to select study sites in more than one WHO region (depicted below), if a WHO PQ pathway becomes available (which generally requires studies performed in at least 2 different WHO regions), this PQ requirement is already met and additional expensive performance studies are not required. Such a strategy also assists in demonstrating the broader ability to detect genotypic differences.

Regardless of where studies are performed, they must comply with the good study practices outlined in ISO 20916:2019, and meet all ethics requirements related to non-interventional studies.

WHO Regions:

- AFR (African Region)
- AMR (Region of the Americas)
- SEAR (South-East Asian Region)
- European Region (EUR)
- Eastern Mediterranean Region (EMR)
- Western Pacific Region (WPR)



ADDITIONAL CLINICAL STUDY CONSIDERATIONS

1. Some RRAs will expect that study specimens will be prospectively collected and immediately tested following the established device workflow as presented in the Instructions For Use. If there is an intention or need to utilize banked samples or prospectively collected samples that are retrospectively tested in batches, this should be discussed with the RRA in advance to ensure they understand and accept this study design. Be aware that there may be a limitation on how many retrospectively tested samples may be allowed (often between 30 to 50% of all study samples).

2. If clinical performance studies have been carried out only on a North American and/or European population it is recommended to source as many samples as possible from LMIC to demonstrate performance on some specimens with relevance to the desired target markets. Not having any data related to these target markets may trigger a need for in-country testing in LMICs where otherwise it may not have been required, adding to the expense and time to market entry.

3. African countries each have their own NRA, and (for some diseases) may require in-country studies in that specific country OR in a neighboring country with similar disease presentation, circulating strains, or disease prevalence, prior to approving an IVD. One mechanism outside of WHO PQ to smooth market entry would be to consider having study sites in representative countries in Africa (e.g. South Africa, one country in East Africa and one country in West Africa). This may be sufficient to pre-empt additional in-country testing, but is not guaranteed.

UNDERSTANDING REFERENCE STANDARDS FOR TB – 1

Terms related to Reference Standards and device performance are presented.

Term	Definition *(Reference)*
Comparator Test	The test to which device performance is being compared; may be either a Reference Standard or a Non-Reference standard.
Index Test	The test under evaluation. (*STARD-2015*); may also be called the "investigational test".
Predicate	A legally marketed device (in a jurisdiction) to which equivalence (of performance) is drawn. (*Modified from US FDA*). A "mixed predicate" would be similar to a composite reference standard, but including two or more devices that are legally marketed in a specific jurisdiction.
Clinical Reference Standard/Reference Standard	The best available method for establishing the presence or absence of the target condition; a "gold standard" would be an error-free reference standard. (*STARD-2015*). When comparing to a Reference Standard, device use must be on the approved test (including the validated specimen typed) as provided by the manufacturer, determined in the literature, or specified by the regulator (if no test for the specific condition/analyte has been approved).
Composite reference standard	A fixed rule used to make a final diagnosis based on the results of two or more tests, referred to as component tests. (*BMJ 2013;347:f5605*). Similar to the CLSI definition of Reference Standard - the best available method for establishing the presence or absence of the condition or characteristic of interest; can be a single test or method, or a combination of methods or techniques, including clinical follow-up (CLSI); see Testing Algorithm.
Testing Algorithm	A pre-determined order of testing to establish the true status (positive or negative, correct quantitation etc) of a specimen (Link)
Non-Reference Standard	A test used to compare an index test to that is not a reference standard. (*FDA Statistical Guidance*)

UNDERSTANDING REFERENCE STANDARDS FOR TB – 2

Terms related to Reference Standards and device performance are presented.

Term	Definition *(Reference)*
Diagnostic Accuracy	The ability of a diagnostic test to method discriminate between diseased and non-diseased subjects or between two or more clinical states (CLSI). By definition, must be determined against a Clinical or Composite Reference Standard.
Sensitivity	Proportion of those with the target condition who test positive with the index test; sensitivity must be determined against a Clinical or Composite Reference Standard *(STARD-2015)*
Specificity	Proportion of those without the target condition who test negative with the index test; specificity must be determined against a Clinical or Composite Reference Standard *(STARD-2015)*
Overall Percent Agreement	The proportion of subjects in whom the new test and the Non-Reference Standard give the same outcome *(FDA Statistical Guidance)*. Note that "Agreement" does NOT mean "correct".
Positive Percent Agreement (PPA)	The proportion of Non-Reference Standard positive subjects in whom the index test is positive. (FDA Statistical Guidance)
Negative Percent Agreement (NPA)	The proportion of Non-Reference Standard negative subjects in whom the index test is negative. (FDA Statistical Guidance)

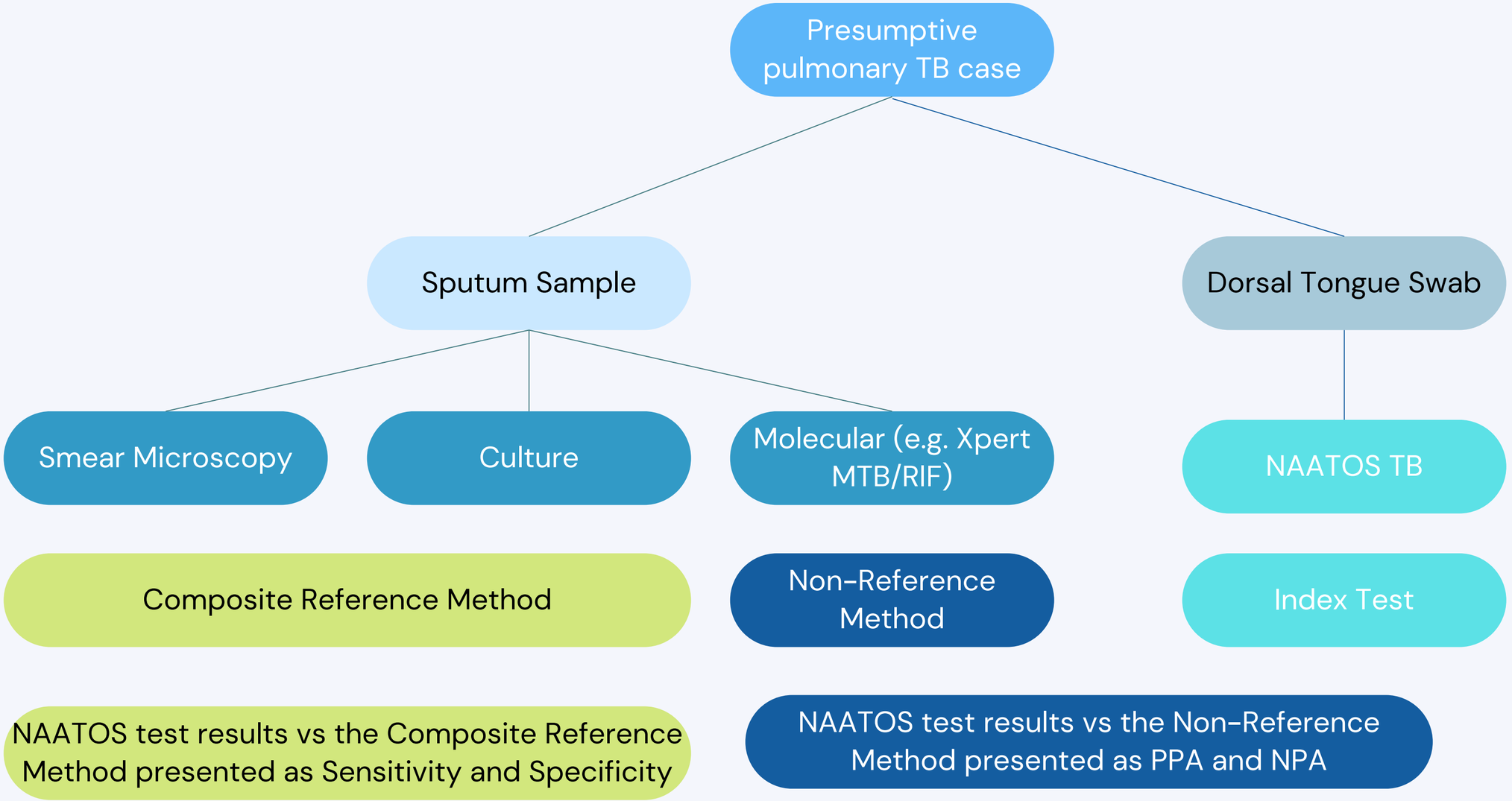
REFERENCE STANDARDS FOR PULMONARY TB – 3

1. There is no single Reference Standard for pulmonary TB as all individual methods (culture, smear microscopy, PCR) have drawbacks (e.g. culture and smear microscopy do not have optimal sensitivity; PCR can can detect residual DNA from a cleared infection which can impact specificity). Therefore a Composite Reference Standard is required for pulmonary TB. It is recommended that the choice of Composite Reference Standard is agreed with each major regulatory agency, ideally before commencing clinical performance studies.

2. While commonly available and often used, molecular methods including Cepheid Xpert MTB/RIF are Non-Reference Standards for pulmonary TB. While performance data may still be obtained for a device when compared to the results of a Non-Reference Standard, this data may or may not be accepted by a regulator as part of a regulatory submission and therefore the risks to relying on this data must be understood. Studies comparing performance of NAATOS TB to a Non-Reference Standard may only be expressed in terms of PPA and NPA.

3. In cases where there is no defined Reference Standard, the path to regulatory approval is challenging. The WHO Consolidated Guidelines themselves are not consistent in the recommended (Composite) Reference Standard for children, with Module 2 referencing symptom screen + chest x-ray, and Module 3 discussing use of Xpert Ultra in symptomatic children even though studies assessing the impact of Xpert MTB/RIF on outcomes in children are lacking. Overall, agreement would be needed in the global health community on how to clearly identify clinical evidence of infection in children, which has not occurred to date. While GHL and partners may choose to pursue studies on children and other vulnerable populations, this would be a challenging task in a field where many challenges already exist. It is recommended that GHL focus on the Aid in Diagnosis claim in order to gain market access. Once this is achieved, as outlined, additional studies may be performed to expand to the claims that have not yet garnered consensus support.

ILLUSTRATION OF REFERENCE STANDARDS FOR TB



IMPACT OF REFERENCE STANDARDS

- Choice of the Reference Standard and appropriate performance acceptance criteria is of critical importance for a successful IVD clinical performance evaluation.
  - If an extremely sensitive Reference Standard is required, there is the risk of false negatives on the investigational device which can impact Percent Positive Agreement. In contrast, use of a less sensitive Reference Standard could lead to a higher prevalence of False Positive results and poor Negative Percent Agreement.
  - The final choice of Reference Standard should be justified in the final report.
- In both cases, if an unrealistically high performance target has been set (either by the manufacturer or a regulator), a good device may not achieve the stated performance target and the device may be denied market access in spite of still being useful according to its intended purpose. Additionally, performance targets may vary according to the assessment body (e.g. US FDA versus WHO PQ).
- It is also important to note that Reference Standards may not be the same for all performance studies – they may vary based on regulatory requirement OR by study population.
  - E.g. for asymptomatic subjects, sputum may not be able to be obtained and therefore another clinical benchmark (like chest radiography) may be needed to detect subclinical TB.
- In addition, regulators also may differ in methods for reporting device performance including if they allow discordant resolution, which impacts device claims.
- It is recommended that GHL determine which Reference Standard they are going to use for each indication for use/study population to be evaluated, and that specific guidance obtained from the regulatory bodies of interest to GHL to ensure alignment on performance expectations, reference standards and discordant resolution ***prior*** to any performance study initiation. Information on two current reference standards (WHO vs US FDA) follow as examples.

