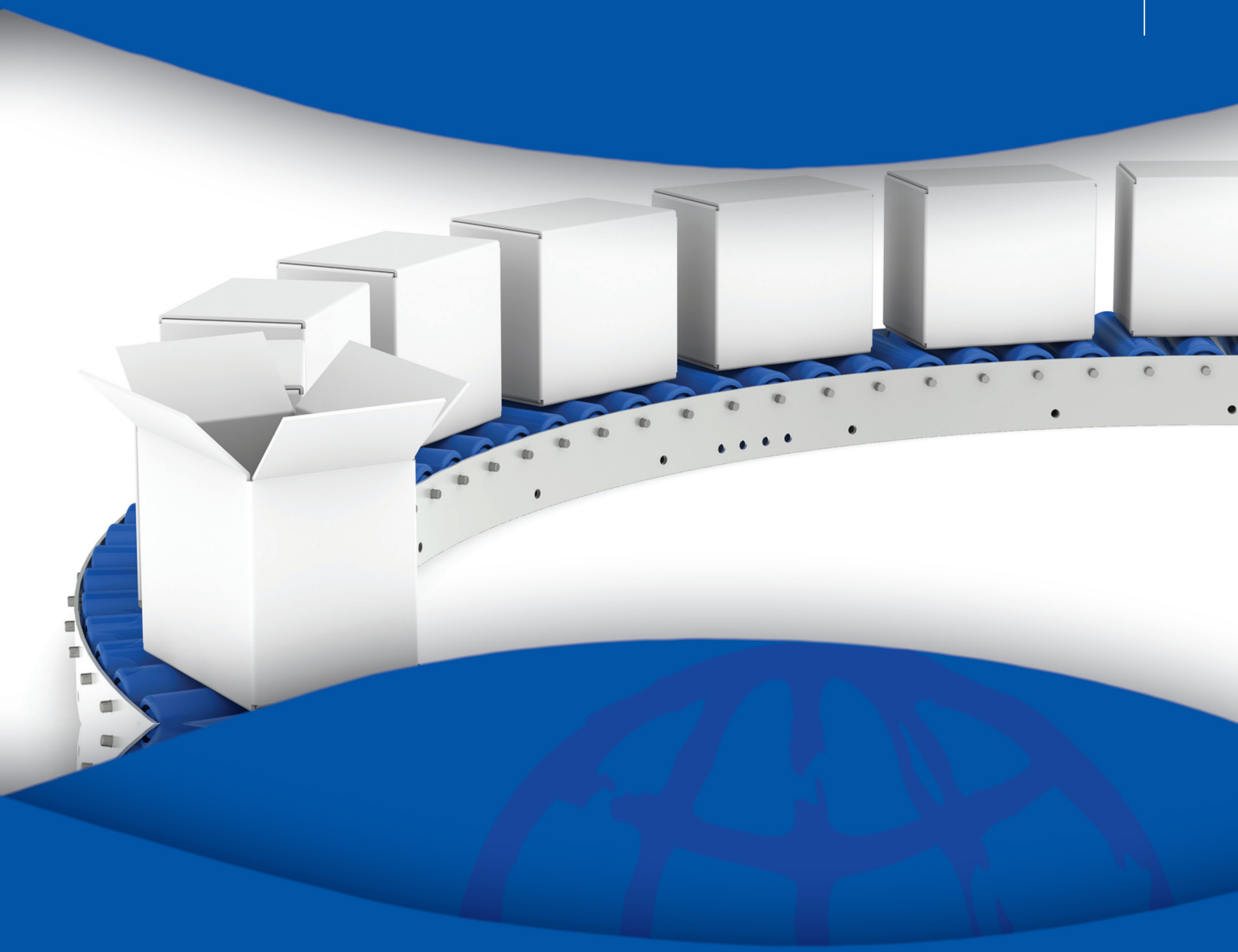
World Health Organization

Guidance for procurement of in vitro diagnostics and related laboratory items and equipment



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CONTENTS

ABBREVIATIONS

CD4	CD4 T-lymphocyte
CFR	cost and freight
CIF	cost insurance and freight
CLIA	chemiluminescence immunoassay
CLSI	Clinical and Laboratory Standards Institute
ECL	electrochemiluminescence immunoassay
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EOI	expression of interest
EQA	external quality assessment
EQAS	external quality assessment scheme
FSCA	field safety corrective action
FSN	field safety notice
GAVI Alliance	The Global Alliance for Vaccines and Immunization
GFATM	The Global Fund to fight AIDS, Tuberculosis and Malaria
ICB	international competitive bidding
IMDRF	International Medical Device Regulators Forum
INCOTERM	International Commercial Terms
ISO	International Standards Organization
ITB	invitation to bid
IVD	in vitro diagnostic medical device
LTA	long term agreement
NAT	nucleic acid testing
NGO	nongovernmental organisation
NRA	national regulatory authority (for medical products)
NRL	national reference laboratory
OD/CO	optical density to cut-off
OTIF	on time and in full
PEPFAR	President's Emergency Plan for AIDS Relief
PO	purchase order
POCT	point of care testing
PMI	President's Malaria Initiative
PMS	post-market surveillance
PSM	procurement and supply management
QA	quality assurance
QC	quality control
QMS	quality management system
RDT	rapid diagnostic tests
RFP	request for proposal
RFQ	request for quote
SOP	standard operating procedure
SOW	scope of work
TCO	total cost of ownership
TOR	terms of reference
UN	United Nations
WHO	World Health Organization

GLOSSARY

Analyte	A substance or chemical constituent that is analyzed (identified or measured) by the assay, e.g. polyclonal or monoclonal antibodies or antigen
Analyser	Equipment that consume reagents, consumables and produce a test result. Usually repaired and maintained by service contracts.
Ancillary equipment	Freezer, washers, readers, incubators, etc. Usually repaired and serviced by in-country biomedical engineers.
Cleaning	Process to remove any type of contamination, visible or not.
Consumables	Items that are used once during testing and are not reused e.g. gloves, pipette tips, etc.
Decontamination	Procedure that eliminates or reduces microbial or toxic agents to a safe level with respect to the transmission of infection or other adverse effects.
Disinfection	Process to reduce the number of microorganisms but not usually of bacterial spores, without necessarily killing or removing all organisms, usually from non-living objects such as laboratory equipment or laboratory benches.
Durables	Items that can be reused for multiple tests such as glassware, plastic ware, etc.
Equipment	Items such as analysers that may be used for a range of specific assays and general laboratory equipment such as centrifuges, pipettes and incubators
External quality assessment	A programme designed to assess laboratory performance, i.e. assessment of the quality of the entire testing process from collection of specimen, the testing procedure, to the reporting of testing results. Usually composed of one or more of the following activities: site visits, participation in external quality assessment schemes/proficiency testing and inter-laboratory comparison.
Hazardous waste	Waste that is potentially harmful to human beings, property or the environment. E.g. used reagent strips contaminated with human blood, reagent solution containing sodium azide, decommissioned instruments containing heavy metals. Includes waste that is flammable, combustible, ignitable, corrosive, toxic, reactive, injurious or infectious.
In vitro diagnostic medical device (IVD)	A medical device, used alone or in combination, intended by the manufacturer for the examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. For example, IVDs can be used for the following test purposes: diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status. IVDs also include reagents, calibrators, control materials and specimen receptacles. Note: Rapid diagnostics tests, enzyme immunoassays, nucleic acid testing technologies, are all examples of IVDs.
Life-cycle	All phases in the life of a IVD, from the initial conception to final decommissioning and disposal.
Manufacturer	Any natural or legal person with responsibility for design and/or manufacture of an IVDs with the intention of making the IVD available for use, under their name; whether or not such an IVD is designed and/or manufactured by that person themselves or on their behalf by another person(s).
Point of care testing	Also referred to as near-patient testing. Testing that is performed near or at the site of the patient leading to a possible change in the care of the patient. Testing performed outside of a central laboratory environment, generally near to, or at the site of the patient.

Procurement and supply management	A systematic activity that ensures the continuous quality and availability of products through optimal procurement planning, storage and distribution from manufacturer to the end-user.
Quality assurance	Part of quality management focused on providing confidence that quality requirements have been met. A comprehensive set of policies, procedures and practices used to monitor the entire testing process of a testing service and to ensure that the testing site results are reliable. Note: QA includes monitoring; evaluating; taking corrective actions, if necessary based on evaluations; and monitoring corrective actions for the testing services preanalytical, analytical and post analytical activities. These activities include, but are not limited to, recordkeeping, calibration and maintenance of equipment, quality control, proficiency testing and training.
Quality control	Part of quality management focused on fulfilling quality requirements. The set of procedures designed to monitor the test method and the results to ensure test system performance. QC includes testing control materials, charting the results, and analyzing sources of error, and evaluating and documenting and remedial action take as a result of this analysis. Note: QC does not control for the provision of correct testing results but rather indicates the test system (assay) has worked correctly.
Quality management system	A management system that directs and controls an organization with regard to quality, comprising an organizational structure, procedures, processes and resources.
Quality improvement	Part of quality management, focused on increasing the ability to fulfil quality requirements.
Reagents	Part of an IVD that produces a signal via a chemical or electrochemical reaction, which allows the quantity to be detect and its value measured in a specimen. A substance that produces a chemical reaction in a specimen that allows for an analyte to be detected and measured. E.g. specific reagents for CD4 enumeration, as well as general reagents such as ethanol , methanol, sodium chloride, etc.
Risk management	Each manufacturer shall establish and maintain an ongoing process of risk management which involves the entire product lifecycle, from the conception to decommission, to identify the hazards associated to an IVD, to estimate and evaluate the risks involved, to control the risks and evaluate the effectiveness of established controls. This program shall include the following elements: analysis, assessment, control and risk monitoring.
Sensitivity	Ability of an IVD to identify the presence of a target marker associated with a particular disease or condition.
Specificity	Ability of an IVD to recognize the absence of a target marker associated with a particular disease or condition.
Sterilization	Process to render a medical device (or other item) as free of viable microorganisms through inactivation of microbiological contaminants.
Supplier	A participant in the procurement process either as a contractor or as an entity that makes a submission (bid or offer).
Vendor	A potential or actual Supplier or provider of goods, services and/or works. A Vendor may take various forms, including an individual person, a company (whether privately or publicly held), a partnership, a government agency or a nongovernmental organisation.
WHO Prequalification of In Vitro Diagnostics	An assessment of the safety, performance/operational characteristics and manufacturing quality of in vitro diagnostics, as performed by WHO.

SCOPE AND INTENDED AUDIENCE

The purpose of Guidance for Procurement of Diagnostics and Related Laboratory Items and Equipment is to provide information on procurement processes specific to HIV and HIV-related in vitro diagnostics, laboratory items and equipment. This guidance is not intended to replace existing guidelines on basic procurement processes but rather to enhance and extend current processes to include specific issues related to diagnostics and related items/ equipment that are considered essential to ensure high quality testing services.

The intended audience are WHO Member States including programme managers, end-users, procurement officers; staff in United Nations (UN) agencies; and non-governmental organizations (NGOs) who conduct the selection and use of in vitro diagnostics and related laboratory items and equipment.

Users of this guidance who procure with financial resources from multilateral or bilateral agencies or sources other than national funds will be obliged to follow the rules, regulations and policies of the funding organization. As such there may be certain guidance that is different to the guidance set down in this document.

Finally, the country programmes themselves should be the ultimate decision makers for procurement decisions.

See section 6 (bibliography) for further useful reading.

ACKNOWLEDGMENTS

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INTRODUCTION

How best practices for procurement benefits programmess

Testing programmes strive to procure products that are appropriate for the intended setting of use at the most reasonable price to ensure that testing is accessible for all who need it. When procurement is not conducted in accordance with documented best practices, the products procured may not be appropriate for use by the intended user or for the intended setting. Therefore, the quality of procurement practices have a direct impact on the effectiveness of programme funding for testing services, for example, when analysers are purchased that require more highly trained staff or when rapid diagnostic tests (RDTs) are procured that are not validated for capillary whole blood specimens. Poorly conducted procurement has a huge programmatic impact if stability of products and allowable shelf life for labile reagents are not foreseen as part of the procurement process. Currently, many testing programmes procure their annual needs to avoid repeating an often long and complex procurement process. This guidance aims to highlight the necessary factors to consider when procuring in vitro diagnostic medical devices (IVDs) and other laboratory items.

It has been documented that without sound procurement policy, ten recurring challenges are likely to present including: lack of adherence to existing procurement policy, misalignment with service delivery policy, tiers of testing network not defined, effective coordinating body lacking, inadequate equipment maintenance and data availability, managing frequent shifts in technology, human resources, competing priorities, and political agendas. (Williams J. et al., 2016)

Therefore, it is critical that laboratory policies, procurement policies and treatment guidelines are aligned so as to provide a responsive and appropriate service to clients.

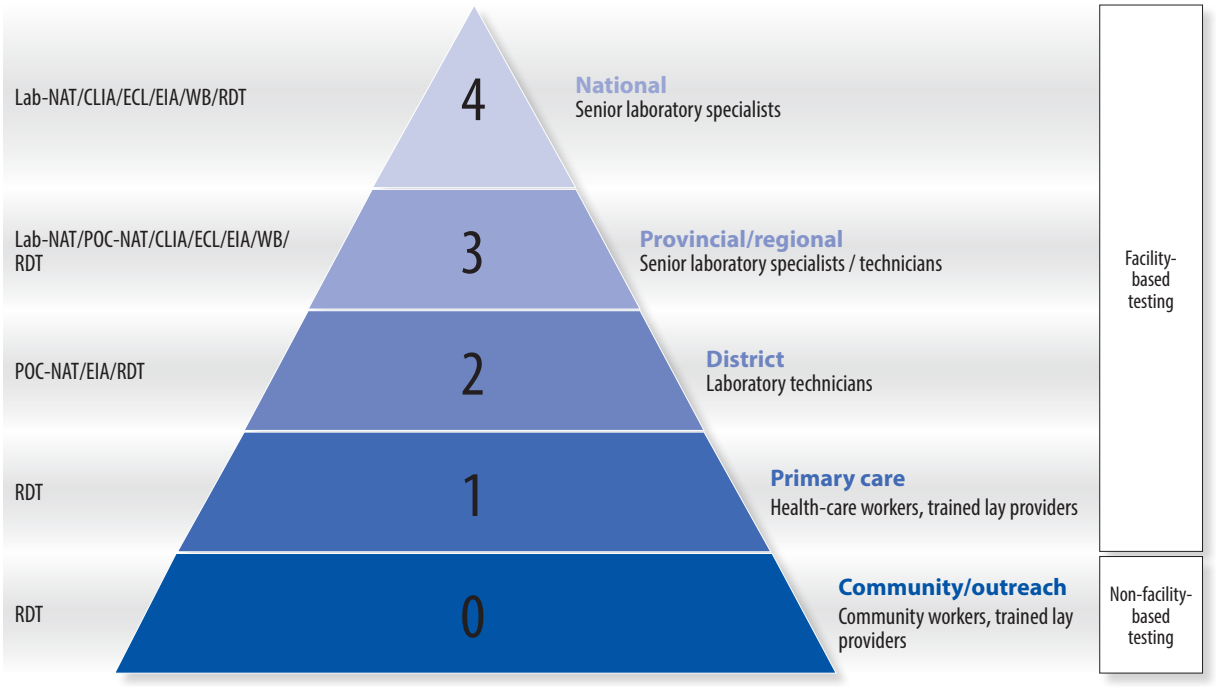
Where to deploy in vitro diagnostic medical devices, including testing at point-of-care

Tiered and integrated testing networks are fundamental to ensure accessibility and equity in clinical testing for diagnosis and surveillance of disease and monitoring of treatment, see Figure 1. An integrated testing network can maximise the impact of limited resources by providing appropriate testing services tailored to the required scope and capacity of each facility. At the national level, services may be targeted towards disease surveillance, training, evaluation, quality assurance, and testing. Conversely, at the peripheral level, the focus may be on early detection of diseases of public health importance using simpler diagnostic tools such as microscopy and RDTs. District and tertiary levels offering expanded diagnostic capacity and scope would serve as referral centres for more complex diagnoses referred from the peripheral levels.

Point-of-care testing is emerging as an indispensable part of national disease control programmes. Certain IVDs are suited for use at point-of-care, particularly those that don't require phlebotomy or cold chain storage of reagents that are robust in adverse environments and for which results can be returned quickly to effect a decision for a given patient. The terminology of point-of-care test or device can be misleading as a product category, as it is where the IVD is used that determines if testing is at point-of-care or near to point-of-care, rather than certain properties of a particular IVD. It is critical that testing undertaken at point-of-care be included, and therefore supported, by the tiered testing network.

Each country will define the scope of testing services through a network that meets their clinical needs and expectations. It is advisable to assess aspects of the laboratory network including, but not limited to: disease patterns, existing supply chain infrastructure and function, laboratory services, infrastructure and personnel.

Figure 1. Illustrative example of the tiered testing network



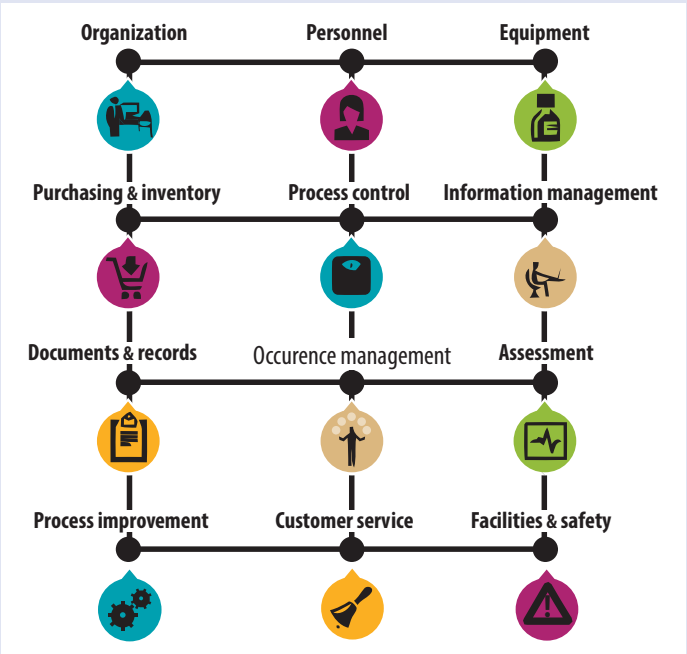
Source: Short, medium, long term product development priorities in HIV-related diagnostics. WHO expert meeting report. Geneva: World Health Organization; 2012
Note: with evolving technology development, POC-NAT may soon be possible at Level 1 health facilities.

Quality of testing

Any site conducting testing using IVDs should operate within a quality management system, see Figure 2. There are twelve components of a quality management system where a quality management system defines a systematic approach to ensuring quality of testing through use of **standard operating procedures**, management of **documents and records**, implementation of **process (quality) control**, and participation in **external quality assessment** (through proficiency testing and on-site supervision). The quality system must also extend to appropriate **physical infrastructure**, procedures for **purchasing and inventory**, equipment **maintenance, customer service, human resource management and review** including pre-service and in-service **competency-based training**, and continual process improvement (otherwise known as **quality improvement**).

Source: ISO 15189:2012 Medical laboratories -- Requirements for quality and competence, International Standards Organization, 2012

Figure 2. Twelve components of a quality management system



USERS OF IVDS

Needs assessment

A needs assessment must take into account the testing requirements at each level of any health system. Health facilities will vary within country, particularly in terms of human resource capacity, infrastructure, and client needs. It is important to ensure that procurement is aligned with country preferences through adherence to laboratory policies, minimum packages of care, and national care and treatment guidelines. In particular, national laboratory harmonization and standardization efforts should be observed and, if necessary, procurement practice should be unified with policy by ensuring that clinical, programmatic, and laboratory development and service delivery expectations are current and are responsive to the evolving public health demands.

In order to conduct or update a needs assessment for instruments and analysers, a checklist of 12 key aspects for procurement should be referenced, see Annex 1.

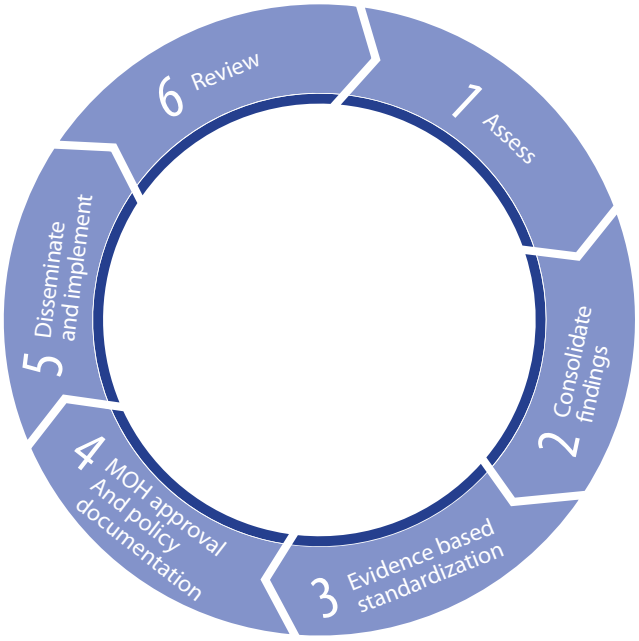
Standardization and harmonization

The 2008 "Maputo Declaration on strengthening of laboratory systems"[1] called on governments, donors, and implementing partners to ensure a commitment to work collaboratively, and in close coordination with national authorities to support sustainable laboratory system strengthening efforts. Moreover, to create a unified and aligned national laboratory network that responds to the public health needs of governments. Standardization efforts shape procurement policies and procurement practice, aiming to create efficient and rational use of reagents and instrumentation, streamlining of product selection and equipment maintenance approaches, and simplify forecasting and quantification.

There are many benefits in harmonization and standardization, but efforts can be challenging due to the implications of evolving diagnostic coverage and shifts in clinical needs that occur as part of health response efforts, health system maturation, existing procurement policies, policy and guideline adherence, as well as changes in existing demographic and morbidity demands. Therefore, attempts at harmonization and standardization should not overlook the requirement to recognize that these efforts are dynamic and require frequent reviews is an important principle to address as part of all standardization efforts and should inform forward planning initiatives (see Figure 3).

Harmonization and standardization policies should not be considered static. Reviews should occur periodically but implementation progress and technology updates can be reviewed more frequently as part of national quantification efforts. As systems and clinical demands shift, technology advances, and existing instruments age and become obsolete, national instrument lists and testing profile updates are required to align service delivery expectations and ensure the ability to provide such services.

Figure 3. The dynamic process of country-driven harmonization and standardization



A harmonization and standardization plan is a country-driven initiative supported by a multi-stakeholder approach usually conducted in a workshop setting through a consensus driven process. Firstly, a national test menu is developed, defined by tiered health care level. This effort should include clinicians and programme managers, as well as laboratory staff and procurement officers to ensure that the diagnostic needs are clearly defined. Then, the proposed test menu is reviewed by laboratory technical experts, to establish appropriate methodologies to be employed to provide such services. Efforts then focus on the development of a proposed harmonized instrument list by tiered level, the necessary ancillary equipment requirements, and staffing required to respond to the defined testing menu. All workshop activities conclude by developing a way-forward approach in advancing the final harmonization proposal and defining future procurement

1 Maputo Declaration to to Strengthen Laboratory Systems. Brazzaville, World Health Organization Regional Office for Africa, 2008. Accessed on 12 October 2016 at http://www.who.int/diagnostics_laboratory/Maputo-Declaration_2008.pdf

practice, see Figure 4. Critically, the outcome of the workshop must be accepted at the policy level in order for it to be effective and implementable.

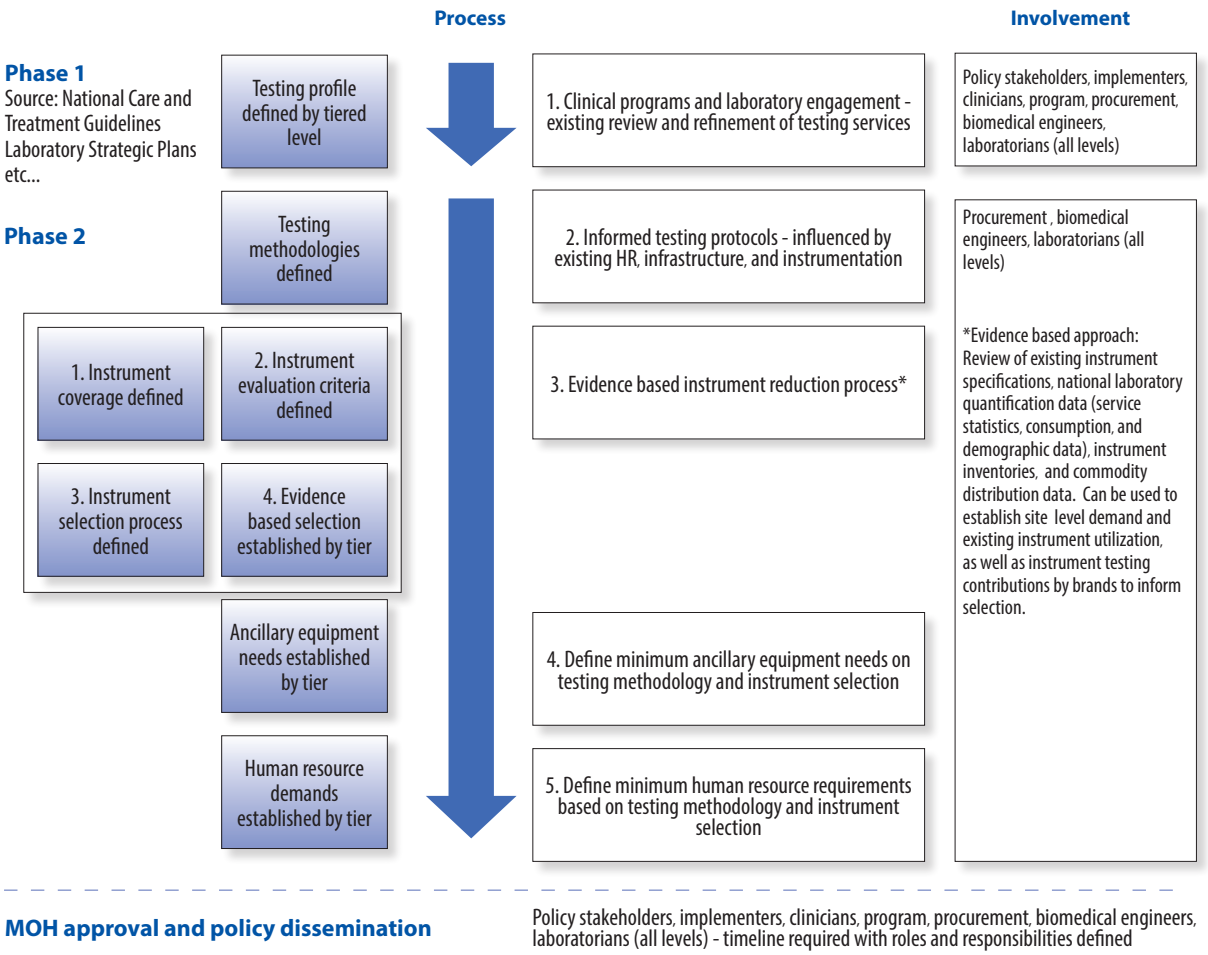
When implemented, standardization efforts streamline product selection, and therefore, procurement processes become more efficient, enabling economies of scale.

A rationalized test menu may simplify equipment maintenance, facilitate quality assurance (particularly external quality assessment) and post-market surveillance as performance can be compared across different testing sites using the same IVDs and allow standardized training of personnel. This can hereby reduce the total cost of ownership over time. Standardization can be of most benefit for analytes where there are multiple test procedures and high levels of instrument diversity, e.g. haematology and clinical chemistry.

It is important to note that standardization should not imply reducing competitiveness, assuming that limiting the number of instruments will lead to sole and single sourcing of instruments and reagents. Harmonization and standardization policies must be dynamic. Ongoing review and evaluation of testing services, instrument performance, as well as vendor performance guides the harmonization and standardization policy over time. Approved lists of instruments and vendors will shift based on technology and performance, potentially encouraging improved service and further competition.

It is critical to foresee instrument retirement or redeployment as a mechanism to maintain ongoing flexibility in technologies and test capacity within the network. Without clarity and national policy on how to retire or redeploy instruments, an inflexibility is created in the market that inhibits entry of technologies with better pricing, better terms and conditions, and diminishes competition. How to transition from one technology to another must be considered as part of procurement planning and later contracting methodology.

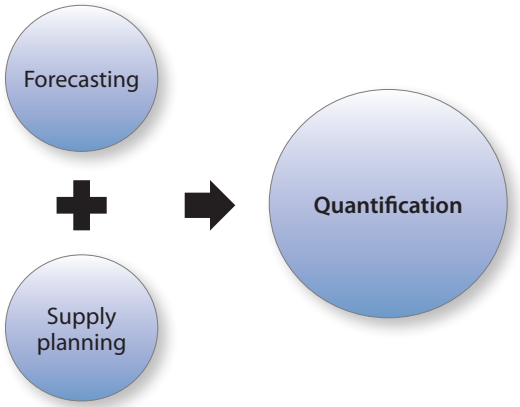
Figure 4. Developing a harmonization and standardization plan (Williams J. et al., 2016)



How to quantify procurement demand and make procurement decisions

Quantification is the broad concept that includes forecasting and supply planning i.e. *"How much will be procured and when will it be delivered."* It entails estimating the quantities and costs of reagents, equipment and consumables required. Quantification determines when products must be delivered to ensure uninterrupted supply by taking into account the expected demand, unit costs, stock already on order, expired stock and other wastage, freight, logistics, insurance and other costs, lead times and buffer stocks. The total commodity requirements and costs are calculated and compared with the available financial resources to determine the final quantities to procure.[2]

Figure 5. Elements of quantification



Additional reagents should be foreseen for the purposes of quality assurance, including lot verification testing, internal/external quality control and external quality assessment.

Standardization as described above should be a prerequisite for quantification. Each step of standardization and quantification (forecasting and supply planning) should proceed with input of all relevant national authorities including testing programmes and laboratories, the regulatory authority or other entity that decides on importation of IVDs, and local procurement agencies, as well as implementing partners such as financing agencies and international procurement agencies. It is critical that the quantification step is used to optimize usage of existing analysers already placed within the country, including those which may be used by other testing programmes. Certain multi-disease analysers are capable of utilising reagents for multiple pathogens, e.g. anti-HIV and anti-HCV or HIV TNA and HCV RNA. Therefore, different testing programmes should coordinate their testing needs and harmonize service and maintenance packages.

Forecasting is *"How much is needed, in quantities and cost, to meet the health demand of the population?"* This means estimating the expected consumption of commodities based on historical consumption, service statistics, morbidity and/or demographic data or assumptions when data are unavailable, to calculate the quantities of commodities needed to meet demand during a particular time frame.[3] It is a projection that is usually made for a 12-month period. The lack of high quality demand data contributes greatly to low quality forecasts and resultant stock-outs and wastage of supplies through under or over forecasting. Repeat testing due to invalid or non-returnable results should be accounted for, and re-tested when recommended programmatically to confirm a result before initiating treatment.

To increase forecasting accuracy, it is important to collect multiple data sets and use mixed forecasting methodologies for comparative purposes. Relying solely on one methodology will ultimately limit validation efforts and reduce forecasting accuracy. Efforts should be made to employ a mixed method approach. For existing programmes, demographic and morbidity based forecasting efforts and procurement history should be complemented with service level test numbers and consumption based forecasts. For new programme start-ups where historical service or consumption data is not available, demographic and morbidity may be the sole option.