COMPOSITE REFERENCE STANDARDS FOR MOLECULAR PULMONARY TB DETECTION FROM SYMPTOMATIC SUBJECTS

Regulatory Reference	Reference Specimen	Smear Microscopy	Liquid Culture	SRA-approved molecular method	MTBC Identification	Discordant Resolution
WHO TSS-17	Sputum	Mandatory Note: sensitivity can vary between 20-80%	Mandatory Note: sensitivity often < 80%	Not part of the composite reference algorithm but recommended; can detect live and dead bacteria	Immunochromatography or SRA-approved molecular identification	Discrepant results should be resolved as much as possible; however performance characteristics will be based on the original result
US FDA (MTB NAAT Respiratory Class II Special Controls)	"Respiratory Samples"	Not part of the composite reference algorithm; used for sub-grouping data only	Mandatory Note: sensitivity often < 80%	Mandatory OR Validated Direct PCR + Bi-directional sequencing	FDA-cleared molecular probes, HPLC, mass spectroscopy, or sequencing	Discrepant results may be investigated using a "resolver" test, but performance estimates must be based on the original result.

DISCUSSION OF DORSAL TONGUE SWABS

- NAATOS was developed for use with dorsal tongue swabs, based on published studies citing the promise of tongue swabs over sputum for pulmonary TB diagnosis.
- This was supported by the 2014 WHO TPP that identified an alternative to sputum be used to reduce infectious risk related to sputum collection.

→

- While studies have been published using tongue swabs, all regulatory approvals obtained to date have been generated using sputum as the sample type for pulmonary TB.
- Initial studies using tongue swabs on Cepheid Xpert had poorer performance than sputum, and concerns remain about the sensitivity of tongue swab methods

→

- In 2023 the WHO PQ pathway for TB tests was opened including POC molecular tests
- TSS-17 does not specifically include or exclude tongue swabs as a sample type; however the stated reference standard for pulmonary TB is smear microscopy and culture ***from sputum***

For consideration for the NAATOS TB System clinical study design:

- To access WHO PQ as a pathway for recognition and reliance mechanisms for entry into LMIC, sputum is currently the prevailing sample type described in the WHO Guideline Development Group documents for pulmonary TB. Therefore even though TSS-17 does not specifically preclude tongue swabs, if WHO PQ is desired it is recommended to carry out a preliminary performance evaluation of NAATOS TB in sputum (either as dipped swabs or concentrated sputum) versus dorsal tongue swabs. Both sample types should be collected in parallel from study subjects and, if not tested immediately, then banked for future evaluation (within limits of defined specimen stability).
- If tongue swabs will be the only or preferred sample type, NAATOS test performance ***must*** be benchmarked against an accepted Composite Reference Standard, which currently as per TSS-17 is sputum smear and culture, with parallel testing in approved molecular systems. Additional reference testing may need to be considered for this atypical sample type (Denkiger 2019). NAATOS should NOT be evaluated versus a molecular method performed in tongue swabs as this will be considered off-label use of a reference test and will not be accepted by a regulator as an appropriate reference standard.

ISO 14971:2019 AND RISK ASSESSMENTS

During the review of the documentation provided on the NAATOS platform to support this assessment, there are several areas where comprehensive risk assessments do not appear to have been carried out to date. For example, the use of tongue swabs as the primary (or only) sample type for the NAATOS TB System requires the careful generation of risk assessments as per ISO 14971:2019.

It is imperative that GHL carry out a comprehensive risk assessment as per ISO 14971:2019 of the NAATOS TB System overall and of each component of the system individually to identify and evaluate potential design changes as soon as possible, before it becomes prohibitively expensive to make any changes.

Every aspect of analytical performance (including cross-reactivity and interference studies), device workflow including pre- and post-analytical variables, and clinical performance risks (including human factors and usability) needs to be carefully addressed and risk mitigations introduced as much as possible into device design to generate a truly successful device.

ANALYTICAL PERFORMANCE CONSIDERATIONS

While the focus primarily remains on clinical performance evaluations due to the scope and scale (and cost) of these evaluations, attention must be paid to key analytical performance parameters. If these are neglected, it can derail a development program and result in large increases in time and costs for a device to be ready for field evaluations. Considerations for analytical performance studies and/or requirements based on ACT-IVD's experience follows. US FDA guidance for molecular TB tests is referenced alongside WHO TSS-17. Even if US FDA is not ultimately considered as part of the final regulatory strategy, it is helpful to understand how one RRA has assessed requirements for molecular TB device performance, as it may be used by other RRAs as a benchmark.

ANALYTICAL SENSITIVITY/LIMIT OF DETECTION

1. Limit of detection (LOD) is a critical performance parameter, even for qualitative tests. It should be assessed early in development and consistently applied to all subsequent studies. It is recommended to be familiar with CLSI EP17-A3 (quantitative tests) and CLSI EP12-A3 (qualitative tests), WHO TSS-17 and US FDA guidance to determine how GHL will define and determine LOD for all future analytical studies.

2. Both TSS-17 and FDA guidance state that while LOD may be presented as genomic copy numbers per mL, LOD must be established using CFU/mL from well characterized samples. US FDA further requires that CFU must be based on colony counts from actual plating and counting of bacteria, and not from a calculation based on an estimated cells/mL number - this is substantial additional work and should be justified in a risk assessment if it will not be carried out. If genome equivalents per mL is desired to be used, data must be produced to support the derivation of genome equivalents per mL to CFU per mL.

3. LOD must be determined using the entire test workflow (i.e. sample buffer can not just be spiked with a certain number of CFU or genome equivalents); studies must use the device from specimen preparation (i.e. a certain number of CFU are spiked into a negative sample matrix) through to results interpretation

4. US FDA and WHO differ on which studies (e.g. LoD, inclusivity, cross-reactivity) that require spiking of samples to a specific “xLOD” must also be confirmed to contain the amount of CFU (by planting and counting CFUs of the final spiked material) or genome equivalents (quantitative PCR on the final spiked material) they were intended to contain; this should be carefully assessed and choice of plating (or not) of inoculum documented in a risk asssessment.

ANALYTICAL STUDY CONSIDERATIONS

1

An area where US FDA and WHO do not agree is the targeting of levels of analyte for various analytical performance studies. For example, TSS-17 defines a Low Positive sample as being 3x LoD; however this is considered too high for the US FDA which requires a Low Positive sample to be 1-2x LOD. While this may not seem substantial, the worst case scenario is that the target regulatory body may choose to apply FDA Guidance and hold the test to the more stringent standard, which could mean multiple analytical studies (eg. precision, stability, interference etc) would need to be repeated, adding to time and cost. It is best practice to use the most challenging recommendation if possible.

2

Once LoD and the xLoD to be used to target performance panel levels is established, it is recommended to carry out preliminary specimen storage and kit lot stability studies as soon as possible to identify the storage parameters and time limits that must be applied for all future studies for both samples and kits/reagents during device development.

3

Un-instrumented, visually read tests have their own challenges, including the variability of visual acuity operator to operator in reading a test result. If not using a reader, it is recommended to develop a visual scoring guide for internal use only to be used in analytical studies and future QC purposes (e.g. + for a very faint test line, and ranging up to a +++ or ++++ categorization for strong positive results). This creates a level of traceability of test results (especially for stability studies where it can become obvious if signal is degrading over time), and can also immediately identify where variability near the cut-off of the test at the weak positive level may be a concern. Similarly, reporting of study results should use this semiquanitative approach (e.g. -, +,++,+++,++++). **However this scoring guide should be for internal use only**; ***clinical performance of the test should NOT use a scoring guide and instead a positive result be flagged based on the presence of ANY visible line.*** This does mean that specificity and the generation of visually clean negative results is key to device performance.

4

Invalid results matter; if invalid results are common it can destroy a test's reputation. It is best practice to identify and record the number of invalid tests in every preliminary device study as well as during the final analytical and clinical performance evaluations and to monitor the invalid rate carefully. If the invalid rate is unacceptable, it is recommended to carry out a root cause analysis as soon as possible to identify the contributing factors and if design changes are required.

PREPARING FOR TECHNOLOGY TRANSFER

1. The current regulatory landscape is increasing the scrutiny on design and development organizations. In order to best support a future manufacturing partner, GHL should implement design development and control procedures that are ISO 13485-compliant. Actual ISO 13485 certification would be a benefit to smooth future technology transfer pathways and regulatory approvals.

2. Challenge between-lot variability of raw reagents early and use this information to develop robust raw material specifications and acceptance criteria to pass along to a partner for smooth technology transfer. This is often overlooked and can lead to lengthy delays post-technology transfer if new reagent suppliers/new materials are needed.

3. Design and justify the analytical performance panels needed to assess precision and/or stability panels with associated acceptance criteria to support technology transfer. It is common that performance panels and targets are not established during transfer and this can lead to issues with regulatory submissions.

4. Unless otherwise considered and justified by GHL, preliminary performance studies can be carried out during the design and development phase of a product lifecycle, but formal analytical verification and clinical validation studies should only be carried out on the final, locked device design, and preferably after scale-up and transfer to the selected partner for manufacturing, to avoid having to incur change notification costs to applicable regulators.

WORKFLOW ANALYSIS

The overall NAATOS workflow was analyzed in detail to identify areas where pre- and post-analytical variability could impact NAATOS performance. The identified areas of concern would commonly have been identified by a robust usability risk assessment and should be considered for risk mitigation prior to device design lock

NAATOS WORKFLOW ANALYSIS

Step 2

Collect tongue swab

- Evaluate specimen storage stability claims to include the worst case scenario/longest realistic storage time and temperature (e.g. community screening).
- "Dry" swabs may be more stable and easier to use/store.

Step 4

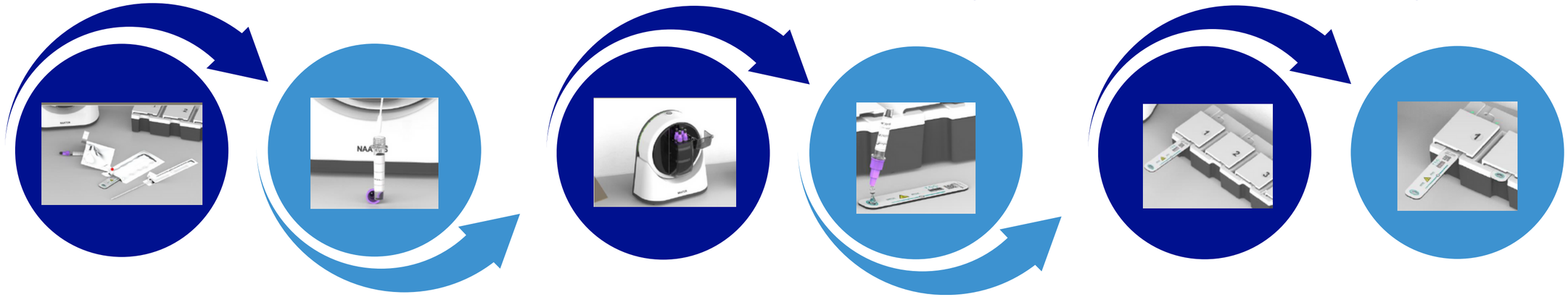
Add processed sample to test cartridge

- Risk of adding incorrect specimen (wrong individual) to test device must be addressed.
- Evaluate the impact on performance if the entire sample is added vs one drop etc.

Step 6

Read and report results

- 3 line format of results is not typical - may generate incorrect result interpretation.
- Visual reading of results can impact performance.
- Manual recording and transcription of results is error-prone.



Step 1

Open and Label Consumables

- Open pouch stability for sample prep tube and cartridge required
- Swab should only be opened immediately before use to prevent contamination
- Swab type/vendor can impact test performance (significant change)
- Risk of mis-labelling tubes/cartridges must be addressed.

Step 3

Process Sample

- Evaluate if there is any impact to lysis and yield if one vs four tubes are loaded, or position of the tube in the module.
- Once processed, need to identify if the sample must be used immediately or evaluate processed specimen storage stability.

Step 5

Run test

- Timing will impact test results; source of error if the cartridge can be pulled out at any time or if there is no timer

RECOMMENDATIONS

The following points were identified as needing further consideration. They may impact device workflow, performance studies (analytical and/or clinical), or kit/device production by a partner.

01

""Wet" vs "Dry" swabs
To avoid the need to validate storage of specimens as both "dry" swabs (replaced in the sheath immediately after sampling) and "wet" swabs (head snapped off and stored in the sample preparation tube) it is recommended to define the tongue swab specimen type as "dry" swabs only. The swab should only be transferred to the sample preparation tube immediately before sample processing and running of the test.

02

Different types of swabs
Swabs can dramatically impact device performance. The current swab is a Copan FLOQ swab. All analytical and clinical validation studies must be performed with this swab. If another swab is to be used in future (e.g. Puritan swab), its use must be validated by performing a subset of analytical and clinical performance studies as determined by a risk assessment.

03

Changing swabs after regulatory approval
If the swab is to be changed after regulatory approval, it must be assessed to determine if it is considered a significant change for each regulator and a change notification submitted PRIOR to implementation of the new swab. The test kit can not be sold with a different swab until approved by each regulator. If versions of the kit will be sold with different swab types, traceability of kit format and impact on UDI must be considered

04

Test interpretation and connectivity
As the system already requires two instruments, it would be optimal to convert the power module to an actual reader. This would improve usability and minimize errors related to misinterpretation of test and control lines and minimize risk of false negative results on low positive samples. If the reader could not transmit results, at minimum it should have a means to print out patient identification and test resuts.

REGULATORY ASSESSMENT

CONCLUSIONS

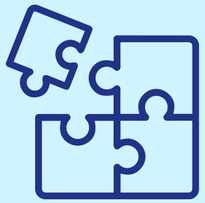
- There are multiple system/test/instrument options for commercialization of the NAATOS instruments and MTBC test that may be of interest to GHL and/or to a future manufacturing partner who will also take responsibility for sales and distribution.
- An area of interest is the use of a novel sample type (dorsal tongue swabs). Care and attention must be paid to the specific studies and Reference Standards required to validate the use of this sample type that will be convincing to both RRAs and NRAs in target countries.
- The NAATOS platform and the TB test includes interesting technology relevant for LMIC deployment. However it is appears that detailed risk assessments for the individual instruments and the TB system as a whole have not been carried out. This has resulted in a molecular diagnostic test system with many of the same issues that has plagued visually read rapid tests for decades. GHL is strongly encouraged to carry out a comprehensive ISO 14971 risk assessment as soon as possible to identify key risks that must be carefully considered before design changes would become prohibitively expensive. Key among these is the visually read nature of the test and lack of a robust method for results recording and communication.
- ACT-IVD recommends that the ongoing device design and development should follow a well-defined design control pathway and is informed by robust risk management processes; these are processes that would be covered by a certified ISO 13485 Quality Management System. It is worth taking the time at this stage of development to assess critical product risks (e.g. can users in the field visually detect samples at the LoD, or will sensitivity be compromised if the test continues to be visually read) now.
- While preliminary analytical and clinical assessments may be carried out to determine the ability to progress to later design phases, ACT-IVD cautions that any analytical and clinical validation studies should only be carried out on locked device designs after scale-up and transfer to a suitable manufacturing partner.

REGULATORY STRATEGY

NAATOS TB SYSTEM

Act-Ivd

WHAT IS A REGULATORY STRATEGY?

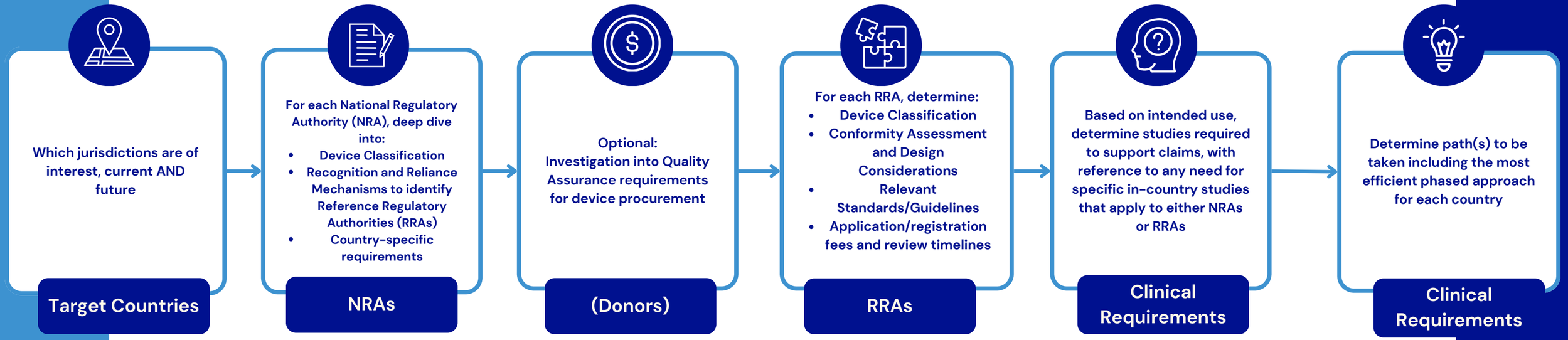


A regulatory strategy aims to find the most efficient pathway for market access by first thoroughly understanding the regulatory requirements and pathways specific to each target market.

It involves assessing the classification and risk level of the IVD based on its intended use, choosing the appropriate regulatory submission route, and leveraging any available expedited programs or harmonized standards.

By planning for streamlined documentation, clinical trials, and post-market surveillance, the strategy minimizes delays and reduces costs while ensuring compliance and patient safety.

DEVELOPMENT OF A REGULATORY AND PROCUREMENT STRATEGY (RPS)



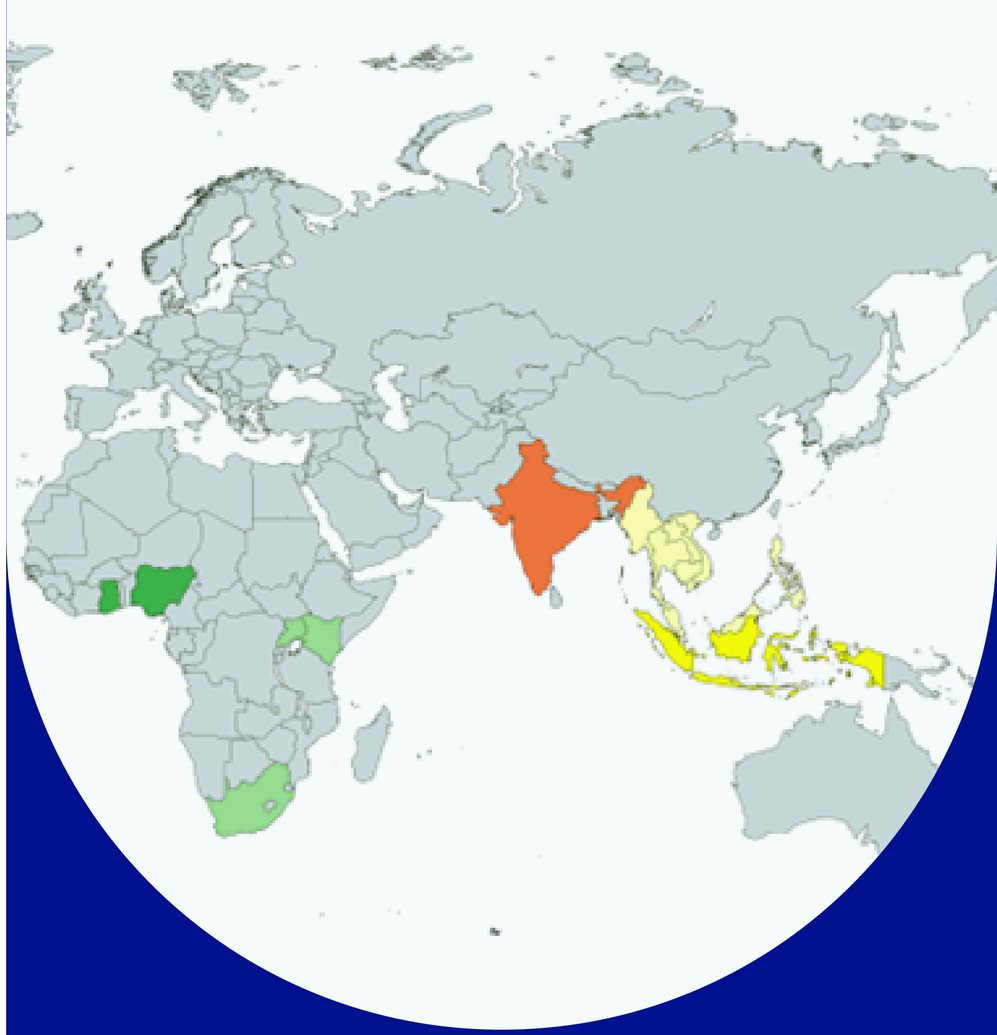
- The primary objective of a RPS is to generate a comprehensive plan outlining the steps necessary to achieve and maintain regulatory approval and compliance for a device.
- The secondary objective is to assess the quality requirements for procurement by large donors (e.g. The Global Fund, PEPFAR) that are attractive to device manufacturers for market access and sales purposes. In these policies, quality is generally defined by a product's regulatory status with respect to market authorisation by defined Reference Regulatory Agencies (RRAs) and/or WHO assessment or endorsement.
- It includes understanding and addressing regulatory requirements, clinical evidence, quality systems, and market-specific considerations to ensures that IVDs meet all legal and safety standards before being marketed and used in healthcare settings.