Conducting multi-method forecasts can assist in measuring laboratory service delivery capacity and supply chain performance, and provide insights into the ability of a laboratory network to respond to overall programmatic expectations. By comparing expected demographic/morbidity estimates against past procurement and service statistics, programmatic gaps in service delivery and excess capacity can be quickly identified for targeted interventions. Comparing service statistics against consumption or issues data can identify wastage or inefficiencies in the existing supply chain. It is also possible to identify broader network issues related to general service delivery, as well as measuring the cost implications and determining approaches to create greater efficiencies.

Supply Planning is the final output of quantification, supply planning details the quantities required to fill the supply

2 Adapted from *Promising Practices Quantification: Forecasting and Supply Planning* http://siapsprogram.org/publication/promising-practices-in-supply-chain-management/

3 Adapted from *Promising Practices Quantification: Forecasting and Supply Planning* http://siapsprogram.org/publication/promising-practices-in-supply-chain-management/

pipeline, costs, lead times, and arrival dates of shipments to ensure optimal procurement and delivery schedules.[4]

USAID and Clinton Health Access Initiative (CHAI) developed **ForLab** (Forlabtool.com)– a laboratory commodities quantification software application. The software requires some level of training which can be provided upon request through CHAI and USAID via the Global Health Supply Chain, Procurement Supply Management (GHSC PSM) mechanism.

Budgeting

Any budget for testing services should consider the following four components:

- Infrastructure and other administrative overheads or operating costs;
- Personnel (salary, benefits, training);
- Reagents, consumables, durables, other supplies; and
- Equipment (analysers, ancillary equipment, other equipment).

The costs of test kits, reagents and associated consumables (e.g. for specimen collection, for waste disposal, biosafety) will be incurred as repeating costs. A quantification exercise can help to ascertain the quantities of each item that are required. Whereas the cost of an analyser may be one-off if managed as a capital purchase or nil if a reagent rental agreement is made whereby a higher unit cost for reagents is off-set by no cost for the analyser. Agreements for leasing of analysers will generally result in less cost for the equipment budget.

Where equipment purchase becomes an option, cost should also consider installation costs, as well as on-going preventive and corrective maintenance. Certain equipment such as biosafety cabinets, autoclaves, and water purification systems might require modification of existing infrastructure and specialised installation and validation, as well as annual certifications. This would need to be accounted for in the total cost of ownership. Certain analysers may require dedicated physical space or reinforced work benches, and dust-free environments through sealed windows and door jambs.

End-users might also contemplate to extend the manufacturer's warranty for certain analysers. Considering that the lifespan of most analysers at least three (five) years, negotiations to extend the manufacturer's warranty at the time of purchasing and installation will likely result in cost-savings and efficiencies in running analysers over time.

When practicable, it is advisable that certain testing programme may be funded across more than one disease programmes, e.g. HIV and antenatal care, HIV and hepatitis C or B, and HIV and tuberculosis. These programmes may be supported by domestic financing such as national health insurance and/or co-payments by end-users. Similarly, bilateral and multilateral agencies may choose to support some or all of the national testing programme.

Product selection for procurement

The methodology for product selection will depend on the procurement procedure used: 1) open tendering or 2) sole-sourced with adequate justification such as harmonisation/ standardization or validated testing algorithms.

Figure 6 outlines the approach as to how product selection fits within the process for uptake of IVDs.

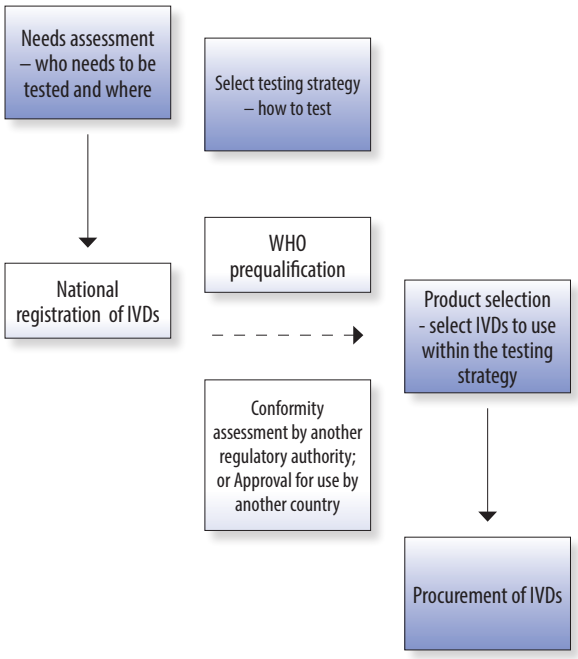
The following sections will outline the following specifications that should be considered for product selection:

- quality specifications
- product specifications (performance and operational specifications)

Quality specifications

It is critical the specifications indicate the requirements for quality assurance of product. With several exceptions, few national authorities have the capacity to evaluate the quality

Figure 6. Product selection procedure



4 Adapted from *Promising Practices Quantification: Forecasting and Supply Planning* http://siapsprogram.org/publication/promising-practices-in-supply-chain-management/

of products intended for procurement, and therefore rely on performance and operational characteristics to guide decisions on product selection. Procurement specifications should include some consideration of products that have been approved by (i.e. conforms to requirements of) WHO Prequalification of In Vitro Diagnostics or any of the founding members of Global Harmonization Task Force[5] (GHTF), see Table 1 for additional details.

Assessments of IVDs conducted by WHO prequalification and GHTF founding members provide an additional quality assessment over and above the nationally led product evaluation processes which will generally be restricted to an assessment of performance and operational characteristics only.

It should be noted that different regulatory versions of products are manufactured, meaning that a product presented for tender is not necessarily identical to that approved by the regulatory authority, with respect to all manufacturing procedures, processes and equipment, product code and labelling.

Table 1 provides information on the types of certificates that may be provided as part of tendering processes, these should be examined for validity and where possible verified with the certifying body.

Important note: Although conforming to certain internationally recognised standards for pre-market assessment and post-market surveillance which may increase confidence, users should be aware that false certificates have been identified and some issuing bodies may not meet international standards of rigour in their assessment process. It is therefore critical that national authorities through their regulatory bodies conduct post-market surveillance on IVDs. See separate WHO guidance on this topic at http://www.who.int/diagnostics_laboratory/postmarket/en/

Product specifications (performance and operational characteristics)

Product specifications are detailed statements of the buyer's requirements covering both the **technical** and **commercial** attributes that the product must satisfy for buyer acceptance. Minimum performance and operational criteria should be agreed for diagnostics to be selected for each level of the tiered testing network. These can be used to build minimum technical specifications for tendering processes.

Specifications must be clearly written to ensure accurate procurement that represents the highest quality for the best price/value. There must be sufficient detail to award the contract to the best and most appropriate vendor (manufacturer/supplier/distributor). Specifications must be clear and concise, and must avoid marketing jargon.

5 Founding members of the Global Harmonization Task Force as Australia, Canada, European Union, Japan, USA

Table 1. Examples of stringent regulatory assessment

Regulatory jurisdiction	Risk class[6]	Documentary evidence
European Union	Annex II, List A	EC Full Quality Assurance Certificate
		EC Production Quality Assurance Certificate
		EC Type-Examination Certificate
United States Food and Drug Administration	Class III	PMA letter or BLA license
Health Canada	Class IV	Medical Device Licence and summary report for a Class IV IVD
		CMDCAS-issued ISO 13485 Certificate
Therapeutic Goods Administration, Australia	Class 4	TGA Licence for Manufacture
		TGA Issued ISO 13485 Certificate
		AUST R Number
		TGA Full Quality Assurance Certificate
		TGA Type-Examination Certificate
		TGA Production Quality Assurance Certificate
Japan Ministry of Health, Labour and Welfare	Class III	JMHLW Minister's Approval
		JMHLW License for Manufacturer (seizo-gyo-kyoka)
		JMHLW Recognised Foreign Manufacturer (gaikoku seizogyosya nintei)

Note: WHO prequalification public report issued by WHO Prequalification Team would also be considered as stringent review. Financing agencies may also conduct certain types of quality assessment of IVDs.

Users of IVDs

For users who need more information on procurement specifications, WHO and its partners have developed a practical tool[6]. When conducting an assay, a range of additional consumables and/or reagents may be required, this tool provides a list of these items for each product listed. It is regularly updated to keep up with changes for inclusion of new IVDs and removal of obsolete IVDs.

For basic descriptions of the most commonly used categories of IVDs, see Table 2 for additional details.

Performance characteristics of IVDs

Minimum acceptable performance criteria must be agreed at national level between care/treatment programmes and laboratory programmes and include the following characteristics, as appropriate for the particular category, see Table 3 for additional details.

If the product has been approved by the country of sale and/or has been evaluated by the national reference laboratory in the country of sale, these performance data should be available. If data is unavailable, the list of WHO prequalified IVDs should be referred to where a link to the WHO prequalification public report can be assessed. WHO Prequalification of In Vitro Diagnostics provides an independent assessment of the safety, quality and performance of commercially available IVDs.

In certain circumstances, neither in-country evaluation nor WHO prequalification may have been conducted for an IVD submitting for tender. In these circumstances, data and documentation submitted by the vendor may be used to review compliance with expected performance characteristics.

6 Specifications and quantities for efficient procurement of essential equipment and laboratory commodities for HIV. Retrieved 12 October 2016 from http://www.who.int/hiv/pub/amds/amds_equipment-commodities-forecast/en/

Table 2. Formats of selected IVDs

Type	Format	Specimen type
Serology IVDs		
Rapid diagnostic tests	Immunofiltration (vertical flow)	Serum, plasma, venous/capillary whole blood
	Immunochromatographic (lateral flow)	Serum, plasma, venous/capillary whole blood, oral fluid
Simple assays	Indirect solid-phase enzyme immunoassays (e.g. comb assays)	Serum, plasma
	Agglutination	Serum, plasma
Immunoassays	Enzyme immunoassay (microtitre plate)	Serum, plasma
	Enzyme immunoassay (simple immunoanalysers)	Serum, plasma
	Chemiluminescence and electrochemiluminescence immunoanalysers	Serum, plasma
Confirmatory assays	Western blot, line immunoassays	Serum, plasma
Nucleic acid testing (NAT) technologies		
• **Polymerase chain reaction (PCR) including reverse transcriptase PCR (RT-PCR)** • **Branched DNA (bDNA)** • **Transcription mediated amplification (TMA)** • **Nucleic acid sequence-based amplification (NASBA)**	Qualitative NAT technologies for use at or near to point-of-care	Venous/capillary whole blood
	Qualitative NAT technologies for use in laboratories	Venous whole blood, dried blood spot (capillary/venous whole blood)
	Quantitative NAT technologies for use at or near to point-of-care	Venous whole blood, dried blood spot (capillary/venous whole blood), plasma
	Quantitative NAT technologies for use in laboratories	Venous whole blood, dried blood spot (capillary/venous whole blood), plasma
Flow cytometry (CD4 enumeration technologies)		
Single platform flow cytometer	Dedicated flow cytometers for use at or near to point-of-care	Venous/capillary whole blood
	Dedicated flow cytometers for use in laboratories	Venous whole blood
Dual-platform flow cytometer	Flow cytometers for use in laboratories	Venous whole blood

Use of HIV serological assays
For individuals over 18 months of age, HIV is typically diagnosed through the detection of HIV antibodies (a serological marker) and/or HIV p24 antigen rather than direct detection of the components of the virus itself (virological markers). Serological assays used for HIV diagnosis detect HIV-1/2 antibodies, with fourth generation serological assays incorporating detection of both HIV-1/2 antibodies and HIV p24 antigen. When HIV testing cannot discern a diagnosis, supplemental assays may be used, such as assays that detect HIV p24 antigen only or assays that can detect specific types of HIV-1 and HIV-2 antibodies.

Use of CD4 enumeration technologies
Immunological techniques such as CD4 enumeration are often used to monitor the immunological response to HIV infection as a predictor of disease progression, and in management of opportunistic infections.

Use of HIV nucleic acid testing (NAT) technologies
For HIV early infant diagnosis (under 18 months of age), virological assays including nucleic acid testing (NAT) technologies and ultrasensitive p24 antigen enzyme immunoassays may be used to diagnose HIV infection.

Nucleic acid testing is also used for monitoring purposes such as to monitor viral suppression, i.e. the virological response to antiretroviral therapy (ART).

Table 3. Performance characteristics for HIV IVDs related to their intended use

Serology assays for diagnosis
Clinical sensitivity
Analytical sensitivity
Clinical specificity
Invalid rate/run
Inter-reader variability, if subjectively read
CD4 enumeration for monitoring
Intra-assay variation
Inter-assay variation
Inter-instrument variation
Carry-over studies
Invalid rate
Trueness of measurement: bias, misclassification
Nucleic acid testing technologies (NAT) for diagnosis – infant and adult
Clinical sensitivity
Analytical sensitivity
Clinical specificity
Invalid rate
Trueness of measurement: misdiagnosis
For all claimed specimen types
Nucleic acid testing technologies (NAT) for monitoring
Intra-assay variation
Inter-assay variation
Inter-instrument variation
Linearity
Invalid rate
Analytical sensitivity for subtypes
Limit of detection
Limit of quantification
Robustness
Trueness of measurement: bias, misclassification rate, specificity
For all claimed specimen types

Table 4. Operational characteristics for HIV IVDs

Operational characteristics		
Specimen type		
According to product's instructions for use	Venous whole blood	Capillary whole blood
	Serum	Oral fluid
	Plasma (including specific anticoagulants)	Dried blood spots
	Any stabilizers used	Plasma separator devices
Detection type		
	Combined or discriminatory detection of antibodies	
	Combined or discriminatory detection of antigen and antibodies	
	Single platform flow cytometer	
	Qualitative or quantitative detection of nucleic acid	
Subtype detection		
Relevant subtypes to be detected	Groups M (including A, B, C, D, F, G, H, J, K, AG, AE) N, O	
Incubation period		
Minimum reading time	May range from read immediately up to 30 minutes, after addition of specimen/buffer	
Maximum reading time	May range from 10 minutes up to 60 minutes, after addition of specimen/buffer	
Ease of use		
Consider combination of the following aspects	Specimen collection requirements, e.g. finger-stick whole blood or venous whole blood by venepuncture	
	Number of steps in the test procedure	Number of steps that require precision
	If visually read, ease of reading the test band, line, spot, e.g. few faint bands	If visually read, ease of interpretation of testing results, e.g. more bands = more complicated
Extent of infrastructure required at testing sites		
Are there any infrastructure requirements that would prohibit use of certain assays?	Refrigeration for storage of reagents	Refrigeration of reconstituted reagents and controls
	Electricity/generator	Temperature-controlled work space
Storage/stability		
Transport requirements for reagents (temperature, humidity)	Any product tolerance excursion ranges accepted during transit? Any specialized shipping requirements?	
In-use stability for specific reagents (temperature, humidity)	Any specific requirements once reagents are opened or once the specimen is added to test device/cartridge?	
Equipment/consumables required but not provided in the test kit		
Reasonable exclusions from the test kit - can these be obtained from the manufacturer/distributor or obtained separately?	Lancets, alcohol swabs, cotton wool for finger-stick whole blood	Blood collection equipment for venous whole blood
	Other general laboratory consumables: gloves, pipettes, etc.	
Specimen throughput and individual testing service delivery models		
Throughput per operator/provider	For RDTs, ≤10 specimens per hour per operator with limited laboratory infrastructure	
	For EIAs, ≥40 specimens per day per operator with standard laboratory infrastructure	
NAT	For POCT, depends on instrument but usually no more than 1-2 specimens per hour per operator	
	For laboratory, depends on instrument but usually no more than 24 specimens per run per operator	
CD4 enumeration	For POCT, depends on instrument but usually no more than 4 specimens per hour per operator	
	For laboratory, depends on instrument but usually no more than 24 specimens per run per operator	
Technical skill of staff conducting testing		
Number of precision steps required	E.g. counting of multiple drops, timing of steps required, use of precision pipette, interpretation of results	
Phlebotomy required	Venepuncture for serum/plasma	
Quality control, including procedural controls		
Serology	RDT: Control line appears when human specimen is added (i.e. qualitative IgG control, likely not to indicate adequate volume of specimen) **AND/OR** RDT: Control line appears when reagents only are added (i.e. does not indicate addition of human specimen)	
	EIA: Colour control upon addition of specimen and/or certain reagents	
NAT	Amplification control, quantification control, contamination control, dilution of specimen	
CD4 enumeration	Control beads	
Availability of internal test kit controls and external quality control specimens	Compatibility with quality control materials; some are available but separate from test kit.	