Act-Ivd

TARGET COUNTRIES

Target countries for the Regulatory and Procurement Strategy for the NAATOS TB System include the following, representing a geographically diverse set of countries with a high burden of tuberculosis:

- India
- South Africa
- Kenya
- Uganda
- Nigeria
- Ghana
- Indonesia
- Other countries in SE Asia



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REGULATORY REQUIREMENTS FOR TARGET COUNTRIES

An overview of requirements for market entry in each target country by their respective NRA and identification of recognition and reliance mechanisms is presented.

Using the intended use statement and pathways identified in the previous sections, a summary of the specific submission requirements of Target NRAs is presented.

The intended use drives the NRAs market authorization requirements given that the higher the risk of the device to a patient, user or the population, the greater the oversight (and requirements) in both premarket assessment and in the post-market setting that a regulator often applies. Many NRAs have adopted the 4 level risk classification approach, which assigns low risk IVDs in the lowest class (eg Class A or 1) and the highest risk IVDs in the highest risk class (Class D or 4). This approach has been supported by the WHO.

Detailed tables on the NRA requirements are presented in Appendix 1; key points are summarized in the following pages.

UNDERSTANDING THE REGULATORY AND PROCUREMENT LANDSCAPE

Regulatory Authorization

Regulatory authorization provides a legal basis for placing a product onto a single market. A country's National Regulatory Agency (NRA) has 3 options for market access. Sometimes a blend of these 3 options is used:

1) Standard Procedure

The NRA will use its own due diligence activities to assess if the device meets its internal requirements for market access. These are generally based on the relative risk of the IVD as identified by the NRA's risk classification system.

2) Recognition and Reliance Procedures

Some country's regulations apply principles of **recognition and reliance** to give products access to their regional market.

- ***Recognition:*** When a regulatory authority accepts the regulatory decision of another authority (also known as the Reference Regulatory Authority or RRA) "as its own" decision.
- ***Reliance:*** When a regulatory authority takes into account the work products of another authority/RRA (e.g. inspection reports, scientific assessment reports) to inform their own decision. Their ultimate decision may be different than the initial authority.

3) WHO PQ and Recognition and Reliance

In LMICs, many countries also refer to products listed on the WHO website following a WHO Quality Assurance (QA) procedure. The most comprehensive of these is WHO Prequalification (PQ). This can result in expedited processes and prioritization by that jurisdiction's regulatory agency.

Procurement

Regulatory authorisation by the target countries provides a legal basis for placing a product onto that single market, but may be insufficient to facilitate procurement by large donors.

RRA and WHO PQ For Procurement

Authorization by a mature regulatory authority can lead to an abridged assessment by WHO and also by multiple LMIC NRAs. In addition, it is often a requirement of a donor's procurement policy. As such, authorization by these RRAs could have an indirect benefit on expediting both regulatory approvals and product sales

WHO PRE-QUALIFICATION

In many Low and Middle Income Countries (LMICs), these jurisdictions also refer to products listed on the WHO website following a WHO Quality Assurance (QA) procedure when deciding on market access.

WHO authorization is often a requirement for market uptake in an LMIC.

The most comprehensive of WHO assessments is Prequalification (PQ). WHO PQ can be expedited if there has been prior stringent regulatory assessment by an RRA.

Not only is WHO assessment an often oblique market access requirement, but in some jurisdictions it will result in an expedited regulatory authorization. It also assists in procurement strategies that can be of interest to commercial partners.

While a PQ pathway is open for TB diagnostics, the published technical specifications (TSS-17) focusses on respiratory samples and do not discuss tongue swabs as a sample type; if WHO PQ is desirable to GHL or to a manufacturing partner and if sputum is not a suitable sample type for on the NAATOS TB System, a pre-submission is recommended with WHO PQ to discuss if a device that only uses dorsal tongue swabs as a sample type would be accepted by WHO PQ, and if yes, what evidence requirements would be required.

As WHO PQ can be leveraged for regulatory authorization in LMICs as well as procurement, and as it involves a stringent evaluation of an IVD, it is referenced as relevant throughout this strategy.

For more information on the WHO PQ process, refer to Appendix 2.

For more information on procurement processes, refer to Appendix 4.

REFERENCE REGULATORY AGENCY (RRA) SUMMARY

RRA	NRA							
	India	South Africa	Kenya	Uganda	Nigeria	Ghana	Indonesia	Singapore (SE Asia)
Australia TGA								
Health Canada								
US FDA								
EU								
Japan								
WHO PQ		*	*	*	*	*		

Based on the risk classification of the NAATOS TB System in each target market as presented in Appendix 1 the applicable RRAs for each NRA was compiled. This is the first step to form a strategy that considers accelerated access in the majority of the identified target countries.

The table identifies that approvals by the Global Harmonization Task Force (GHTF) founding members (i.e. the regulatory agencies of Australia, Canada, USA, EU and Japan) are of immediate interest.

*As identified in Appendix 1, WHO PQ is an option for the same purpose, based on a potential collaborative registration procedure for accelerated registration if a device achieves WHO PQ.

REGULATORY REQUIREMENTS FOR REFERENCE REGULATORY AGENCIES (RRA)

Building on the understanding of the Target NRA QMS requirements and the available Recognition and Reliance Mechanisms, requirements for RRAs of interest are now assessed. As noted, these include the GHTF Founding Members; however due to the requirement of translation of all technical documentation into Japanese, this survey does not cover Japan MHLW requirements. In addition, due to the interest in Indonesia and South-East Asia, Singapore has been included as an important RRA for the ASEAN countries.

While approval and commercialization of the entire TB System is the ultimate goal, as presented in the Regulatory Assessment there is value in offering individual instruments or other components as separate devices/systems. Therefore the risk classifications for all possible devices/systems were evaluated in the relevant SRAs. Summarized results follow; details are presented in Appendix 3.

SUMMARY OF RRA RISK CLASSIFICATIONS

	WHO/IMDRF	US FDA	Health Canada	Australia TGA	EU IVDR	Singapore HSA
NAATOS TB System (TB kit [swab, sample processing tube and consumable test device], Power Module and Sample Prep Module)	Class C	510(k): Class II, Special Controls Or De Novo	Class III	Class 3	Class C	Class C
NAATOS TB Kit	Class C	510(k): Class II, Special Controls Or De Novo	Class III	Class 3	Class C	Class C
Sample Prep Module	Class A	Class 1, 510k exempt	Class I	Class 1	Class A	Class A
Individual Bead Beating Consumables	General laboratory product (non-IVD); NA	Ancillary reagents - no submission required	General laboratory product (non-IVD); NA	General laboratory product (non-IVD); NA	General laboratory product (non-IVD); NA	General laboratory product (non-IVD); NA
Bead Beating Kit (microtubes with dropper cap, glass beads, bottle of TE buffer)	Class A	Ancillary reagent, included in test kit submission	Class I	Class I	Class A	Class A
Sample Preparation System (Bead Beating Kit, Sample Prep Module)	Class A	Class A	Class I	Class I	Class A	Class A

NAATOS TB SYSTEM: DEFINING THE REGULATORY STRATEGY

Using the identified RRA risk classifications and considering the classification-driven submission requirements outlined in Appendix 3, a high-level Pros and Cons table helps to define the options to move forward.

Topic	Australia TGA	Health Canada	EU CE-IVDR	US FDA	Singapore HSA
Pros	• Submission/review fees are relatively low • Facilitates entry into key target markets • Does not require in-country data if relevance of clinical evidence to Aus. population can be demonstrated • Recognized for procurement and WHO PQ abridged assessment	• Published review timelines appear short, but are not always adhered to • Submission/review fees are relatively low • Facilitates entry into key target markets • Recognized for procurement and WHO PQ abridged assessment	• Facilitates entry into key target markets • Recognized for procurement and WHO PQ abridged assessment	• If 510(k) pathway is accessible, cots are reasonable, especially for a small business • Reliable review time and predictable pathway • Recognized for procurement and WHO PQ abridged assessment	• Open up SE Asian countries (ASEAN) • Multiple paths to accelerate review based on cost • Does not require in-country data
Cons	• Target processing time of 255 days (~51 weeks) is longer than published targets for other SRAs	• Requires all manufacturers to have MDSAP certification for Class III devices (not all partner manufacturers will have; costly and time-consuming to achieve) • Generally requires North American data	• High cost due to Notified Body fees • Long timelines for Notified Body review; lack of consistency between NBs can be unpredictable	• If De Novo pathway required is expensive and longer review times • Generally requires North American data	• Does not facilitate access to primary target markets
Preferred Path?	Yes - Priority 1 to open up all primary target markets and WHO PQ	No	No	No	Yes - Priority 2 to open up SE Asian countries

STRATEGIC ASSESSMENT

- Now that the RRAs have been identified that would open up multiple target markets, the strategy has to consider a number of factors identified in the Regulatory Assessment, including the desirability of various device claims, the order in which studies could be designed to achieve selected claims, and the significant cost to complete these various studies. This has been translated into a flow chart on the following page.
- This represents a multi-year strategy that can be addressed sequentially or with various regulatory submissions being pursued in parallel. There is no right way or wrong way to pursue this strategy, and it may change based on the continuing evolution of the global regulatory landscape and on the goals and objectives of GHL and/or its chosen manufacturing partner.
- As TGA was selected as the initial RRA for submission, and the TGA requirements are currently being reviewed and revised, GHL may review the current draft of the TGA Guidance for IVD Sponsor, available here to understand more about the TGA process.

NAATOS TB SYSTEM: SUGGESTED REGULATORY STRATEGY

Lock device design and complete technology transfer to manufacturing partner; complete analytical performance studies

Initiate studies in two WHO regions: 1) South Africa and 2) India

Generate data for Claim 1 (Aid in Dx). Using data from one or both countries (as availalble):

Submit to Australia TGA

TGA approved

Submit to Singapore HSA

HSA approved

Submit to Indonesia and South Africa

Submit to other ASEAN countries as desired

Once data is available for India, submit to CDSCO

Submit to other African target markets

OR

Once data is available for 2 WHO regions, submit for WHO PQ if applicable

Apply for procurement pathways as desired

Generate exploratory pre-clinical data on asymptomatic subjects for Claim 2 (Systematic Screening - symptomatic or asymptomatic close contacts)

If acceptable performance is obtained, intiate full clinical performance studies for Claim 2. Once complete, submit data for claim expansion to TGA and update other registrations as required (based on approvals obtained to date)