Operational characteristics of IVDs

The operational aspects of diagnostics are equally as important as the performance characteristics, and thus both must be considered in product selection, and within technical specifications. Consideration should be given to the platform, costs and logistics required to perform the assay including but not limited to the following, see Table 4 for additional details.

Specific issues related to IVDs that require equipment

Laboratory equipment can be divided into several broad categories:

- Analysers – those that consume reagents, consumables and produce a test result. Usually repaired and maintained by service contracts.
- Ancillary equipment – freezer, washers, readers, incubators, etc. Usually repaired and serviced by in-country biomedical engineers.
- Other equipment – biosafety cabinets, autoclaves, water purification systems. Requires infrastructure modifications, installation and validation, as well as annual certifications.

Increasingly laboratory information management systems (LIMS), and connectivity-related equipment and software are being deployed to testing services. These should be considered when conducting procurement, particularly as an aid for integration between disease programmes that may use the same analyser. It will be critical to determine the compatibility of analyzers with built-in connectivity solutions to existing LIMS i.e. their ability to interface with open source LIMS.

Analysers can be further classified as closed systems and open systems. Closed systems are those analysers which use manufacturer-specific reagents only. Closed systems may be advantageous due to the use of specific reagents that are validated by the manufacturer to assure accuracy and reproducibility of test results and maintenance of equipment integrity and warranty. Open systems are those analysers that use reagents from other manufacturers. These are sometimes referred to as open polyvalent platforms. These open systems must be validated by the end-user before testing commences.

The major benefit of an open system is the potential for lower cost reagents, see Table 5 for additional details.

Table 5. Comparison of open and closed systems (analysers)

Closed Systems	
Advantages	**Disadvantages**
Greater control over reagent quality	Reagents are single or sole-sourced
Tighter inventory control may be required	Increased commodity diversity across the laboratory network
	Required use of vendor specific controls and service providers
Open systems	
Advantages	**Disadvantages**
Increased competition for reagents	Potential for lower quality
Decreased difficulty in obtaining stock	Potential for greater variability in test results
Reduced commodity diversity – ability to share products across multiple open platforms	

Specifically for procurement of laboratory-based IVDs

Reagents are items that generally require specific adherence to cold chain with very narrow range of temperature tolerance/excursion. Reagent transport and storage temperatures usually range from 2° to 8°C but can be as low as -10° and -25° C, depending on the reagent. It is important to recognize that standard cold chain transport packaging can maintain these levels of temperature control for upwards of 72 hours without repackaging, although frozen reagents create further challenges due to the requirement for viable dry ice. Any delays at customs or with a shipping agent could place these high cost items immediately at risk upon arrival in-country. Once in-country, these products must then be transported either to a centralized facility for wider distribution, or directly to the end user facilities within the cold chain range specified by the manufacturer.

To ensure commodity viability, it is recommended prior to selecting and procuring a specific analyser to:

- Understand cold chain requirements for reagents;
- Address any existing logistics challenges associated with the importing and distribution of such reagents, prior to instrument procurement and deployment decisions being made;
- Ensure roles and responsibilities are clearly delineated, with responsible parties held accountable for lost product if cold chain is compromised;
- Ensure that manufacturers are engaged to provide possible logistics and infrastructure support, even if analyser are donated;
- Ensure proper storage facilities, transport procedures, and policies are in place to avoid the potential of significant loss of product due to breaks in cold chain between the procurement agent and the end user;
- Whenever possible, ensure in-country distributors of such products are used, with direct deliveries to end users to further reduce risk of product loss and liability; and
- Ensure close coordination between the national authorities, laboratory personnel, implementing partners, procurement agencies, and commodity distribution and other logistics services to ensure that all logistics challenges are addressed for this product type.

Testing strategies, validation of testing algorithms, and standardization and harmonization

Countries should have developed national policies and strategic plans[7] for testing services, including laboratory-based testing services, other health facilities and community-based settings. National guidance will provide the expected scope and standardization of testing services. It is important to remember that considerable heterogeneity of testing needs will exist within a single country, and so a single testing algorithm may not fit all needs.

National authorities and technical experts should be consulted to ensure that any proposed selection of specific products is harmonized with the relevant national policies including policies on standardization and national validated testing algorithms, as described below.

Standardized testing strategies for specific testing objectives

WHO recommends standardized testing strategies to maximize the accuracy of diagnosis while minimizing cost and increasing simplicity. **A testing strategy** describes a testing sequence for a specific objective, taking into consideration the presumed disease prevalence in the population. Whereas, a **testing algorithm** describes the specific branded products (assays) that will be used within a given testing strategy.

This terminology can be applied to a variety of testing objectives, e.g. testing strategy for diagnosis of HIV infection, testing strategy for monitoring the response to antiretroviral therapy, etc.

Standardized testing strategies should apply equally to facility-based testing (for example, in laboratories, stand-alone testing sites, clinical facilities and other testing services) and non-facility-based testing (for example, community-based testing conducted outside of the conventional health facilities). All personnel who perform testing, including specimen collection, the testing procedure and reporting of results should adhere to these testing strategies. This includes both laboratory staff and other health workers who are trained for these tasks, including through task sharing.

Refer to the relevant WHO guidance on testing strategies for specific testing objectives, e.g. WHO consolidated guidelines on HIV testing services, WHO consolidated guidelines on viral hepatitis testing services, WHO laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus, etc.

Product selection - validated testing algorithms

Once a testing strategy has been selected, the products to be used must be validated as a testing algorithm – another form of standardization through product selection. Product selection at national level should be conducted by the national reference laboratory or another facility designated by national authorities for this task. Such studies should validate a product or combination of products, as they will be used within a standardized testing strategy.

A pre-selection of candidate assays should be selected taking into account the considerations for desired quality specification, and product specifications (performance and operational characteristics). For testing strategies that use more than one assay (e.g. HIV diagnosis), it is critical to ensure that assays do not share common false reactivity for the same specimens. Therefore, selection of assays with different antigen preparations should be considered as a preliminary step. Although, it is acknowledged that this information is rather difficult to obtain and increasingly, original manufacturers sell semi-finalized or finalized product to other manufacturers who re-assemble test kits as re-branders/re-labellers. This practice makes it difficult to determine the exact provenance of diagnostics, and therefore, predict common false results between assays.

Validated testing algorithms are preferable at each level of the health system with additional products available as back-up options, in case of stock-outs, certain defective lots or product failures. Where a nationally validated testing algorithm exists, only assays that are part of the algorithm should be procured unless otherwise indicated, with sufficient justification, by national authorities.

See annex 2, for guidance on how to conduct a verification study for product selection.

Equipment Maintenance

Preventive equipment maintenance should be scheduled on a daily, monthly, quarterly, and annual basis, depending on the type of analyser/equipment. Some tasks, as listed in the instructions for use accompanying the analyser should be performed by the operator and be part of the training at the time of installation. It is important that standard operating procedures (SOPs) are developed for all equipment maintenance with associated records maintained. Failure to perform required operator preventive equipment maintenance may invalidate the maintenance contract. More complex tasks may require supplier-approved trained and certified service personnel.

7 WHO guidance on development of national strategic laboratory policy and plans http://www.wpro.who.int/health_technology/documents/docs/Nationalhealthlab2_0F38.pdf

It is imperative that end-users are aware of the terms and conditions of preventive maintenance contracts for analysers and equipment that has been assigned to them. Ensuring that vendors conduct equipment maintenance activities that have been contracted, is also required.

Post-market surveillance, including lot testing and complaint reporting

Ensuring continuous product quality and compliance with minimum performance criteria through post-market surveillance is another necessary part of the procurement cycle. Post-market surveillance of IVDs empowers national authorities (and WHO) to detect, investigate, communicate and contain events that threaten public health security and to take appropriate action. Post-market surveillance can be divided into reactive and proactive measures.

Reactive - Information on quality, safety or performance of an IVD on the market is collected reactively through notification by users and evaluation by manufacturers of complaints (including adverse events). The reactive nature of this statement refers to the fact that the problem has already occurred, and may have affected a clinical decision.

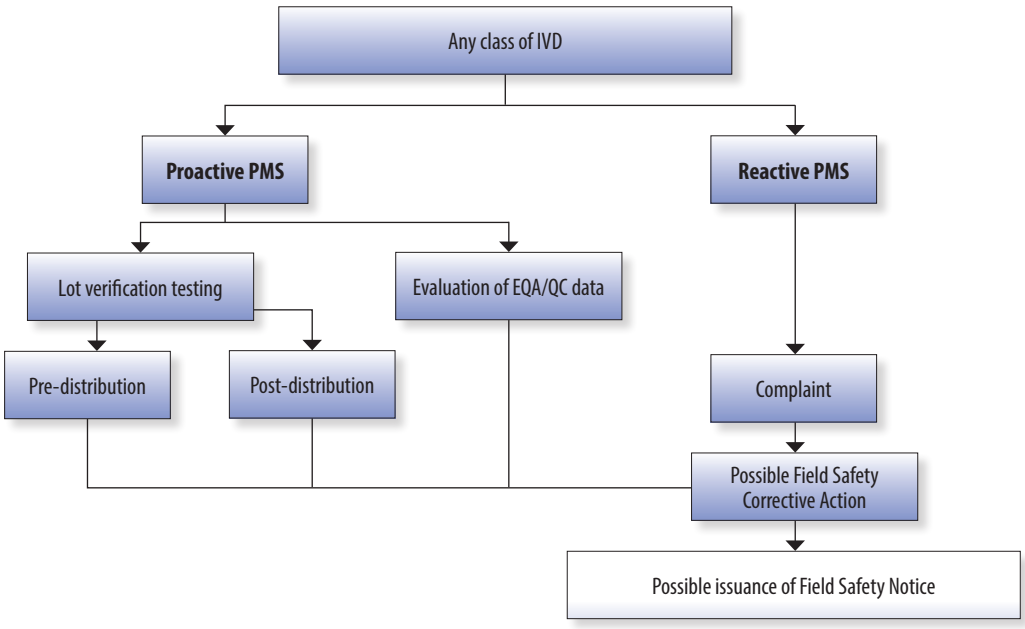
Proactive - Additional information on quality, safety or performance may also be collected proactively through lot verification testing. This relates to proactively trying to identify a problem before it affects a clinical decision. Lot verification testing is conducted after shipment to the buyer (countries) and can be performed both pre-distribution and post-distribution to end-users.

Manufacturers should also collect post-market surveillance through actively gathering evidence from the literature on their product or similar products, through seeking feedback from customers, and post-market clinical follow up. This is a critical aspect that will not be widely covered in this guidance as has been published elsewhere[8]. Figure 7 illustrates the post-market surveillance processes for IVDs.

Health facilities that perform testing within a functional quality management system are more likely to be able to detect substandard lots of reagents and faulty or malfunctioning equipment.

An experienced end-user may often be able to identify problems related to the diagnostic and/or related laboratory equipment. Daily quality assurance measures will assist the user to obtain information about potential quality problems; routine quality control (QC) e.g. with test kits controls provided within the test kit and/or available from manufacturers separately, or external QC material; regular participation in external quality assessment schemes (EQAS); equipment maintenance schedules as well as other QA measures such as good recordkeeping and competency-based training.

Figure 7. Post-market surveillance for in vitro diagnostics



8 WHO. Guidance on post-market surveillance for in vitro diagnostics. Geneva. 2015. http://www.who.int/diagnostics_laboratory/postmarket/en/

The following quality indicators should be monitored, as appropriate:

- Percentage of defective consumables e.g. specimen transfer pipettes, lancets;
- Percentage of invalid test devices (if single use devices such as RDTs);
- Percentage of invalid runs (disaggregated by error codes);
- Percentage of equipment breakdown and respective down time
- Percentage of out-of-range QC results; and
- Percentage of discrepant results within a testing algorithm consisting of two or more assays.

Monitoring complaints, including adverse events

Complaints about product quality and performance can be submitted to the relevant regulatory authority, and to WHO if the product is WHO prequalified, for follow-up and action[9]. Manufacturers are obliged to investigate reports of poor performance as part of their quality systems requirements.

Complaints may include:

- **Administrative/contractual complaints or inquiries** related to any aspect of the procurement contract not fulfilled e.g. agreed delivery time not adhered to, agreed guaranteed shelf life upon delivery not adhered to, incorrect product and/or quantity delivered, etc.
- **Technical complaints**, affecting the safety, quality or performance of an IVD, for example: malfunction or deterioration in the characteristics or performance, inadequate design or manufacture; inaccuracy in the labelling, inappropriate instructions for use and/or promotional materials, or any other issues might be reported that result in a significant public health concern. Information about such issues may become available in other ways than through reporting (for example through literature and other scientific documentation).

Adverse events should be reported in any of the following circumstances:

1. When an incident leads to death of a patient, user or other person.
2. When an incident leads to serious deterioration in health of a patient, user or other person (also known as serious injury).
3. No death or serious deterioration in health occurs but the event might lead to death or serious deterioration in health.
4. When an incident might happen as a consequence of a medical decision or action taken or not taken on the basis of results given by the IVD, typically:
   - Misdiagnosis:
   - Delayed diagnosis;
   - Delayed treatment;
   - Inappropriate treatment;
   - Transfusion of inappropriate (contaminated) materials including blood products, tissues or organs.
5. Use errors that did result in death or serious deterioration in health or that have a negative trend with the potential for death or serious deterioration in state of health or public threat.

Users should document any problems using information taken from the testing logbook/register and inventory records including affected product code(s), affected lot number(s) and expiry date(s), serial number of affected instrument, affected consignments or test kits, affected users, and any measures taken, including taking photographs of affected test devices and/or test kits to illustrate the complaint.

If a field safety corrective action (FSCA) is required, it is usually communicated to affected users in the form of a Field Safety Notice (FSN). It is critical that procurers are aware of any relevant FSN that might affect products they have procured.

A FSCA may include:

- Return of an IVD to the manufacturer or its representative;
- IVD modification (retrofitting an instrument, changes to labelling or instructions for use, software updates, modification to clinical management of a patient through re-testing affected patients or with closer clinical supervision) ;
- IVD exchange;
- IVD destruction; or
- Advice given by the manufacturer regarding the use of the IVD (e.g. where the IVD is no longer on the market or has been withdrawn but could still possibly be in use).

Lot testing

To ensure that IVDs continue to meet their specifications, manufacturer must assure that in-process and final quality control lot release testing is conducted. As a complementary measure, national regulatory authorities have the mandate to arrange proactive lot verification testing including:

- Pre-distribution to testing sites (when a consignment of test kits arrives in country); and
- Post-distribution to testing sites (after the lot has already been in use).

See later section for national regulatory authorities for guidance on lot verification testing.

9 For more information and IVD complaint reporting forms in English and French see the WHO website http://www.who.int/diagnostics_laboratory/procurement/complaints/en/index.html

PROCURERS OF IVDS

The United Nations Commission on International Trade Law (UNCITRAL) developed the Model Law on Public Procurement that countries, organizations and private entities are encouraged to adopt. The UNCITRAL provides detailed definitions and regulatory framework that should be reviewed by readers of this guidance.

The following methods may be used to procure IVDs, and related products:

- International competitive bidding; or
- Restricted bidding.

Standard procurement practices rely on international competitive bidding. However, due to the highly-specialized nature of certain IVDs, and particularly analysers, **bidding may need to be restricted to products stated in national standardization exercises and/or national validated testing algorithms.** It is essential that such restricted bidding be fully justified with written evidence for selection such as a national validated testing algorithm study.

However, there may be certain categories of consumables, durables and auxiliary equipment[10] that may be purchased through competitive bidding.

Sourcing vendors

Potential vendors (manufacturers, suppliers and distributors) should be identified through a fully transparent process. Due to the wide range of IVDs and their suppliers, it is pertinent to pre-select suppliers. Pre-selection, as defined according to the UNCITRAL procurement law is: "*… to identify, prior to solicitation, a limited number of suppliers or contractors that best meet the qualification criteria for the procurement concerned*"[11].

Regardless of whether vendor pre-selection is employed or not, certain information should be collected and evaluated to ensure that the vendor is commercially viable and capable of supplying to the terms of the bid. This would usually take place in the context of the bid evaluation.

Methods for sourcing vendors include:

- Publication of a request for expressions of interest (EOI);
- Communication with technical organizations such as WHO or other relevant bodies;
- Invitation of specific vendors based upon market research.

10 See glossary for examples.

11 United Nations Commission on International Trade Law. 2011. UNCITRAL Model Law on Public Procurement. Accessed on 12 April 2013 at http://www.uncitral.org/pdf/english/texts/procurem/ml-procurement-2011/ML_Public_Procurement_A_66_17_E.pdf

When procuring a range of laboratory products, it may be possible, and more efficient, to break down the list of products into functional lots to enable suppliers to bid on ranges of products offered. For example, a single lot may contain larger ancillary equipment such as autoclaves, centrifuges and ultralow temperature freezers, whereas a second lot may contain small consumables such as gloves and pipette tips. The laboratory product market is fragmented such that not all suppliers will have the capacity to bid on all lots. Breaking items down into lots provides the greatest opportunity to receive high quality products at the lowest price.

Embargos

During vendor selection, any embargos enforced by the country of sale and intended use should be noted. Any embargo should be stated in the bidding documents or at the very least, bidding documents should carry a statement requiring vendors to check legal obligations for international trade.

Bid solicitation

The method of bid solicitation (invitation) will vary according to the rules of the procuring organisation. The following section conforms to guidance set out in the United Nations Procurement Manual. However, certain donors and other implementing partners may have specific procurement guidelines and conditions for countries benefitting from their funding.

Methods of solicitation

The method of solicitation may vary according to the product type, see Table 6.

Table 6. Three methods of solicitation for international bidding

Bid solicitation	Criteria
Request for Quotation (RFQ)	For procurement of simple, uncomplicated goods with standard specifications (with smaller value, less than US$ 40 000).
Invitation to Bid (ITB)	For procurement of simple, uncomplicated goods and services of standard specifications (with larger value, in excess of US$ 40 000).
Request for Proposal (RFP)	For procurement that cannot be quantitatively or qualitatively expressed in sufficient details to permit use of ITB.

Only in exceptional circumstances would a deviation from these methods of solicitation be permissible. Such decisions should be made with respect to rules of the national authorities and/or funding agencies.

Solicitation documentation

The solicitation documentation should contain a number

Table 7. Key considerations for bid solicitation documents

Element	Consideration
Quality management system specifications	Provision of appropriate quality management systems for manufacture, e.g. ISO 13485 Medical devices -- Quality management systems -- Requirements for regulatory purposes for IVDs, ISO 9000 series for other laboratory products, etc. Evidence of meeting WHO prequalification requirements in the form of a valid WHO prequalification public report may also be accepted. Certain financing agencies may have their own quality policies.
Product specifications	Minimal acceptable criteria for performance and operational characteristics for IVDs and the accepted method for authenticating such claims, e.g. manufacturer's instructions for use, performance evaluation report from national reference laboratory, conformity assessment report, WHO prequalification public report, etc. Should not refer to brand names, product codes or be specific for branded items unless the sole-source bidding is in effect. In case of sole-source bidding, documented justification should be part of the bidding documents, and the bid submission. For example, IVDs that have been validated as part of a national testing algorithm require sole sourcing so the technical specifications should include the brand name, product code and regulatory version to be supplied.
Delivery terms	Inclusion of expected date of delivery in calendar days (e.g. 60 days) at place of delivery as per INCOTERMS 2015.
Guaranteed shelf life upon delivery	**Guaranteed shelf life upon delivery differs from shelf life upon manufacture.** It is important to specify required shelf life upon delivery in the bid solicitation documents. For IVDs, it is generally accepted that the reagents have a minimum of 80% of the shelf life upon delivery remaining at the time of delivery. For example, a rapid diagnostic test may have claimed shelf life upon manufacturer of 24 months. The manufacturer may decide to only agree to a guaranteed shelf life upon delivery of 18 months, this allows for rotating stockpile of product within their warehouse. Therefore, they would need to supply product with at least 14 ½ months. However, this guarantee is highly dependent on the INCOTERM that is selected, see Annex 3. For example, if EXW then the responsibility for the product is no longer on the seller (manufacturer) when the buyer picks up the goods from the factory. The seller therefore, can control how long it takes for the goods to arrive at the end user. If using so-called longer INCOTERMS such as CPT, CIP, DAT, DAP, DDP, the guaranteed shelf life upon delivery will be easier for the seller (manufacturer) to control. Provision for staggered deliveries should be considered when guaranteed shelf life is short and annual procurement is favoured. Staggered deliveries allow for annual purchase of diagnostics under a single procurement contract but with multiple delivery times. For example, annual supply of HIV RDTs could be delivered in quarterly intervals to ensure best guaranteed shelf life and avoid the need for large storage areas. The additional costs for shipping should be off-set against wastage due to expired products.
Clauses with a price impact	These will include but are not limited to: insurance, INCOTERMS (transfer of ownership), warranties, guarantees, distributor or agent fees.
Consideration of "total cost of ownership"	Total Cost of Ownership (TCO) refers to all costs relating to the acquired product whether direct or indirect, fixed or variable. TCO may include final price (distributor's share), upgrade, storage, supplies, additional operating costs, disposal costs, volume discounts, internal processing costs, etc.
Provision for installation, training, maintenance	Explicit provision for installation, then pre-service and in-service training. Explicit provision for preventive and corrective maintenance schedules for the expected lifespan of the analyser/equipment.
Warranties	Warranties are usually required for ancillary and other large laboratory equipment. A warranty requires the manufacturer (or vendor) to ensure manufacturing faults are rectified within a specified time period, usually 12 months. Warranties usually include provision for equipment repair that includes parts and labour and/or total replacement where necessary. Warranties should not be expected to cover problems related to poor/incorrect installation, if not performed by the vendor or vendor-specified agent, use or maintenance. The exact nature of the warranty should be clearly specified in the contract.
Regulatory versions	Which regulatory version will be supplied and which regulatory version was used to generate evidence to meet the technical specifications.

of necessary elements to ensure a successful, transparent and unbiased bidding process, see Table 7.

Sole-source justification

In some cases, no or too few in-country suppliers exist to make open competitive bidding a realistic option. While this scenario is undesirable, it may exist where manufacturers have exclusive agreements with a sole distributor or where few products are registered. Reagents for closed systems will require sole-source justification. If there is a direct request for a specific assay or analyser, there would need to be evidence to show that brand selection is justified in a fair and open manner. An important consideration in the justification of specific products is their inclusion in national policy and/or guidelines.

INCOTERMS and insurance

INCOTERMS are commercial terms established by the International Chamber of Commerce which are used to govern procurement contracts by defining the responsibilities and liabilities of the buyer and the seller. It is a series of three letter trade terms to communicate tasks, costs, when risk passes from the seller to the buyer, and when delivery legally occurs.

INCOTERMS must be specified for each product or range of products and are particularly important in consideration of the complex shipping and storage requirements of IVDs. For example, maintenance of cold-chain storage must be assured for the duration of the shipping and distribution process can be assured using the correct INCOTERMS. Some products are very sensitive to fluctuations in environmental conditions and cold packing or dry ice may require replenishment during shipping. Responsibility for transportation and storage conditions should be made clear by indicating the specific INCOTERM on the bidding documents, see Annex 3.

The contract should ensure that the vendor (seller) has responsibility until the products have reached the delivery point and that the delivery point should be clearly defined.

The procuring organisation must have appropriate insurance for all products, including reagents, equipment, consumables and durables throughout the transportation and storage process. This is especially important when the INCOTERM states that vendor (seller) responsibility ends when the consignment is delivered to the port of entry as the designated place. Complex requirements for customs clearance may be required and the correct storage of goods must be observed while waiting for the goods to clear.

Certain goods will require transportation at specified temperatures. The specified transportation and storage temperatures must be ensured at all times. If cold chain storage is not specified, goods will usually be transported as general cargo. Caution should be taken to ensure goods such as reagents remain within temperature ranges validated by their manufacturer. In some cases, IVDs are validated as stable at 2 to 30 °C, yet storage facilities in tropical climates may exceed such temperatures.

For some settings, goods are delivered from the port of entry to a centralised warehouse (e.g. central medical stores). From this point, the goods are distributed to testing sites according to demand and pre-determined delivery schedules. It is particularly important that sellers and/or buyers have insurance on storage facilities throughout the supply chain.

Central medical stores should have standard operating procedures in place for storage of IVDs including reagents, durables, consumables, equipment, and analysers.

Bid evaluation

Clear directions on the bidding process must be provided in the solicitation documents and must be adhered to strictly. Receipt of bids must be carried out in a transparent and consistent manner and must ensure fairness to all bidders. Bids may be received by hardcopy and can be stored in electronic format.

Commercial and technical evaluation of the bids should be performed separately. The bid evaluation committee should consist of a specialist evaluator for each of these parts i.e. a technical evaluation team and a commercial evaluation team, consisting each of at least two or more appropriately qualified members. The technical and commercial parts of the bid can be evaluated concurrently at the discretion of the bid evaluation committee.

Quality and appropriateness for the intended purpose should be the primary evaluation criteria. A product that does not conform to minimum quality standards or is not appropriate for the intended use should never be procured, no matter the price. Once quality, safety, performance, and appropriateness have been determined, UN practices can be followed: (1) best value for money, (2) fairness, integrity and transparency, (3) effective international competition, and (4) the interest of the end-user.

The bid evaluation is separated into three stages:
1. The bid response;
2. Preliminary examination of bids;
3. Evaluation of substantially responsive bids.

Bid response

Bids must be opened at the time specified in the solicitation documents and all participating vendors are permitted to be present. At the opening, bids must fulfil the requirements set out in the solicitation documents. Minor corrections that do not affect the substance of the bid may be made at this time.

The procurer can reject a bid at this stage if:
- Bidder is not qualified;
- Bidder does not accept required minor corrections;
- Bid is not fully responsive;
- Bid is abnormally low; or
- Unfair competitive advantage or conflicts of interest are found.

Successful bid responses are registered and will then pass to the next stage of bid evaluation. Unsolicited submissions should be rejected.

Important note: Negotiations between procurer (buyer) and vendor (seller) must never occur with respect to any tender as this represents unfair advantage during/after the tendering process.

Preliminary examination of bids

This preliminary review of bids examines eligibility, completeness, errors, legal validity, bid validity, bid security, plus substantial responsiveness to commercial and technical specifications. It is usual to confirm that each vendor responded completely to every lot. A preliminary review may be made of the technical specifications. At this stage, a check is made to verify that required documentation is present to support the bid evaluation. The quality and correctness of that documentation is further assessed in the next stage.

Evaluation of substantially responsive bids

After preliminary review and initial qualification, each bid is closely reviewed and the technical, quality and performance characteristics of offered goods are evaluated. Quality and appropriateness for the intended use are primary criteria. Price comparisons should only be made after the technical review.

Evaluation criteria are based upon technical specifications and commercial requirements. It is important to ensure evaluation criteria are measureable and objective, where possible. A bid may be found non-responsive, and therefore be disqualified at any stage of the evaluation process. Any reasons for disqualification should be made and incorporated into the final bid evaluation report. In general, the pool of substantially responsive bids that make it to the post-qualification stage is likely to be small.

The lowest evaluated responsive bidder must be established i.e. the post-qualified bidder with the lowest price that offers best value for money. Domestic preference and prevailing import duties on goods may also be considered at the final stage of the decision process. In cases where the manufacturer rather than the manufacturer's distributor or agent submits a bid, it is important to ensure prices are provided taking into account local fees and charges. Price transparency is important to ensure financial resources are sufficient to cover all procurement costs.

All bidding vendors should be informed of the final decision; selection or rejection.

Commercial considerations of the vendor

The commercial viability of the manufacturer and sustainability of the product or technology must be examined. Reagents and technical support for diagnostic platforms should be available for the working life of the analyser or equipment.[12] Commercial considerations of the vendor are important especially for procurement of closed systems . The procurer, in conjunction with technical experts, must assess the potential risks such changes in platform technology, discontinuation of future technical support, and financial stability of manufacturer/ supplier/ distributor and therefore long term viability.

The prior commercial track record of manufacturer (or vendor) must be examined to ensure capacity to deliver reagents on-time in-full, and provision of post-sales technical support. It may be that in-country agents or distributors carry out some or all of these tasks on behalf of the manufacturer. Some common example commercial specifications include: evidence of previous large transactions, ability to maintain supply of reagents at specified temperatures during transit, prior experience with country of supply or equivalent setting, etc.

Contracting

The contractual process begins once a bid has been awarded. It is important that both legal and technical expertise is involved in the development of contracts for laboratory products, particularly for analysers. The method of contracting may vary and will depend on the nature of product, see Table 7.

Table 8. Types of procurement contracting

Contract type	Considerations
Purchase order (PO)	POs are reserved for low value procurements, usually less than US$ 4,000. Terms and conditions are set forth within the PO which constitutes a legally binding contract between seller and buyer. Any related documents must be clearly indicated and supplied with the PO.
Customized contracts	Due to the complexity of laboratory products, customized contracts that are individually worded (as opposed to a set of Standardized provisions) are usually required. Customized contracts required detailed written information/ instructions that clearly define the obligations of both seller and buyer.
Systems contract, blanket POs and long term agreements (LTA)	These types of contract are used for products that may be required on a recurring basis or over an extended period of time. The buyer enters a mutual arrangement with a supplier (the seller) to provide goods or services with quantities to be determined at prescribed prices or pricing provisions. Long-term purchase agreements are common practice to ensure a reliable source of supply goods and services at the lowest price [14] This is most suitable for instrument-based IVDs whereby reagents and consumables need to be replenished.

Customized contracts usually contain the following information:

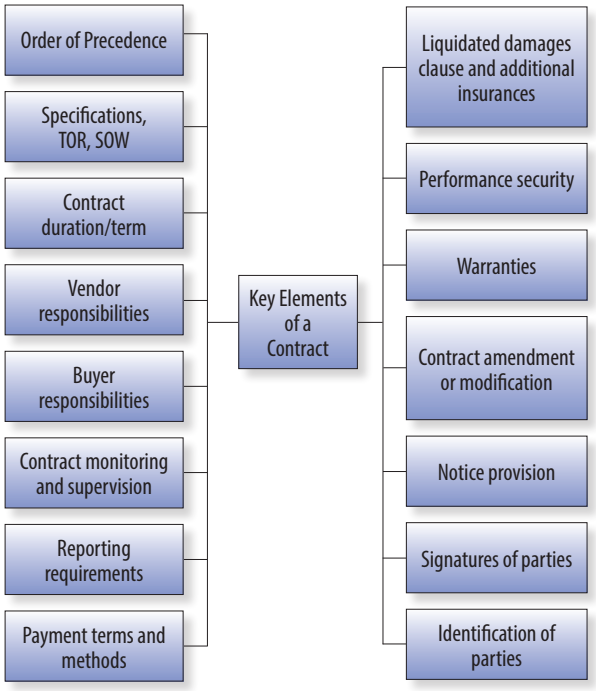
- an overarching document containing specific contractual provisions agreed between seller and buyer;
- relevant portions of the solicitation documents including specifications, terms of reference or scope of work;
- the vendor's submission including best and final offer provided in response to the tender.