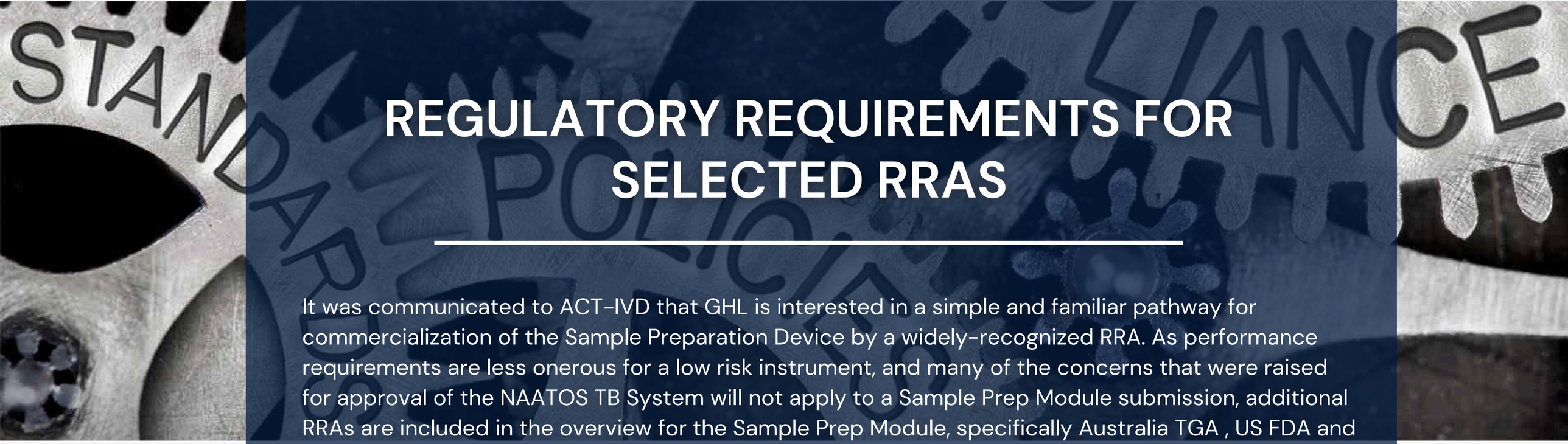
Generate exploratory pre-clinical data on community screening of asymptomatic subjects (Claim 3)

If acceptable performance is obtained, initiate full clinical performance studies for Claim 3. Once complete, submit data for claim expansion to TGA and update other registrations as required (based on approvals obtained to date)

REGULATORY STRATEGY

SAMPLE PREPARATION MODULE

Act-Ivd



REGULATORY REQUIREMENTS FOR SELECTED RRAS

It was communicated to ACT-IVD that GHL is interested in a simple and familiar pathway for commercialization of the Sample Preparation Device by a widely-recognized RRA. As performance requirements are less onerous for a low risk instrument, and many of the concerns that were raised for approval of the NAATOS TB System will not apply to a Sample Prep Module submission, additional RRAs are included in the overview for the Sample Prep Module, specifically Australia TGA , US FDA and EU (CE IVDR) which are most familiar to many device manufacturers. While Health Canada does NOT require MSDSAP certification for a Class I/A device, it was not included in this assessment due to the wider familiarity and simplicity of the other RRA pathways.

While there is often familiarity with SRA requirements for the higher risk classification devices, there is often less familiarity with the requirements for the low risk (i.e. Class I/Class A devices). In many cases technical documentation is not submitted to regulators for these low risk devices; however documentation including objective evidence of device performance including the need to meet safety requirements (e.g. electrical safety) is required. This information was collated and is presented for GHL reference and consideration.

As the Sample Prep Device will be used in LMIC ACT-IVD strongly recommends some form of usability and clinical performance data be generated in a representative LMIC intended use setting and intended user population.

SAMPLE PREPARATION DEVICE PATHWAY OVERVIEW

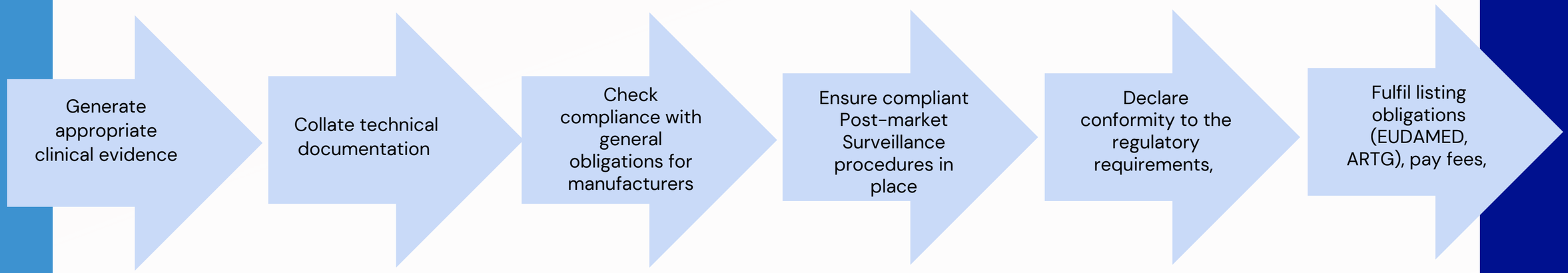
Topic	US FDA	Australia TGA	CE Marking
Local Sponsor/Agent	**Yes – US Manufacturer or Agent**	**Yes – AU sponsor**	**YES – EU Authorized Representative**
QMS	For (non-sterile) LXG products, GMP exempt except for general requirements for records (820.180) and complaint files (820.198)	For Class I – No QMS certificate required, however MFR must have a post-market monitoring program to monitor post-production use/complaints, a CA program to correct deficiencies, and ability to report AE/incidents/performance issues/recalls to Sponsor/TGA	YES – EU Authorized Representative
Techincal Documentation (TD)	LXG is 510k exempt No TD to be submitted to FDA, but must be available	AU EP checklist and DoC TD at MFR must be in IMDRF ToC or STED format (to be supplied w/in 20 days ofTGA request for any reason)	Class A No Annex XI or X EU QMS CE certificate required (IVDR); Full compliance with other parts of the reg apply, including substantial control of distributors and importers, proactive QMS etc.
Administrative Costs	Establishment Fee – 7,653 USD per year + FURLS Device Listing	Legal documentation (attestations, DoC, sponsor contracts etc) and fee payment of 7,837 AUD	Class A IVD - TD required as per Annex II and III and must show conformance to GSPR (Annex I), but not required to be submitted. Performance Evaluation Report required. EU DoC (Annex IV) required
Timeline	1-2 days based on receipt of PIN and PCN from FDA to complete FURLS listing	24 hrs unless flagged for an Application Audit (v rare for Class I IVDs)	No Notified Body fees required
Permit	Mfr registration and Device Registration on FDA websites	Once approved, ARTG listing number is issued and available on the TGA ARTG database webpage	<24 hrs to complete registration in EUDAMED
Validity/Renewal	Annual payment of establishment fee 7,653 USD	Annual payment of registration fee of 807 AUD	Annual NB fees do not apply

SAMPLE PREPARATION DEVICE PERFORMANCE REQUIREMENTS

Topic	TGA Class 1	FDA Class 1 510k exempt (LXG)	EU Class A IVD
Manufacturing site details	YES - EU QMS CE certificate or ISO 13485 or MDASAP can be used, so will have as part of QMS. It is not required but it provides evidence of a QMS in place.	Not referenced	EU QMS CE certificate or ISO 13485 or MDSAP cert can be used, so will have as part of QMS. It is not required but it provides evidence of a QMS in place. There are additional requirements to an ISO/MDSAP that need to be covered.
General description of device and intended use	Yes	Not submitted but required	Yes
Diagrams/drawings and explanation of components, sub-assemblies and/or circuits	Yes	Not referenced	Yes – as required to fulfill requirements of conformance to EPs and GSPRs
Documentation of how device complies with EPs	Yes	Not referenced	Yes
Results of Design Calcs, risk analyses, investigations, technical tests, analytical or clinical tests	Yes. E.g. Demonstrate ability to lyse cells of at least one pathogen in at least one sample type, and demonstrate that isolated nucleic acid can be used in one downstream amplification applications (1 target only). •Will need to demonstrate compliance to IEC ES/EMC requirements (e.g. IEC 61010-1; 61326-2; any related to specific battery use). •Clinical performance should be presented; e.g. a usability study to ensure device can be used safely as per its IFU in the intended use setting	Not referenced	Yes – as required to fulfill requirements of conformance to EPs and GSPRs. This will be similar to the TGA Class 1 requirements.
If connected to another device, evidence of continuing compliance with EPs	Yes	Not referenced	Yes
Device labelling including packaging and IFU	Yes	Not submitted but required	Yes

STRATEGIC ASSESSMENT

COMMON ELEMENTS FOR MARKET AUTHORISATION OF CLASS 1/A IVDS: US FDA, EUROPEAN UNION, AUSTRALIA TGA



Due to predictability in terms of time and cost, FDA or TGA paths are preferred.
If TGA is selected as the pathway for the NAATOS TB System, it could make sense to keep all registrations with the one regulator if the same manufacturing partner is selected for both the TB System and Sample Prep Module.

FINAL COMMENTS

FINAL COMMENTS

1. To best support the success of this and future projects, GHL should strengthen their QMS to become fully compliant with ISO 13485 Clause 7 (Design and Development) and implement a full risk management system during product design based on ISO 14971:2019. This will impact on the success of the design with safety and performance features being identified and “built in” at an early stage.

2. To ensure seamless technology transfer and smooth regulatory approvals, GHL should ensure the technology transfer file and all required procedures are comprehensive and meet international regulatory expectations, highlighted in this report.

3. The regulatory strategy provides an efficient pathway for approval in the desired target markets based on current regulatory requirements. This represents the viewpoint and opinion of ACT-IVD but it is not the only pathway to market and other options may work as well or better for GHL and future partners. The final strategy will also likely require revision based on the choice of a manufacturing partner and their business objectives.

4. As the NAATOS platform is still in design and development and the final product may not be available for several years, given the pace of changing device regulation this strategy and its recommendations will need to be revisited at the time of product readiness.

APPENDICES

Appendix 1 – Target NRA Detailed Overview
Appendix 2 – WHO PQ
Appendix 3 – RRA Detailed Overview
Appendix 4 – Procurement

APPENDIX 1: TARGET NRA DETAILED OVERVIEW

A1: TARGET COUNTRIES: OVERVIEW

Topic	India	South Africa	Kenya	Uganda	Nigeria	Ghana	Indonesia	Singapore (SE Asia)
Regulator	CDSCO [Website]	South African Health Products Regulatory Authority (SAHPRA) [Website]	Pharmacy and Poisons Board [Website]	National Drug Authority (NDA) [Website]	NAFDAC	Ghana Food and Drugs Authority [Website]	Directorate General of Pharmaceuticals and Medical Devices [Website]	Health Sciences Authority (HSA) [Website]
Relevant Legislation & Guidance	India has an established legal framework form medical device regulation, GSR 78(E) - India Medical Devices Rules, 2017	Medicines and Related Substances Act, 1965 (Act 101 of 1965) (amended 2017).	The Health Act 2017, Health Products and Technologies Regulations (Gazette Notice 35 2014). Many requirements are internationally harmonized. 3 guidance docs of most relevance: [Link], [Link], [Link]	Medical devices are regulated under a ministerial decree ADM.140/323/01 of 20th July 2020 and statutory Instrument no 77 of the Surgical Instruments and appliances Regulation 2019. [Link]	NAFDAC Act CAP N1 (LFN) 2004 Medical Devices, In vitro Diagnostics and Related Products Registration Regulations 2024 **References:** Regulation: [Link] [Link] Guidance: [Link] [Link]	Public Health Act, 2012, Act 851 Guidelines	number 62 of 2017, with regulatory processes aligned with the ASEAN Medical Device Directive.	Health Products Act 2007 Health Products (Medical Devices) Regulations 2010 Regulation HSS Guidance documents
Risk classifica-tion for TB IVDs	These classification rules are broadly aligned to IVDR and IMDRF classification rules. • **Class C**	According to guidance Classification rule 1. • **Class D**	Follows GHTF/IMDRF guidelines See Page 51 of guidance for rules. • **Class C**	Medical devices are classified based on risk. [Link] However there are no published IVD classification rules.	Follows GHTF/IMDRF guidelines See Page 19 [Link] • **Class C**	According to Guidelines, Classification rule 2. • **Class IV**	Follows GHTF/IMDRF guidelines, being harmonized to ASEAN MDD • **Class C**	Follows GHTF/IMDRF guidelines Link • **Class C**