Long term agreements (LTAs) are designed to facilitate rapid processing of requests for procurement. LTAs are particularly effective when the same goods (reagents and consummables) are required repeatedly over a period of time. Even without an accurate forecast, LTAs can be leveraged to negotiate lower pricing, more assured supply, improved service and maintenance terms, and a greater investment in suppliers servicing a market in a consistent manner. One potential disadvantage which is a drop in prices can be mitigated by re-negotiating the LTA terms on an annual or biennial basis. These types of contract require continuous close monitoring. Generally, an LTA

12 See Definitions

13 Definition adapted from UNDP website http://www.undp.org.tr/Gozlem2.aspx?WebSayfaNo=240#5

Figure 8. Key elements of a contract



with a supplier for a prequalified product (if IVD) or with a prequalified supplier (if durable or consumable) is most desirable. Other benefits of an LTA include protection against unreasonable increases in price for the same product and saves costly and time-consuming procurement processes and procedures.

A LTA can be made for the period of one to five years depending on the product and the volatility in the market. Entering into a LTA when it is presumed that prices may decrease may be unwise, however, it usually guards against unreasonable price increases that may result from a monopolisation. A term of 1-2 years is generally most suitable to weigh the pros and cons of the IVD market.

The following Figure 8 illustrates key elements that may be included in a contract[14]. Each element should be carefully considered and appropriate language included in the contract to ensure protection for both buyer and seller. Failure to address common issues and establish a plan for unforeseen circumstances may lead to lengthy court proceedings and substantial financial loss.

The method of payment must be clearly defined of that is that suited the contract including handling fees, insurance, payment terms and general and/or specialised terms and conditions that should be considered and especially where reagent require cold-chain conditions during transport.

Contracts should ensure a clause for rejection or refusal of goods that do not conform to the specifications, as stated in the bidding documents. Payment of goods should not been deemed as acceptance of goods. Specific terms and conditions may also be stated in the contract such as guaranteed shelf life upon delivery, manufacturing standards, lot testing requirements, etc. In addition, a critical part of the procurement contract is to ensure the manufacturer conducts post-market surveillance as part of their regulatory obligations.

Lot testing conducted independently of the manufacturer may be used to flag potential for "out of specification" goods. Such testing must follow a standard operating procedure that is suited to the testing objective. Any testing data that is generated should be forwarded to the manufacturer as a complaint. All components of the test kit should be verified as part of lot testing, e.g. lancets, specimen transfer devices, instructions for use, packaging. For further guidance, see *WHO Post-Market Surveillance of In Vitro Diagnostics, 2015* http://www.who.int/diagnostics_laboratory/postmarket/en/

Contracting for equipment

Analysers and ancillary laboratory equipment may be purchased using the following methods:

1. Outright purchase;
2. Lease; and
3. Reagent rental.

"Purchasers should carefully evaluate acquisition contracts to identify minimum volume commitments, service requirements, training that is included, user support, warranty provisions and reagent pricing discounts. Negotiation of these elements in the contract is required to guarantee that the best value and the lowest costs are obtained from the vendor. Everything in the contract is negotiable. The input of the Ministry of Health officials would be desirable in the procurement and negotiation for laboratory equipment, service, reagents, and supplies".[15]

Outright purchasing relates to the complete acquisition of a piece of equipment or an analyser. Outright purchasing may be the most practical method for ancillary equipment such as centrifuges, pipettes, refrigerators, heating blocks, etc. However, reagent rental and leasing options may be efficient for analysers such as those for clinical chemistry, haematology, and serology, where the platform costs are

14 Adapted from United Nations. 2010. United Nations Procurement Manual, Revision 6. Retrieved 13 April, 2013 from http://www.un.org/Depts/ptd/pdf/pmrev6.pdf

15 p.12, Consultation on Technical and Operational Recommendations for Clinical Laboratory Testing Harmonization and Standardization: Meeting Report page 12. Access 29 May 2013 at http://www.who.int/management/facility/laboratory/Maputo_Meeting_Report_7_7_08.pdf

considerable and platforms must be maintained (preventive and corrective) regularly to ensure functionality. A reagent rental agreement provides greater incentive for the vendor (seller) to ensure the equipment is functional as payment is based upon test throughput (see Table 8).

Reagent rental is a most attractive option when an all-in pricing option is negotiated. All-in pricing refers to the cost per returnable result for the reagents, certain consummables, the analyser, service/maintenance and training.

Quantifying procurement demand

End-users will typically undertake a quantification exercise to establish a 12-month forecast for all commodities.

Monitoring procurement practices

A wide range of indicators may be monitored i.e. routinely tracked over time through either a specific system for monitoring or existing data sources. Effective monitoring allows for better evaluation of the effectiveness of procurement procedures, and therefore impact on programmes. The following indicators have been developed for pharmaceutical procurement and supply systems but could be adapted to meet the needs of IVD procurement:

- Product selection in accordance with national guidelines/national validated testing algorithms;
- Consumption;
- Procurement efficiency in terms of pricing, supplier performance and port clearance;
- Quality control; and
- Distribution and inventory control in terms of loss, and minimum stock levels.

Evaluating supplier performance

Evaluating the supplier is an integral component of the procurement cycle. It is necessary to collate information concerning each consignment in accordance with the principles of On-Time In-Full (OTIF) as an indicator of performance, including:

- if the goods must be delivered in acceptable condition;
- if orders are full and complete;
- if guaranteed shelf life is delivered;
- if complaints are handled appropriately; and
- if responses to breakdowns dealt with efficiently.

Data should be collected continuously and for each consignment and across the period of the procurement contract, preferably by the procuring entity. The degree of implementation of the contacted details for service and maintenance can vary. It is critical that the supplier's ability conduct service and maintenance in a timely manner is monitored.

Table 8. Types of procurement contracting[17]

Purchase	Lease	Reagent rental
More substantial initial cash outlay	Minimal initial cash outlay	Minimal initial cash outlay
Risk of obsolescence, after more than 5 years	Less risk of obsolescence, unless lease term is more than 5 years	Less risk of obsolescence, unless contract does not allow for upgrades
	Vendors may be reluctant to set up agreements in resource-limited settings, will be dependent on how testing programmes are financed.	
Equipment expense can be depreciated. Can be used as a trade-in for upgraded models (rarely).	Equipment can be returned after the l12 month ease period, and upgraded for a new model. Allows for trying out the equipment before buying it.	Equipment can be upgraded for a new model during the contract.
Equipment must be decontaminated and decommissioned at some point	Difficulties exporting (returning) analysers from certain countries.	Equipment issues regarding import and export (return) are similar as for leasing
Reagent cost must be negotiated considering the capital outlay for equipment purchase.	Total cost is higher than purchase due to financing arrangement; a buy-out option may exist.	Total cost is higher than purchase due to financing arrangement, as for lease; a buy-out option may exist. Predictable fixed costs per month.
	Reagent pricing must be negotiated separately from the lease based on volumes	Cost of equipment, reagents and service is spread across each test, payment is a fixed amount on a per returnable result basis. So reagent costs (price per test) are higher. May also be negotiated as all in pricing.
		Volume commitments must be accurate as these are the basis for pricing
		Most desirable for changing technologies and high-cost systems due to risk of obsolescence in 5 years

16 Table is adapted from Consultation on Technical and Operational Recommendations for Clinical Laboratory Testing Harmonization and Standardization: Meeting Report page 12. Access 29 May 2013 at http://www.who.int/management/facility/laboratory/Maputo_Meeting_Report_7_7_08.pdf

MANUFACTURERS OF IVDS

Manufacturers through their suppliers (distributors and agents) play an important role in the procurement process. Certain aspects usually outlined in procurement contracts are described in this section.

Delivery of goods

Timely delivery of the expected goods can be measured as On-Time In-Full (OTIF) in the following terms: if the expected product as ordered was delivered, if the quantity was delivered as ordered, at the place specified by the Buyer, and at the time expected. If delivery is delayed past the time agreed or if the goods do not match those ordered, testing programmes may incur a stock-out or shortage of supplies.

Certain customs procedures may occur at port/airport of entry, all means necessary should be taken to minimise these delays including thorough knowledge of importation requirements in countries of destination.

Installation, training, maintenance

All contracts related to analyser/equipment installation, training and maintenance must be considered as part of the procurement process. It is expected that there must be an explicit provision in the procurement contract for installation, pre-service and in-service training, and preventive and corrective maintenance schedules for the expected lifespan of the analyser/equipment. Contracts should cover a minimum of two years, in addition to the usual one-year manufacturer's warranty, but should preferably be longer. The initial contract should be made at the time of procurement (as part of vendor requirements and detailed specifications). Contract extensions beyond the initial time period should be made well in advance and ensure manufacturer approved service personnel are provided.

The terms of installation and training must be negotiated in advance of purchasing. The need for and intensity of training will depend upon the number and competency of staff, as well as expected staff turnover.

Requirements for installation

General equipment and analysers should be installed by appropriately qualified staff. The vendor must be contractually obligated to provide manufacturer-approved installation either through the manufacturer, by the vendor themselves or using an in-country agent (sub-contracted by the manufacturer). The vendor must ensure that required calibration and/or QC reagents, where necessary, have been ordered and arrive in a timely manner. Details of all installation requirements must be included in the contract. Successful installation of the equipment according to the manufacturer's specifications must be documented.

Training requirements

Training requirements must be specified in the contract. The vendor is obliged to train laboratory personnel in the calibration, operation, (basic preventive maintenance and repair) of particularly analysers such as haematology, clinical chemistry, serology, etc. Training is usually divided into pre-service and in-service (meaning on-going) training, in order to maintain an acceptable level of proficiency, it is crucial that staff be appropriately trained and refresher training regularly provided. High quality training results in improved equipment operation and less frequent breakdown. Records of such training must be retained.

Maintenance

All equipment must be must be regularly maintained with both preventive and corrective schedules, irrespective of the claims made by vendors. In all circumstances, basic regular maintenance can prolong the lifetime of equipment. Preventive and corrective maintenance must be specified in the contract.

HELPFUL PUBLICATION: The WHO Maintenance Manual for Laboratory Equipment, 2nd edition gives an overview of the technical requirements for installation, use and maintenance for ancillary and other laboratory equipment.

Other aspects that should be considered as part of the procurement process are:

- Provision for upgrades, particularly for software;
- Trouble-shooting;
- Replacement spare parts;
- Labour and travel; and
- Loaner instruments in event of instrument breakdown or instrument swap-out, in case of some analysers that are used at point of care.

It is essential to define and negotiate these additional maintenance costs up front, preferably as part of the contract. If a separate contract is made for maintenance, the reliability of the vendor should be used to determine if these services will be paid for upfront or only after the service has been completed.

Warranty

A warranty is a commitment made by the supplier to replace goods, usually instruments (analysers and ancillary equipment), within a certain period of time at no additional cost, when a quality or performance issue arises.

Post-market surveillance

Manufacturers should implement an effective post-market surveillance system with both active and passive collection of post-market information, including complaints. Manufacturers must establish a documented procedure for a feedback system to provide early warning of quality problems and for corrective action/preventive action.

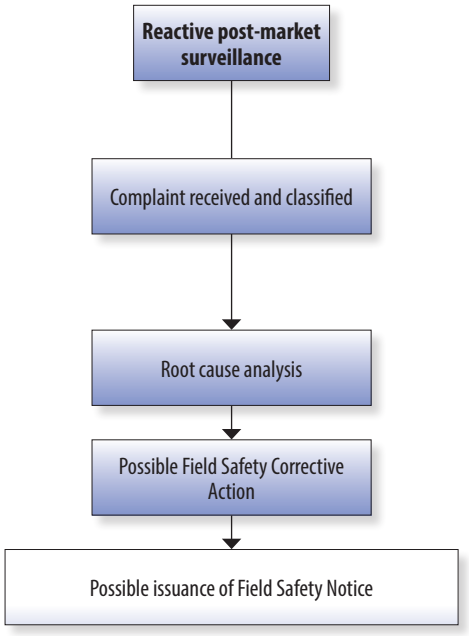
Reactive post-market surveillance comprises of complaint handling by the manufacturer through the following steps:

1. Classify complaint;
2. Conduct root cause analysis;
3. Take corrective action.

A field safety corrective action (FSCA) is an action taken by the manufacturer to reduce certain risks related to use of a given IVD. Such problems include malfunction or deterioration affecting the performance or operational characteristics of an IVD, as well as any inadequacy in the instructions for use which might lead or might have led to the death of a patient, user or other individual or to a serious deterioration in his/her state of health.

When the need for a FSCA of an IVD has been established, the manufacturer of the affected product assumes the responsibility for recovery of the goods and implementation of the corrective action. WHO and the relevant NRAs may assist by monitoring the overall action.

Figure 9. Complaint handling for post-market surveillance



FSCA may include:

- Return of an IVD to the manufacturer or its representative (product recall);
- IVD modification (such as revised instructions for use);
- IVD exchange (with new instrument);
- IVD destruction (product recall);
- Advice given by the manufacturer regarding the use of the IVD (e.g. where the IVD is no longer on the market or has been withdrawn but could still possibly be in use).

Standards that are applicable to post-market surveillance

Manufacturers of IVDs are expected to adhere to available international standards such as ISO 2859:2006 *Sampling procedures for inspection by attributes series* and ISO 3951: 2013 *Sampling procedures for inspection by variables series* to verify the safety, quality and performance of each lot manufactured of their products.

Manufacturers are obliged to perform quality control lot release as part of the requirements of ISO 13485:2003 *Medical devices -- Quality management systems -- Requirements for regulatory purposes*, which states that there must be adequate monitoring and measurement of product and evidence of conformity with an agreed upon acceptance criteria. Where manufacturers purchase key components for the product, these components must be verified to ensure they meet specified purchasing requirements. Furthermore, there must be a process to identify and control product that does not conform to requirements and to prevent its unintended use or delivery.

In assessing the need for field safety corrective action, the manufacturer is advised to use the methodology described in the standards: ISO 14971:2007 *Medical devices - Application of risk management to medical devices and "Implementation of risk management principles and activities within a Quality Management System"* (GHTF/SG3/N15R8).

- Any **serious adverse event** should be reported by the manufacturer to the relevant national regulatory authority within their respective timelines (and to WHO within 10 days).
- Any **moderate adverse event** or **change in trend of mild adverse events** should be reported by the manufacturer to the relevant national regulatory authority within their respective timelines (and to WHO within 30 days).
- All complaints (both administrative and technical including serious, moderate and mild adverse events) to be reported by the manufacturer annually to the relevant NRA.

As soon as it is received, any complaint must be classified by the manufacturer as part of the risk management file for the product. The degree of risk will determine the timeline for action, and who should be informed. The requirement for root cause analysis will remain, irrespective of the classification.

Decommissioning IVDs

Even after sale of an IVD, the manufacturer has the obligation to ensure that any risks related to use of the IVD throughout its life cycle (i.e. installation, use and disposal of the IVD) are managed through their risk management framework. This means that the manufacturer is responsible for ensuring that their product can be disposed of in a safe manner. This responsibility of the manufacturer should be accounted for in the procurement contract.

There are a range of reasons for an IVD to be disposed of, or otherwise decommissioned, including:

- Single-use IVDs that are disposed after use, such as an anti-HIV-1/2 RDT;
- Due to unacceptable levels of wear and damage or unreliability;
- Under instruction for field safety corrective action (FSCA) issued by the manufacturer (e.g. IVD return through a recall to manufacturer or IVD destruction by user under instruction from manufacturer);
- Obsolescence of technology; and
- Reagents or consumables that are no longer commercially available.