A1: TARGET COUNTRIES: RECOGNITION AND RELIANCE MECHANISMS

Topic	India	South Africa	Kenya	Uganda	Nigeria	Ghana	Indonesia	Singapore (SE Asia)
Market Authorisation / Premarket assess-ment	**Yes**: [Blog] Required elements of the registration application include: - Proof of reference country approval - ISO 13485 certification of the manufacturing facility - Full technical details as per the prescribed requirements of the device master file.	**Yes:** High risk classes (including C & D) require proof of premarket registration from **at least one reference reg agency** or **WHO PQ[1]**	**Yes:** Full assessment only at this time; personal communications indicate that although not fully implemented as per their guidance, and expedited route available by approval by RRAs including **WHO PQ[1]**.	**Yes:** Different "tracks" based on previous approvals. **Track 1** – products registered and approved in IMDRF countries **Track 2** – products that have received WHO PQ or SRA registration **Track 3** – No prior SRA or IMDRF country approvals or **WHO PQ[1]**	**Yes:** At least one RRA ***Or* WHO PQ[1]**	**Yes:** IVDs require proof of premarket registration (Certificate of Fee Sale or Certificate to Foreign Government) from **at least one reference reg agency**. ***Or* WHO PQ[1]**	**Yes:** Reference country approval is required prior to registering an IVD device in Indonesia.	**Yes:** Class A products must conform to Essential Principals. Class B-D products require product registration. Immediate, expedited or abridged assessments are available
Reference regulatory agencies (RRAs) listed	• Australia • Canada • Japan • EU • USA [Link]	• Australia • Canada • Japan • EU • USA • *Brazil*	• Australia • Canada • Japan • EU • USA • *SwissMedic* • *Ireland HPRA* • *Saudi Arabia FDA*	• Australia • Canada • Japan • EU • USA	• Australia • Canada • Japan • EU • USA • *Iceland* • *Liechtenstein* • *Norway*	• Australia • Canada • Japan • EU • USA	• Australia • Canada • Japan • EU • USA [Blog]	• Australia • Canada • Japan • EU • USA

Note: Included in italics are additional RRAs which for efficiency we will not cover in detail in this report

1 https://extranet.who.int/prequal/vitro-diagnostics/collaborative-procedure-accelerated-registration. At time of writing this report, no TB IVDs heve been prequalified. Once this changes, there may be the potential for a CRP procedure for accelerated registration based on WHO PQ.

A1: TARGET COUNTRIES: ADMINISTRATIVE REQUIREMENTS

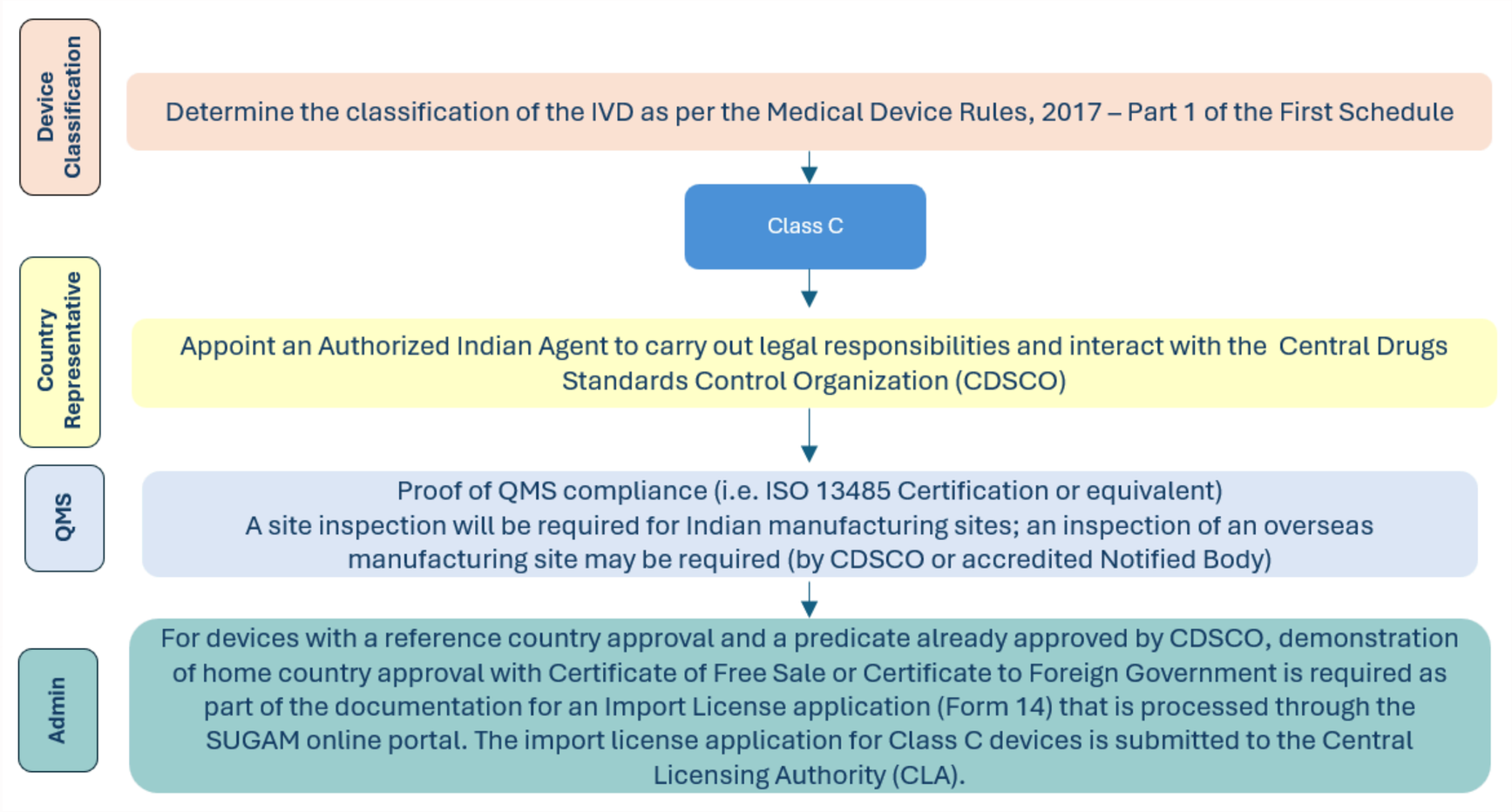
Topic	India	South Africa	Kenya	Uganda	Nigeria	Ghana	Indonesia	Singapore
Local Authorized Representative (LAR)?	**Yes:** In order to place a product on the Indian market a manufacturer is required to legally appoint a country representative, a distributor and an importer.	**Yes:** As part of the license required for importing / distributing MDs in ZAF.	**Yes:** Any manufacturer based outside the Kenya must designate a local authorized Representative (LAR).	**Yes:** A Uganda agent is required to carry out legal responsibilities and interact with the Authority.	**Yes**: Legally appointed in-country representative is required	**Yes:** Legally appointed Ghanaian local agent	**Yes:** Prior to importation, medical and IVD devices must receive a registration number and product license (AKA marketing license) issued by the Ministry of Health to a local, licensed distributor.	**Yes:** A legal representative is required to have a dealers license and carry out legal responsibilities, including interacting with with HSA.
Registration Timelines*	All classes 9-12 months.	'To licence as a manufacturer … 2-3 Months' from receiving documents in the MD unit.	TAT does not include 'stop-clock time', classes B, C, D qualify for fast tracking processes.	Products with SRA authorization: 6 months (132 days) [Link]	60 to 120 working days	"All new applications… would be processed within a minimum period of 6 months" Evaluation may be **expedited** if a product is for a public health programme (includes TB)	Class C = 30 Days	Higher risk class = longer review time Immediate - Class A-C only Expedited - Class C-D only - 5-6 months Abridged - Class B-D only - 4-8 months Full - Class B-D only - 6-12 months
Fees*	Class C: $3000 for one MFG Site + $500 for each distinct IVD	Establishment Listing fee: 1000 USD Submission application fee: 1000 USD	New Class C Application ($1000 USD) + ($300 USD - Annual retention of license)	Fee register published for drugs; no mention of IVDs Link	Company registration : 250,000 N (171 USD) New Class C/III Application : 21 million N ($14,379 USD) [Link]	Establishment License: 400.00 GHC Class IV submission: 2,400 USD Annual fee: Class IV, 160 USD	New Class C Application Indonesian Rupiah 3,000,000 ($230 USD)	Establishment License Fee: 1,110 SGD (825 USD; new and annual renewal) Submission fees vary by risk class and route. Class C: from 3.340 to 9,000 SGD (1,500 to 6,700 USD)

** Note: Information on Registration timelines & Fees presented here were collected from secondary sources and should only be considered as loose estimates, actual timelines and fees may differ between products, with prior reference agency approvals, or any unforeseen circumstances.*

A1: TARGET COUNTRIES: COUNTRY-SPECIFIC TECHNICAL REQUIREMENTS

Topic	India	South Africa	Kenya	Uganda	Nigeria	Ghana	Indonesia	Singapore
QMS Requirements	QMS certificate or Full QA or Production Assurance certificate. ISO 13485 or GMP may apply.	Proof of QMS Compliance (ISO 13485 Certification or equivalent)	Proof of QMS Compliance (ISO 13485 Certification or equivalent)	GMP required	Proof of QMS Compliance (ISO 13485 certification or equivalent)	ISO 13485	ISO 13485 or GMP	ISO 13485 certificate or equivalent Accepts MDSAP
In-country studies required for TB IVDs?	**Yes:** In-country studies and further performance evaluation by the National Institute of Biologicals is required for IVD devices and kits related to a range of disease areas of interest, including Tuberculosis. [Blog]	**No**: "Local testing is not required. However, additional license might be required for electronic products listed in the Schedule …" Blog	**No**: "Foreign manufacturer on-site audit, local test, or local clinical study is not required." Blog Class C and D IVDs will require internal reference laboratory performance evaluation; it is unclear if this is a responsibility of the manufacturer or of the regulator. Clarification is being sought.	**No**: Link states only required for HIV *However please confirm with regulatory authorities.*	**No**: *However NAFDAC will notify the applicant if a local analysis is required.*	**No**: *However please confirm with regulatory authorities.*	**No:** Prior to approval, the regulatory authority does **not** require in-country studies for Tuberculosis IVDs, however this is a requirement for HIV diagnostics.	**No**: *However please confirm with regulatory authorities.*
Labelling Requirements (Language)	Labeling requirements state that English is the only language requirement.	English	English	English	English	English	Specific advertising rules: Certain information must be stated in Bahasa Indonesian. [Link]	English
Technical Dossier Submission format	Indian Technical File Format Link to Drug format here	STED format	Common Submission Dossier Template (CSDT)	Not required.	Not required.	STED format	ASEAN Common Submission Dossier Template (CSDT)	TD required in ASEAN CSTD format or IMDRF ToC

A1: INDIA CDSCO CLASS C FLOWCHART– PART 1



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A1: INDIA CDSCO CLASS C FLOWCHART– PART 2

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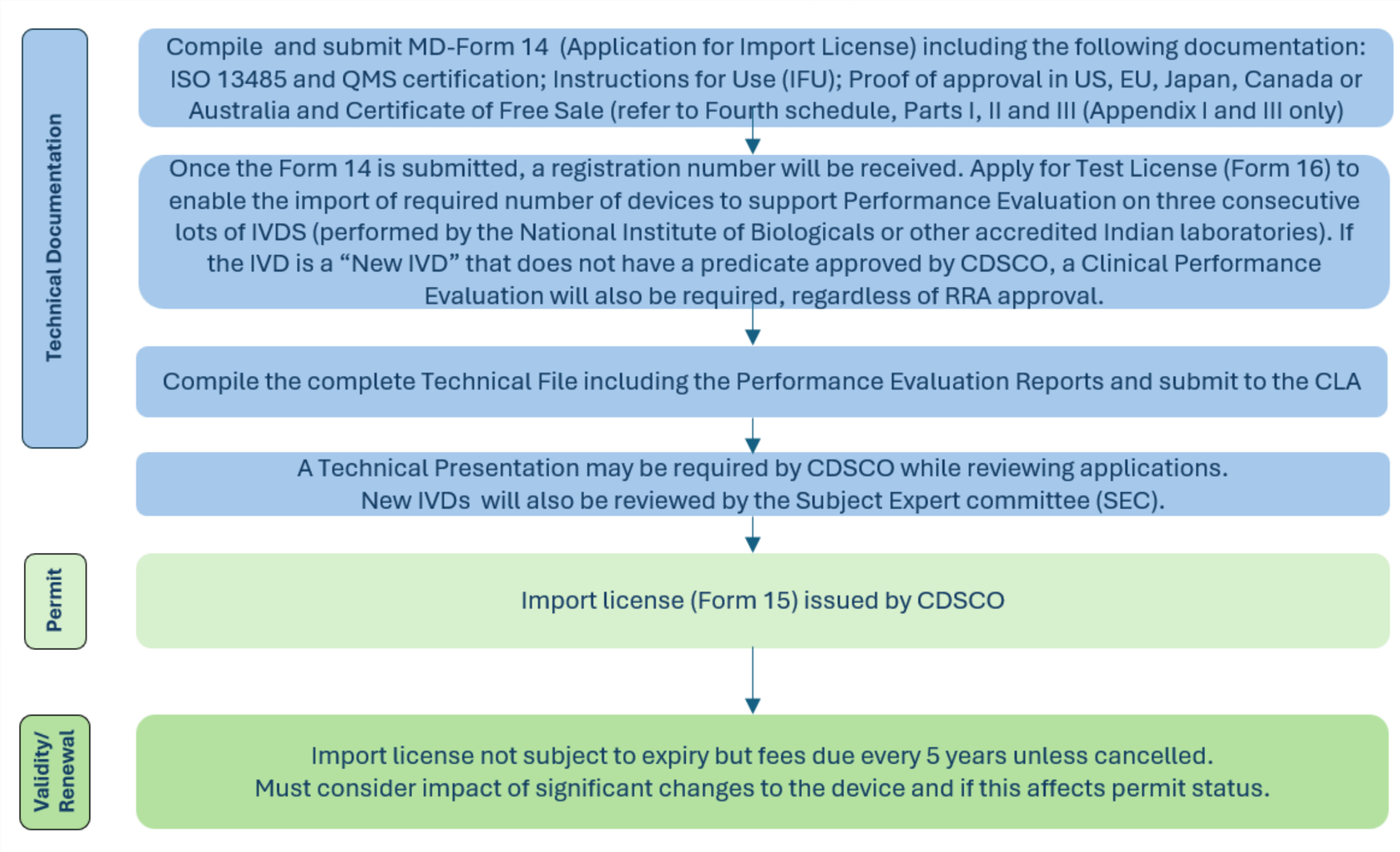


This information has been compiled from multiple conversations with informed individuals and regulatory research; it is strongly recommended to validate this information with an Indian manufacturing partner if CDSCO becomes relevant for device approvals. It is also strongly recommended that IVD regulatory experience in general, and with CDSCO in particular, be included in partner selection activities.

APPENDIX 2: WHO PQ

WHO PQ ASSESSMENT PATHWAYS

WHO is not a regulator, but as the PQ assessment mirrors that of a stringent regulatory assessment, it is recognised by many LMICs to either replace or assist registration in country.
There are two pathways for WHP PQ assessment: a full assessment or an abridged assessment

Prequalification stage	Full prequalification assessment	Abridged prequalification assessment
Review of a product dossier	Full product dossier	Abridged product dossier
Inspection of a manufacturing site	Manufacturing site(s) inspection	Manufacturing site(s) inspection
Performance evaluation, including operational characteristics	Yes	Yes
Labelling review	Yes	Yes

Eligibility for an abridged assessment is limited to IVDs of relevant risk classes that have been assessed by specified RRAs (generally risk classification C/D or III/IV as applicable) where the version of the product submitted to WHO is identical to that which received SRA approval.

Note that devices considered for WHO PQ require clinical performance studies carried out in a minimum of 2 WHO regions as previously discussed.

General information about the WHO PQ process can be found here.

	WHO PQ [Link]
Relevant guidance	WHO has compiled an extensive library of guidance documents on aspects of the PQ process for reference Link
QMS requirement	An ISO 13485 certified QMS is preferred. MDSAP may potentially lead to an abridged QMS assessment. Manufacturers will be subjected to a site inspection as discussed below unless they are able to benefit from an abridged assessment
Technical file requirements	Must be submitted using the IMDRF ToC format [Link]
Anticipated Review Time/Time to Approval	A full prequalification assessment ranges from 12 to 18 months. An abridged assessment can take between 5 to 9 months. [Link]
Device Application Cost	In 2018, WHO PQ introduced new fees for services [Link]. These include the following fees • A prequalification assessment fee per product; (17000 USD for full assessment, 8000 USD for abridged assessment) • An annual fee per product; (4000 USD/year) and • A change assessment fee per product (3000 USD if significant change).
Establishment License Cost	No additional establishment license is required. However as part of the PQ application a site inspection is required which may be a full on-site inspection or may leverage outputs from inspections conducted by other stringent regulatory authorities.[Link]
"In Country Studies" and Performance Evaluations	As per TSS-17, to be eligible for PQ clinical performance studies must be performed in 3 geographically different locations, in "more than one" WHO region; this may changed based on the outcomes of the generation of the final LF-LAM TSS. As part of the PQ application, all devices must undergo a performance evaluation as per a defined WHO PQ evaluation protocol. Link This evaluation may be commissioned and coordinated by WHO at a site listed by WHO ("Option 1"), or may be commissioned directly by the manufacturer from an independent laboratory listed on the WHO List of Performance Evaluation Laboratories.

APPENDIX 3: RRA DETAILED OVERVIEW

A3: RRA IN-DEPTH ASSESSMENT

Using the identified risk classification and pathways identified in the previous slides, summaries of the classification-driven submission requirements with highest impact on cost and time to market are presented.

Items in green font indicate a positive aspect of assessment, while items in red font indicate challenges or risks to the assessment.

A3: SRA – US FDA AND HEALTH CANADA CLASSIFICATION

	Sample Prep Module	NAATOS TB Test Kit OR NAATOS TB System	Bead Beating Kit OR Sample Preparation System
US FDA	As a stand-alone instrument, as per 21 CFR 862.2050 - LXG - general purpose lab equipment labelled or promoted for a specific medical use – Class 1, 510(k) exempt Would also be able to be listed as part of a System	21 CFR 866.3373 – System, NAT, MTB complex, resistance marker, direct specimen. Code PEU. Class 2 Special Controls. Is currently only the GeneXpert, and is listed as specifically for respiratory specimens. *If NAATOS falls under this category, a 510(k) would apply; if not, device may need to be submitted through the De Novo pathway; a pre-submission with FDA would be required.* Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of Mycobacterium tuberculosis Complex and Genetic Mutations Associated with Antibiotic Resistance in Respiratory Specimens	Would be Ancillary Reagents to either the TB System or the Sample Prep System - no submission required
Health Canada [Link]	As part of the TB System, will be same classification as the consumable test device as per Rule 7 - IVDDs specifically intended to be used together. OR As a stand-alone instrument Class I – as per Rule 8, "all other IVDDs".	Class III (Rule 2 subrule b(i)) IVDD used to detect the presence of, or exposure to, a transmissible agent that causes a serious disease where there is risk of propagation in the Canadian population. NOTE: Near-patient IVDD are Class III	For use with the Sample Prep Module as a general Sample Preparation System for IVD use, will be the same classification as the Sample Prep Module - Class I as per Rule 8

A3: SRA – CE IVDR CLASSIFICATION

NOTE: For EU under IVDR, as per Implementing Rule 1.2, if a device is intended to be used in combination with another device (i.e. as a system), the classification rules shall apply separately to each of the devices.

	Sample Prep Module	NAATOS TB Test Kit	Bead Beating Kit
CE IVDR [MDCG 2020-16 Rev 2]	As a stand alone instrument: Class A - Rule 5(b) – Instrument specifically intended by the manufacturer for in vitro diagnostic procedures.	Class C - Rule 3 (c) for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring; OR Class C - Rule 3 (e) for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring. NOTE that Rule 4b classifies devices for near patient testing in their own right.	As per Implementing Rule 1.3, accessories for an in vitro medical device shall be classified in their own right, separately from the device with which they are used. Therefore, for use with the Sample Prep Module: Class A - Rule 5(a) - as an "accessory which possesses no critical characteristics... intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination."