Different categories of IVDs will have different safety considerations when the device is disposed of, see Table 9 for additional details.

Table 9. Decommission or disposal of different types of IVDs

Category of IVD	Example of IVD	Safety consideration
Disposable, single use	Reagents or test kits.	Chemical and biological safety of the user, patient and environment
Auxiliary equipment	Centrifuge, vortex, pipette, microplate washer and reader, incubator, microscopes, heating plates, etc.	Biological, electrical safety of the user, patient and environment
Analysers	Dedicated equipment for clinical chemistry, haematology, serology, nucleic acid testing (NAT).	Electrical, chemical, biological safety of the user, patient and environment

Whereby, **biological safety** refers to measures taken to protect the user, patient and environment from any biological source of contamination. Universal precautions refers to an approach to infection control to treat all human blood and certain human body fluids as if they were known to be infectious for HIV, HBV and other bloodborne pathogens. Biological safety can be achieved through a variety of means such as disinfection (using antimicrobial agents, other than antibiotics or antiseptics), sterilization (using autoclave), and use of other biocides. Most practically, single-use HIV-1/2 RDTs could be autoclaved or incinerated prior to disposal.

Chemical safety refers to measures taken to protect the user, patient and environment from any harmful effects of chemical exposure.

Radiation safety refers to measures taken to protect the user, patient and environment from the harmful effects of radiation.

Electrical safety refers to measures taken to protect the user, patient and environment from the harmful effects of electrical malfunction.

Although, the final responsibility for disposal of an IVD rests with the manufacturer, the practicalities of how non-disposable IVDs such as auxiliary equipment or analysers are decommissioned might be affected by how the IVDs were procured. For example, under reagent rental or leasing options, a clause should be inserted into the procurement contract to ensure that equipment to be decommissioned is decontaminated and removed safely by the manufacturer in a timely manner. For procurement as an outright purchase, the manufacturer should assist the user to decontaminate and dispose of the equipment in the most environmentally friendly manner possible.

Figure 10. Life cycle of an IVD

NATIONAL REGULATORY AUTHORITIES FOR IVDS

Regulatory approvals[17]

Regulation, specifically for IVDs, can be non-exhaustive and may be poorly enforced, particularly for resource-limited settings. Manufacturers are obliged to seek national registration in markets where they intend to market their product. The procedure for national registration with the relevant regulatory authority begins the procedure to approve a product for sale and use, bearing in mind that national registration may not always confer stringent and/or sufficient regulatory control. Adequate pre-market assessment should be conducted by national authorities through national regulatory authorities and national reference laboratories.

A range of documentation that may be offered as evidence of safety, quality and performance to determine product registration, and later, decisions on product selection. These include certificates issued by conformity assessment bodies, audit reports, and study reports.

Regulators that are founding members of Global Harmonization Task Force (GHTF) will consider if there is a high potential for unreasonable risks created by the use of the product, but when used only in their jurisdiction. Therefore, the stringency of pre-market assessment is then determined by the level of risks the diagnostic poses when utilized in the population of the regulator. For example, if the product is used to screen blood donations for HIV, the individual and public health risk is considered high, and therefore most regulatory authorities will undertake a stringent pre-market assessment. But importantly, a product that is not considered one that poses a high risk in many well-regulated settings, may indeed be a high risk in another setting, such examples are malaria RDTs and CD4 enumeration technologies. In most countries with a stringent and effective regulatory authority, malarial disease has a minor impact on that jurisdiction's population. As such, pre-market assessment of quality, safety and performance by the regulator is often minimal in comparison with, for example, diagnostics for HCV, HBV or HIV.

However, the level and stringency of assessment may not be the same across product categories. For example, assessment of HIV RDTs has been well established in many countries, while introduction of CD4 technologies that can

Table 10. Regulatory approvals for diagnostics

Type of regulatory approval	Details
Regulatory approval in country of manufacture	Approval in the country of origin, i.e. where the product is manufactured, either approval for sale and use in the country of manufacture or approval for export only[19]. Regulatory requirements "for export only" are less stringent than "for sale and use". Approval "for export only" does not provide evidence of sufficient regulatory review of safety, quality and performance.
Regulatory approval in country of intended use	Approval of diagnostics that are manufactured elsewhere and imported, approval for sale and use in the country of intended use conducted by national authorities. Assessment by national authorities (national regulatory authority or national reference laboratory) includes studies to validate national testing algorithms, and other performance evaluations and studies to gather clinical evidence.
Regulatory approval by other national authorities	Global efforts towards harmonization of regulatory approaches have led to internationally accepted standards for a risk-based approach for the pre-market assessment of safety, quality and performance of diagnostics. Assessments undertaken by the WHO Prequalification Team - Diagnostics and regulatory authorities that are founding members of the Global Harmonization Task Force i.e., European Commission, Health Canada, US Food and Drug Administration, Australian Therapeutic Goods Administration, Japan's Ministry of Health, Labour and Welfare and Pharmaceuticals and Medical Devices Agency (PMDA) could be considered for categories of diagnostics that are stringently assessed. Given the slight differences in regulatory requirements, manufacturers may supply different regulatory versions of the "same" product such as versions for markets with stringent regulatory controls and versions for markets with little or no regulatory control, the latter are often referred to as "rest of world" regulatory versions. Therefore, a less-regulated or un-regulated version of seemingly the same product may be supplied without any assurance that same quality controlled components and procedures were used to manufacture the product to be procured.
Approval by implementing partners and funding agencies	Implementing partners and multilateral/bilateral donors may have their own quality assurance policies and/or their own mechanisms for assessing diagnostics for procurement such as Global Fund, UNITAID and USAID, etc.

17 Approval is otherwise known as registration, certification or licensing, hereafter referred to as approval in this document.

18 Sometimes referred to as a "Certificate of Free Sale"

be used at point-of-care has been hampered by lack of standardized assessment procedures.

As a minimum, the technical specifications must state the **exact nature of the regulatory approval** required from the country of origin and from the country of intended sale and use. Supportive documentation must be submitted as part of the bidding process to verify the exact regulatory status of the product that will be procured.

Given the range in differences between regulatory versions of seemingly the same product, national authorities should pay special attention to the regulatory version marketed in their jurisdiction. For instance, if a change is made to a regulatory version in another jurisdiction, how would this impact other regulatory versions. For post-market surveillance, are mechanisms in place to allow for reporting of incidents that have occurred with a different regulatory version in a different jurisdiction.

Post-market surveillance

Lot testing of consignments

To ensure that IVDs continue to meet their specifications, national regulatory authorities have the mandate to arrange proactive lot verification testing including:

- Pre-distribution to testing sites (when a consignment of test kits arrives in country); and
- Post-distribution to testing sites (after the lot has already been in use).

Pre-distribution lot verification testing should take place in a nationally designated facility, usually the national reference laboratory, before the consignment is released for distribution nationally. The sampling interval and procedure should be agreed upon between the national authorities and the procurer beforehand and may be risk-based depending on the value and/or volume of the consignment.

A panel of biological specimens should be tested on an appropriately collected sample of tests from a given consignment received. Acceptability criteria must be assigned and a process in place to handle products that do not comply to pre-determined technical specifications. It may be useful to monitor lot to lot variation over time with the same specimen panel to identify any shifts or trends in test performance that could foreseeably impact the test result.

Sampling of tests from field conditions

In addition to pre-distribution lot verification testing, samples may be taken at regular intervals throughout the year and tested accordingly, as appropriate based on the above mentioned risk approach taking into account excursion of recommended storage temperatures.

Field Safety Corrective Action

If the need for a field safety corrective action (FSCA) has been taken by the manufacturer to reduce certain risks related to use of a given IVD, the regulatory authority should help to enforce the recommended actions.

FSCA may include:

- Return of an IVD to the manufacturer or its representative (product recall);
- IVD modification (such as revised instructions for use);
- IVD exchange (with new instrument);
- IVD destruction (product recall);
- Advice given by the manufacturer regarding the use of the IVD (e.g. where the IVD is no longer on the market or has been withdrawn but could still possibly be in use).

WHO

WHO prequalification assessment

WHO prequalification assessment fills a gap for some national regulatory authorities by assessing the quality, safety and performance of in vitro diagnostics that are most suited for use in resource-limited settings.

The final WHO prequalification assessment outcome depends on:

1. Results of the dossier review and acceptance of the corrective action plan, if required.
2. Results of the site inspection(s) and acceptance of the corrective action plan, if required.
3. Meeting the minimum acceptance criteria on the laboratory evaluation.

Eligibility for WHO prequalification assessment

WHO determines whether an application will be eligible for prequalification assessment based on (1) WHO eligibility criteria and (2) programmatic suitability. Products that have already undergone a stringent regulatory assessment by certain regulatory authorities may proceed to an abridged WHO prequalification assessment. If so, submission of a product dossier for WHO review is not required. However, abridged WHO prequalification assessment still requires the conduct of the laboratory evaluation and a shortened inspection that leverages the findings of previous inspections.

Product dossier review

A product dossier contains documentation and data to demonstrate that the IVD conforms to the Essential Principles of Safety and Performance of Medical Devices. Guidance issued from the International Medical Device Regulators Forum (IMDRF) (formerly the Global Harmonization Task Force) is considered the international best practice related to regulation of medical devices, including IVDs. Other standards and guidance issued by the International Organization for Standardization (ISO) and Clinical and Laboratory Standards Institute (CLSI) can provide specific information on specialized areas such as stability testing for IVDs. The product dossier requested by WHO should be submitted according to the "Instructions for compilation of a product dossier" (http://www.who.int/diagnostics_laboratory/evaluations/PQDxInfo/en/)

The WHO prequalification assessment reviews the performance and use of IVDs specifically from the perspective of WHO Member States, that is, stability, risk assessment and instructions for use. National regulatory authorities (NRAs) undertaking stringent review may not review these aspects in the same way. WHO rates any non-conformities, and the manufacturer is expected to file a corrective action plan that outlines how and when requirements will be met.

Inspection of the site of manufacture

The WHO inspection schedule is divided into stages:

Stage	Content
Stage 1	Evaluation of readiness for inspection through desktop review of quality documentation or a brief on-site inspection.
Stage 2	Initial full on-site inspection to determine implementation of the quality management system, facility and warehousing, competence of staff, critical suppliers including outsourced activities, internal audit and management commitment or review. Also, with dossier assessor attends the inspection to confirm aspects of the dossier.
Follow-up	Confirmation of implementation of the corrective action plan submitted in response to Stage 2 inspection; may or may not require another on-site inspection.
Surveillance	Risk-based; at least annual reporting required.
Re-inspection	Risk-based; conducted after 3—5 years holding WHO prequalification.

All sites inspected must meet prequalification requirements and must demonstrate:

1. a fully implemented quality management system (design, development and manufacturing including quality control, storage and distribution);
2. risk management;
3. product stability;
4. routine manufacturing;
5. sufficient capacity to ensure reliable delivery.

Independent evaluation of performance and operational characteristics

WHO conducts performance evaluations, whereby each product is tested on a worldwide-sourced clinical specimen reference panel, commercially acquired seroconversion panels and panels of specimens containing low antibody titers and antigen concentrations. These evaluations aim to assess technical and performance characteristics such as diagnostic sensitivity and diagnostic specificity, as well as seroconversion and low titer sensitivity relative to those of other assays of similar format.

Manufacturers send one or more production lots to WHO Collaborating Centres or other laboratories designated by WHO to conduct the evaluation testing. WHO issues a technical report of the performance and operational characteristics and determines if the assay meets WHO prequalification requirements. Specific minimum acceptance criteria are applied to each assay format, see Table 11, Table 12, Table 13.

Table 11. Minimum acceptable performance for HIV serology assays for WHO prequalification

Characteristic	RDT	EIA
Sensitivity	>99%	100%
Specificity	>98%	>98%
Inter-reader variability	<5%	N/A
Invalid rate	<5%	<5%

Table 12. Minimum acceptable performance for HCV serology assays for WHO prequalification

Characteristic	RDT	EIA
Sensitivity	>98%	100%
Specificity	>97%	>98%
Inter-reader variability	<5%	N/A
Invalid rate	<5%	<5%

Table 13. Minimum acceptable performance for HBsAg serology assays for WHO prequalification

Characteristic	RDT	EIA
Sensitivity	>99%	100%
Analytical sensitivity for screening of donations AND for testing of asymptomatic and symptomatic individuals for diagnostic purposes	LoD< 0.13 IU/mL	LoD < 0.13 IU/mL
Analytical sensitivity for testing of asymptomatic and symptomatic individuals for diagnostic purposes	LoD < 4 IU/mL	LoD < 4 IU/mL
Specificity	>98%	>98%
Inter-reader variability	<5%	N/A
Invalid rate	<5%	<5%

Final prequalification decision

When the prequalification decision has been made, WHO issues a public report, and the product is added to the list of WHO prequalified products. It is, therefore, eligible for WHO and UN procurement as well as direct procurement by countries, and other implementing partners and donors such as UNITAID and Global Fund. In the post-prequalification stage, the manufacturer is obliged to conduct post-market activities to continue to assure the quality, safety and performance of a WHO-prequalified IVD. The manufacturer is also obligated to notify WHO of any changes to the product or the quality management system, so that these may be evaluated to determine any implication for their listing as WHO-prequalified.

Post-market surveillance for WHO prequalified products

The purpose of post-market surveillance is to protect individual health and public health through continued surveillance of IVDs once they are placed on the market. Post-market activities ensure that manufacturers are aware of any event that may affect the quality, safety or performance of their assay. Manufacturers must then evaluate and assess any residual risks and, as appropriate, take risk mitigation measures. Figure 7 shows the components of post-market surveillance.

A centralized collection of post-market data on WHO-prequalified IVDs enables coordinated action in WHO Member States and ensures traceability of information. These post-market data include results from pre-distribution and post-distribution lot verification testing as well as complaints and evaluation data. Regulators and users submit these post-market data to WHO in the form of lot testing reports and IVD complaint forms. National regulatory authorities, procurers and implementing partners, such as nongovernmental organizations, are notified of certain reports of adverse events through vigilance information exchange.

Other actions that WHO might take on post-market information include:

- post-market surveillance information exchange with national regulatory authorities
- post-market surveillance information exchange with manufacturers
- publishing post-market surveillance information on WHO's website
- additional surveillance of the IVD concerned
- removal of the product from the list of WHO-prequalified IVDs, if needed
- inspection of the manufacturing site to ensure that corrective or preventive action as a result of any complaint has been implemented.

WHO's Guidance for post-market surveillance of in vitro diagnostics provides further information. (http://www.who.int/diagnostics_laboratory/postmarket/en/)

DONATIONS

Many countries are faced with decisions concerning acceptance of donated equipment, both new and second-hand. Some donations may not be registered or supported in country and may not be listed in national guidelines that describe standardization and harmonisation policies. Donated products should be refused if they do not conform to existing national policies including testing algorithms and closed testing systems.

Donations of reagents close to expiry should be considered in the context of work load and capacity for storage and distribution. It is important that countries understand the supply chain constraints for dealing with close-to-expiry products and set minimum acceptance criteria. The appropriate disposal of expired product can be more costly than the purchase price.

The WHO Guidelines on Donation of Medical Equipment may be used as a guide in addition to the following caveats. Donated equipment must be part of the PSM plan and/or national guidelines and thus potential donors of equipment should be involved in national laboratory planning processes. Countries should have clear national policies about donations of diagnostics and other perishable reagents. If a donation is to go ahead, the donors should send the equipment specifications to the laboratory ahead of delivery (to ensure that the necessary physical infrastructure is present). Donated equipment and reagents should have at least 50% of their useful life remaining at the time of donation. Donated equipment should follow the usual procurement process to ensure that adequate reagents and supplies are procured, that installation, maintenance (preventive and corrective) and training are also procured. Equipment retirement (decommissioning) procedures should be developed and followed for donated and other equipment.