A3: SRA – AUSTRALIA AND SINGAPORE CLASSIFICATION

	Sample Prep Module	NAATOS TB Test Kit OR NAATOS TB System	Bead Beating Kit OR Sample Preparation System
Australia TGA [Link]	Class 1 as per Rule 1.6 – Reagents, Instruments as general laboratory products (reagents, instruments, apparatus, equipment or system) that are manufactured, sold or represented for use for IVD examinations. OR As a System (subregulation 3.3(7)) as the highest classification of any device in the system or procedure pack (see TB System, or as Sample Preparation System).	Class 3 as per Rule 1.3 – Detection of transmissible agents or biological characteristics posing moderate public health or high personal risk. NOTE: TGA does not have a classification rule related to near-patient testing.	Class 1 as per Rule 1.6 (stand-alone or Sample Prep System) as a "general laboratory product… sold or represented for use for in vitro diagnostic examinations."
Singapore HSA [Link]	Class A (Rule 5b) - Standalone instruments (inclusive of software) intended by the product owner specifically to be used for in vitro diagnostic procedures, not intended for use in specific medical diagnostic procedures. IVD Test Kits and Analyzers may be grouped as a System.	Class C (Rule 3a) - IVD medical devices intended for use in detecting the presence of, or exposure to, an agent that presents a moderate public health risk. NOTE: Rule 4 - IVD medical devices intended for… near-patient testing are classified as Class C.	Class A as per Rule 5 (stand-alone or Sample Prep System) as an "accessory which possess no critical characteristics, intended… to make them suitable for in vitro diagnostic procedures related to a specific examination…"

A3: SRA – WHO/IMDRF CLASSIFICATION

	Sample Prep Module	NAATOS TB Test Kit or NAATOS TB System	Bead Beating Kit OR Sample Preparation System
WHO/ IMDRF [IMDRF LINK]	Class A – Rule 5 (ii) –Instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures May be included in a System	Class C – Rule 3 – IVD medical devices classified intended for use in detecting am agent that presents a moderate public health risk … The devices provide the critical, or sole, determinant for the correct diagnosis or monitoring… Note: Class C – Rule 4 – IVD medical devices intended for use by lay users (such as for self-testing or near-patient testing) are classified as Class C.	Class A - Rule 5 (i) - Reagents or other articles, which possess no critical characteristics intended by the manufacturer to make them suitable for in vitro diagnostic procedures related to a specific examination. As a Sample Preparation System, also Class A.

A3: SRA REQUIREMENTS

Topic	Australia TGA	Health Canada	EU CE-IVDR	US FDA	Singapore HSA
QMS Requirement	TGA QMS conformity assessment certificate issued by TGA or a TGA-designated CAB OR MDSAP certificate OR EU IVDR Annex IX (QMS)/XI (PQA)	MDSAP required for Class II-IV devices RISK: long wait times to schedule Stage 1 and 2 MDSAP audits; cost varies from ~18,000 to >30,000 USD for the first audit cycle	EU QMS CE Certificate (EU MDR/IVDR) (for Annex IX Ch 1 or Annex X)	21 CFR 820 or MDSAP NOTE: Transition from 21 CFR 820 to QMSR in Feb 2026	ISO13485 certificate or equivalent; accepts MDSAP
Technical File Requirements (TD = Technical Documentation)	AU DoC to EPs TD Required in STED or IMDRF ToC format Class I: Not submitted Class III: Submission required	TD Required in STED or IMDRF ToC format Class I: Not submitted Class III: Submission required	TD required as outlined in in Annex II of the IVDR. Class A: Not submitted Class C: Submission to NB required	Based on class of submission. Class I Exempt - Not submitted Class II - 510k submission De Novo classification request needed for "unclassified" devices, followed by submission requirements based on identified risk class	TD required in ASEAN CSTD format or IMDRF ToC Class A - Not submitted Class C- Submission required
In Country Studies Required?	No	Yes - Canada or US data generally required- Pre-Submission discussion recommended	Yes – EU or representative population	Yes - some US data generally required. Pre-submission discussion recommended	No

A3: SRA COSTS AND REVIEW TIMES

Topic	Australia TGA	Health Canada	EU CE-IVDR	US FDA	Singapore HSA
Anticipated review time / time to approval	Class 2-4 IVDs: Mean TGA processing time (working days): 152 for IVDs (~8 months)[Link] Target TGA processing time (working days): 255 working days (~ 51 weeks)	Medical Device Establishment Listing: 2-4 months Medical Device License: 3-6 months HC performance standard: 120 Calendar days (~4 months) [Link]	Timelines directly related to Notified Body resources and services. Average reporting times from MedTech Europe: 13-18 months [Link]; personal communication ~24 months	Approval timelines: Class II (510k): 6-9 months De Novo: 180 days	Immediate - Class A-C only Expedited- 5-6 months Abridged - 4-8 months Full - 6-12 months Higher risk class = longer review time
Device Application Cost	As per June 2024: Full QMS assessment (not incl Part 1.6)= 33,623 AUD Application Fee: 1416 AUD [Link]	MDL fee: Class II – 478 CAD; Class III - 8,895 CAD	Notified Body fee estimates: Initial dossier review ~1-2 day desktop plus 2-5-day on-site audit @ 445 €/hr = ~11,000 € to ~25,000 €.	510k: 21,760 USD Standard or 5,440 USD small business De Novo: 145,068USD Standard or 36,267 USD small business [LInk]	Submission fees vary by risk class and route. Base application fee for all classes: $560 From $1000 (Class B) to $17,500 (Class D) Annual retention fees $39 (Class B) to $134 (Class D)
Establishment License Cost	N/A	MDEL fee: 4,737 CAD or 3,435.75 CAD for small business	N/A	7,763 USD per year	Establishment License Fee: $1,110 (new and annual renewal)
Approval Facilitates Assessment in:	India, South Africa, Kenya, Uganda, Nigeria, Ghana, Indonesia	India, South Africa, Kenya, Uganda, Nigeria, Ghana, Indonesia	India, South Africa, Kenya, Uganda, Nigeria, Ghana, Indonesia	India, South Africa, Kenya, Uganda, Nigeria, Ghana, Indonesia	Only “Other Countries in SE Asia”

APPENDIX 4: PROCUREMENT

DONOR PROCUREMENT QUALITY ASSURANCE POLICIES

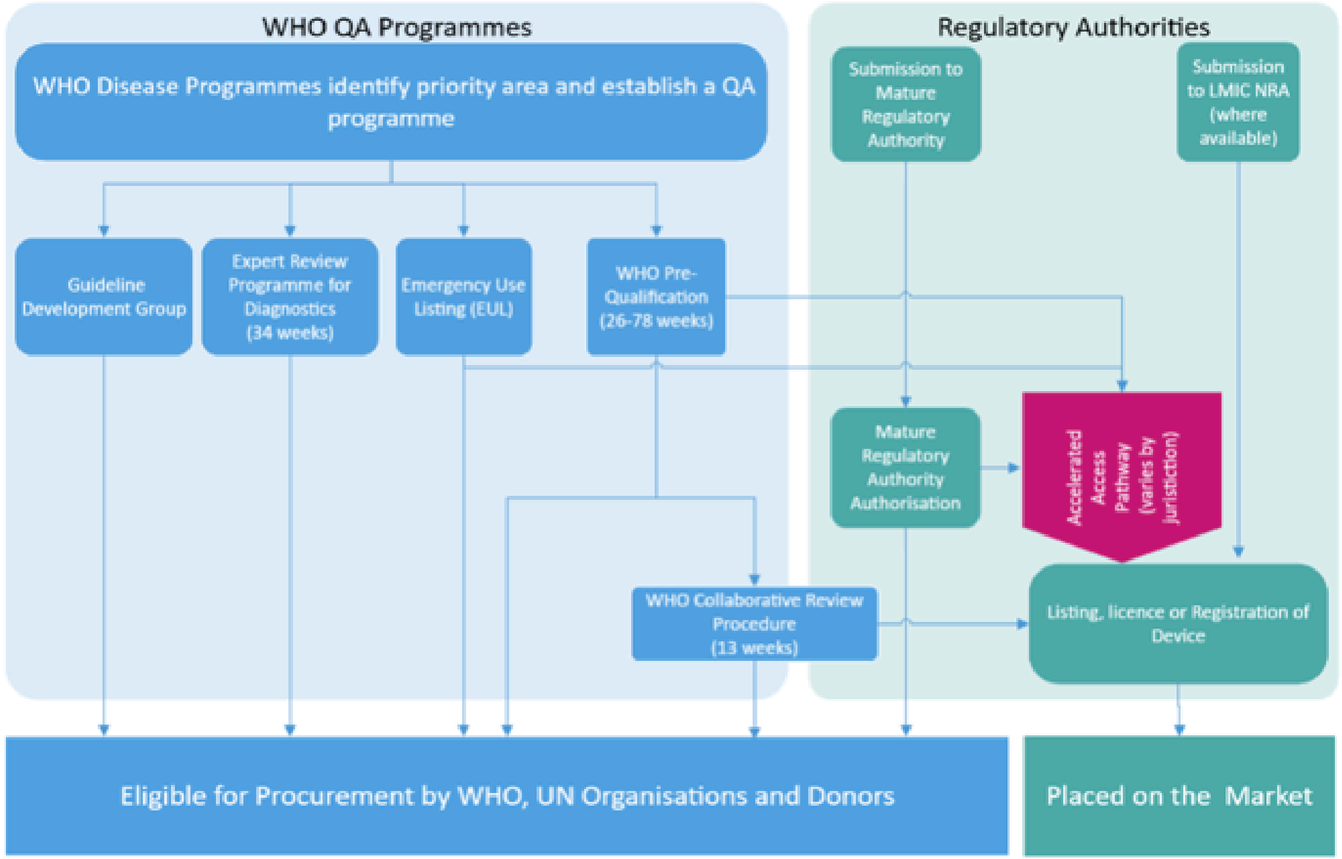
UN Organisations, national governments and large donors (e.g. The Global Fund, PEPFAR, UNICEF, WHO, MSF), have policies governing which priority therapeutic and diagnostic products can be purchased, to ensure value for money purchasing.

The requirements are found in their Quality Assurance (QA) procurement policies.

Most of these entities have a procurement QA policy that requires purchased IVDs to have undergone “stringent regulatory assessment” (usually undefined) by a limited number of (defined) regulatory agencies, and/or have successfully undergone WHO QA assessment (either PQ or EPRD; the latter is not covered in this report).

Tuberculosis is a major disease focus for the procurement agencies and therefore their QA policies were reviewed.

OUTLINE OF THE RELATIONSHIP BETWEEN WHO QUALITY ASSESSMENTS AND HOW THEY ARE APPLIED TO BOTH REGULATORY AUTHORIZATIONS AND DONOR PROCUREMENT, VERSUS USING NRA PATHWAYS FOR PLACING A DEVICE ON THE MARKET



OVERVIEW OF DONORS & PROCUREMENT PATHS

Donor/Procurer	WHO PQ [Link]	WHO TB Programme	GHTF/IMDRF Founding Members	WHO ERPD	Additional Comments
The Global Fund [Link]	✓	✓	✓		*There is an open call for ERPD Tuberculosis through Global Fund [Link]*
PEPFAR [Link]	✓	✓	✓		Disclaimer: Although unable to verify for TB, PEPFAR appears well aligned with the Global Fund QA requirements for procurement of medicines and IVDs.
Global Drug Facility/Stop TB Partnership (add Link)	✓	✓	✓		EUL by WHO / IMDRF founding members
UNICEF [Link]	✓		✓		
MSF [Link]	✓		✓		When this is not available, MSF conduct their own assessment of a product dossier and manufacturing site (e.g. GMP audit)…
UNITAID [Link]	✓		✓	✓	Shall be acceptable for procurement, as determined by Unitaid, based on the advice of a Unitaid/GF Expert Review Panel (Unitaid/GF ERPD)…

NOTE: To be eligible for procurement, only one of the following categories for approval is required (e.g. WHO PQ or RRA or WHO ERPD etc.)

Initial analysis: Listing by WHO PQ and market authorization by RRAs are the most common requirements for major donors.

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