REFERENCES

ISO 13485 Medical devices -- Quality management systems -- Requirements for regulatory purposes

ISO 15190 Medical laboratories — Requirements for safety ISO 14971 Medical devices — Application of risk management to medical devices

WHO. Manual for procurement of diagnostics and related laboratory items and equipment, 1st edition (2nd edition under preparation). Geneva. 2013. http://www.who.int/diagnostics_laboratory/procurement/131024_procurement_of_diagnostics_finalversion.pdf

WHO. Post-market surveillance of in vitro diagnostics. Geneva. 2015 http://www.who.int/diagnostics_laboratory/postmarket/150819_pms_guidance_final_version.pdf?ua=1

WHO. Specifications and quantities for efficient procurement of essential equipment and laboratory commodities for HIV. Geneva. 2015. 2nd edition. Accessed 27 May 2016 from http://www.who.int/hiv/pub/amds/amds_equipment-commodities-forecast/en/

WHO. Guidance on development of national strategic laboratory policy and plans. Manila Accessed 27 May 2016 from http://www.wpro.who.int/health_technology/documents/docs/Nationalhealthlab2_0F38.pdf

WHO. Consolidated guidelines on HIV testing services. Geneva. 2015. Accessed 27 May 2016 at http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en/

WHO. Consolidated guidelines on viral hepatitis testing services. Geneva. Publication forthcoming in 2016.

WHO. Laboratory diagnosis of sexually transmitted infections. Geneva. 2013. Accessed 27 May 2016 at http://www.who.int/reproductivehealth/publications/rtis/9789241505840/en/

European Commission, DG Health and Consumers (SANCO). Guidelines on medical devices vigilance system (MEDDEV 2.12-1 rev 8). January 2013. http://ec.europa.eu/growth/sectors/medical-devices/index_en.htm

MHRA. Management of In Vitro Diagnostic Medical Devices. December 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/371813/Management_of_In_Vitro_Diagnostic_Medical_Devices.pdf

MHRA. Management and use of IVD point of care test devices. December 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/371800/In_vitro_diagnostic_point-of-care_test_devices.pdf

Williams J, Umaru F, Edgil D, Kuritsky J. Progress in harmonizing tiered HIV laboratory systems: challenge and opportunities in 8 African countries. Global Health: Science and Practice, 2016, 4(3):467-80.

ANNEXES

Annex 1. Checklist for 12 key aspects for needs assessment for instruments and analysers

The following checklist may be used to assess new instrument or analyser procurement.

1. Is the product on the nationally approved list, e.g. national registration, national standardization list?
2. Is the request to replace existing old instruments? If yes, is there an instrument replacement strategy?
3. If these instruments are for new locations, is there an instrument deployment plan for the proposed instrument?
4. What is the current estimated diagnostic capacity for this particular instrument type in country?
5. What is the diagnostic burden at the proposed sites? Is the instrument selected appropriate, based an instrument capacity vs. diagnostic demand?
6. Is there suitable infrastructure at the proposed sites - any additional peripheral needs?
7. Is there expected service delivery expansion at the proposed sites? (scale up)
8. Have the additional costs of reagents, staff training, and maintenance been considered - what are the funding sources and estimated costs?
9. Will the instrument require an extended warranty after its warranty expires?
10. Is a local Authorized Manufacturer Distributor available to service the instrument?
11. Is there a Maintenance Service Agreement (MSA) in place for similar instruments you have currently on-hand? If yes, is the MSA still valid and who is managing the Agreement?
12. Is an equipment inventory list available for similar instruments on-hand? If so, was an inventory conducted in the past 12 months with updated serial numbers and site locations?

General principles for all categories of equipment	
Criteria	**Considerations**
Laboratory infrastructure	• Constant/intermittent/no electricity • Capacity of an uninterruptible power supply to run analyser or alternatively to "save" a result for test in-progress
Environmental conditions	• Temperature and humidity for storage of reagents • Operating temperatures and humidity in the testing area • Dust-free testing area
Safety	• Consider biological, chemical, electrical safety to the user, to the patient, to other people in the vicinity, and to the environment
Staff skills level and training	• Number of precision steps required, including need for phlebotomy • Computer literacy required
Simplicity of operation (ease of use)	• Number of precision steps required, including need for phlebotomy • Computer literacy required
Maintenance and calibration requirements	• Preventive maintenance that can be carried out by operator, or by supplier. Certain daily maintenance carried out by the operator, with less frequent scheduled maintenance carried out by the supplier. • Corrective maintenance that can be carried out by operator, or by supplier • Calibration needs when instrument is moved, can be carried out by operator or by supplier • Inclusion of the costs for maintenance (both preventive and corrective) and calibration - might be certain trade-offs for relatively cheap instruments for use of POC
Supplier/vendor support	• Procurement contracting (possibility for long term agreements, reagent rental, etc.) • Availability and reliability (in-country and/or within region) for: technical support (maximum testing down-time permitted) • pre-service and in-service training
Total cost of ownership	• Inclusive of entire testing system which includes reagents and consumables, analysers, and other equipment • Cost of preventive/corrective maintenance and training • Consider cost of changing from one IVD or analyser to another, cost of re-training, re-writing SOPs, etc.
Additional specific considerations for analysers	
Criteria	**Considerations**
Specimen type	• Serum, plasma (check any restrictions on anticoagulants), venous whole blood, capillary (fingerstick/heelstick whole blood), oral fluid, sputum, etc.
Stability (transport, storage, in use) for reagents, controls and calibrators	• Temperature and relative humidity validated by manufacturer • Shelf-life upon manufacture • Shelf-life upon delivery, to be negotiated within procurement contract
Test menu available	• Consider scalability for various volumes • For example: - more than one serological marker, anti-HIV/anti-HCV - more than one immunological marker, - more than one molecular marker, HIV RNA/HCV RNA/HBV DNA
Quality control (QC)	• Internal quality control mechanisms • Availability of external quality control material, e.g. artificial controls, control beads, etc.
External quality assessment (EQA)	• Compatibility with existing programmes for EQA/proficiency testing (inter-laboratory comparison)
Workload of testing service	• Expected turn-around-time • Expected specimen through-put • Ability to batch test runs, or not
Connectivity	• Data management capability; interface capability
Availability of back-up methods	• If analyser is unusable, is a loaner analyser made available?

Annex 2. Methodology for product selection – using the principles of verification

National programmes may wish to maintain the option of performing a small-scale laboratory verification study, and/or point-of-use verification study to determine that the product (or testing algorithm) performs well before widespread roll-out.

1. For qualitative IVDs such as RDTs (where a qualitative result is taken from an quantitative scale), the difference between the new candidate testing algorithm(s) and the pre-existing status quo testing algorithm should be verified.
2. For quantitative IVDs such as viral load, verification of precision and estimation of bias can be used to determine if the assay is operating in accordance with manufacturer's claims.

Qualitative assays

Panel of specimens for verification of product performance should include specimens that react near to the cut-off. These will have the most value in challenging the qualitative accuracy of the candidate testing algorithm(s).

Prepare three specimens, one that is at the cutoff, then one that is 20% above the cutoff and one that is 20% below the cutoff.

- One specimen with +1 reactivity intensity on a scale of 0 to 3.
- One specimen with inconclusive (+/-) reactivity intensity on a scale of 0 to 3.
- One specimen with +2 reactivity intensity on a scale of 0 to 3.

Test each of the three specimens up to 40 times (40 replicates per specimen) on both the new candidate testing algorithm(s) and the status quo testing algorithm. More than one operator can conduct testing and this may provide for even more representative data.

Compare the rate of false positive or false negative results for each of the testing algorithms, per operator. Given that the target value for each specimen will be generated through characterisation according to the status quo for the three specimens used (2x HIV-positive and HIV-negative), then run experiment to obtain overall mean value and the overall mean's standard error.

Quantitative assays

Verification of precision can be evaluated by repeated measurements of two or more specimens over at least 5 days in one run/testing session (generating at least 25 replicates per specimen on each assay). More than one operator can conduct the testing, and this may provide for even more representative data. Testing does not have to take place on consecutive calendar days. However, to ensure to ensure that specimen integrity is assured aliquot and freeze specimens, and thaw each day so that aliquots are subjected to identical storage conditions. If aliquots are stored at 2 to 8 °C, then the aliquots might have different properties by day 5 of storage.

Control materials should be run, if available. If either the positive or negative controls do not give the expected results, the run is rejected and the results are not accepted for the verification study. If more than one invalid run, cease testing and contact manufacturer.

Review data generated each day to check for outliers, out of range results, and pre-analytical errors such as transcription, specimen mix-ups, clots, insufficient specimen volume. Do not reject if the result just seem aberrant.

Determine the allowable bias (i.e. what is clinically acceptable, which is generally 100% concordance). Compare each assay with the target value.

Phase 1: Prepare for verification study

a. Determine candidate testing algorithms to be verified

From the following lists of quality assured IVDs and in accordance with national requirements:

- List of national registered in vitro diagnostics; **and**
- WHO list of for prequalified in vitro diagnostics; **and/or**
- List of products eligible for procurement under donor arrangements.

By choosing assays that are WHO prequalified or other approved by other agencies conducting stringent regulatory assessment, assays have been assessed to determine if the manufacturer has sufficient validation and verification data to support the claims they have made about the performance and operational characteristics for the product.

Therefore, the aim of the verification study is not to repeat an evaluation of diagnostic accuracy (for diagnostic sensitivity and diagnostic specificity) but rather to determine if the testing algorithm(s) works as well as the status quo testing algorithm that has been in place.

Combinations of RDTs to diagnose HIV infection must be shown to not share false (incorrect) test results for the same specimens.

b. Request test kits

It is the responsibility of the study principle investigator to obtain sufficient number of tests from one lot of each assay from the manufacturer (or distributor in the country of study). These test kits should be stored in conditions stated in the manufacturer's instructions for use. Any additional consumables that are required to perform each of the assays must are available.

c. Recruit specimens for the verification study

See above for qualitative and quantitative assays

Serum/plasma specimens will be used for their ease and ability to be collected in larger volumes. As the manufacturer will have validated the candidate assay on other specimen types such as capillary whole blood, if it is claimed in the instructions for use, as part of the validation and verification studies. The validation panel should be stored according to the instructions of the panel provider which will usually be -20 °C or -80 °C.

Phase 2: Conduct verification study

a. Study site

The verification study may be conducted in any setting, as designated by national authorities. Ideally firstly in a laboratory setting, then at point of use settings.

b. Study staff

All testing providers (operators) should follow standard operating procedures, and be trained in the performance of each candidate assay with adequate documentation in the form of standard operating procedures and standardized run worksheets. Accurate recordkeeping is crucial, and it should be emphasized that transcription errors are common. Each operator testing the candidate assays should be blinded to the expected reference result for each of the specimens.

c. Verification specimen panel

Each specimen of the verification panel should be labelled with specimen ID numbers that do not reveal their expected reference result. All candidate testing algorithms should be tested on the same verification panel, preferably by the same operator. It is critical to be judicious when using the verification panel, aliquots should only be removed when needed. It is preferable to test all assays with the same specimen on the same day, this will reduce inter-aliquot variability.

d. Results interpretation

Results for visually read assays (RDTs, other simple assays)

Ideally, a second reader should make a blinded rereading of any visually read assay after the first reader (usually the operator) has read and recorded the overall test result. In addition, the intensity of the test line/band should be recorded.

- If the two readers interpret the test results the same way, then the status of the specimen is recorded as is.
- If the two readers do not agree, a third reader should adjudicate on the reading. With the majority reading taken.

If a result cannot be conclusively reached, the result should be recorded as inconclusive and the specimen retested on a new test device from the same lot. These should be included in the data analysis as a misdiagnosed specimen.

Results for instrument based assays (EIA, CLIA, ECL)

Certain immunoassays will display an OD/CO ratio that is within the grey zone, according to the manufacturer's instructions for use (usually 0.90 – 1.10). These specimens should be repeated in duplicate on the same lot. These should be included in the data analysis as a misdiagnosed specimen.

Invalid results

For RDTs, invalid test results are typically when the control line does not appear, irrespective if the test line appears or not, and when high background colour completely obscures the result window. Other anomalies should also be recorded such as streaking across the membrane, non-migration of specimen, debris on the membrane, etc.

For instrument-based assays (including immunoassays such as EIA, CLIA, ECL), invalid results or invalid runs occur when the internal and/or external test kit controls (HIV negative, HIV positive) are not within the acceptance range specified in the manufacturer's instructions for use.

All invalid results should be recorded in the data analysis.

e. Study data analysis

If the initial testing result does not agree with the expected reference result, the specimen in question should be tested again in duplicate on the same lot.

- If the same result is observed, then the result is recorded as not in accordance with the reference result and is included in the data analysis. For example, if a HIV-1 subtype O specimen is found non-reactive by a candidate testing algorithm, the specimen would be repeated on the same testing algorithm (same lots), if the specimen is still non-reactive, then the assay does not detect that HIV-1 subtype O specimen, i.e. disagreement with the expected reference result.

- If the results remain discrepant from the reference result, the result is recorded as discrepant and the result is included in the data analysis. For example, if a HIV-1 subtype O specimen is found non-reactive by a candidate assay, the specimen would be repeated on the same assay (same lot), if the specimen is then found to be reactive, then results are discrepant for detection of HIV-1 subtype O specimen, i.e. initially false non-reactive, final reactive result.

f. Study results

The results of the verification study should remain valid for a period of 3-5 years.

Phase 3: Monitor implementation of the testing algorithm(s)

a. Implement the newly proposed testing algorithm in parallel with an existing algorithm for a period of two weeks for high throughput testing sites or four weeks for low throughput testing sites. Data should be collected on the rate of reported HIV-inconclusive status and the rate of invalid test results (no more than 5% is acceptable) and any comments related to test procedures or other operational characteristics should be documented. A discrepancy rate of >1% between new and existing algorithms is significant and requires investigation and possible repeat of the validation study.
b. Monitoring of the testing algorithm(s) should continue in keeping with quality systems principles.

Annexes

Annex 3. INCOTERMS 2010

Abbreviation	Full Name	Implications
Applicable to all modes of transport		
EXW	Ex Works (..named place)	The Seller fulfils their obligations to deliver when the goods are made available at the Seller's premises. The Buyer must bear all the costs and risks involved in taking the goods from the Seller's premises to the destination.
FCA	Free Carrier (..named place)	The Seller's obligation to deliver occurs when he is handed over the goods, cleared for export, into the charge of the carrier named by the Buyer at the named place.
CPT	Carriage paid to (.. named destination)	The Seller pays the freight for the carriage of the goods to the named destination. The risk of loss or damage is transferred to the Buyer when the goods have been delivered into the custody of the carrier.
CIP	Carriage and insurance paid to (.. named place of destination)	The Seller's responsibility is the same as under CPT expect they must also obtain and pay for insurance against the Buyer's risk of loss or damage.
DAT	Deliver at terminal	Transfer to the Buyer of responsibility for loss or damage occurs when the goods are placed at the disposal of the Buyer in a named terminal at the place of destination.
DAP	Delivered at place	Delivery and transfer of risk occur when the goods are placed at the disposal of the Buyer on the arriving means of transport.
DDP	Delivery duty paid	The Seller is responsible for delivering the goods to the named place in the country of importation, including paying all duties, taxes, customs.
Applicable to sea and inland waterway transport		
FAS	Free alongside ship	The Seller has fulfilled their obligations when the goods have been placed alongside the vessel at the port of shipment. From that moment, the Buyer is responsible for all costs and risks.
FOB	Free on Board (. . .named port of shipment)	The Buyer is responsible for all costs and risks once the goods have passed over the ship's rail at the port of export.
CFR	Cost and freight	The Seller must pay the costs and freight necessary to take the good to the named port of destination. The risks of loss or damage transfer to the Buyer when the goods pass over the ship's rail at the port of shipment.
CIF	Cost, insurance and freight (.. named place of destination)	The Seller has the same obligations as under CFR but is also required to provide insurance against the Buyer's risk of loss or damage to the goods during transit.

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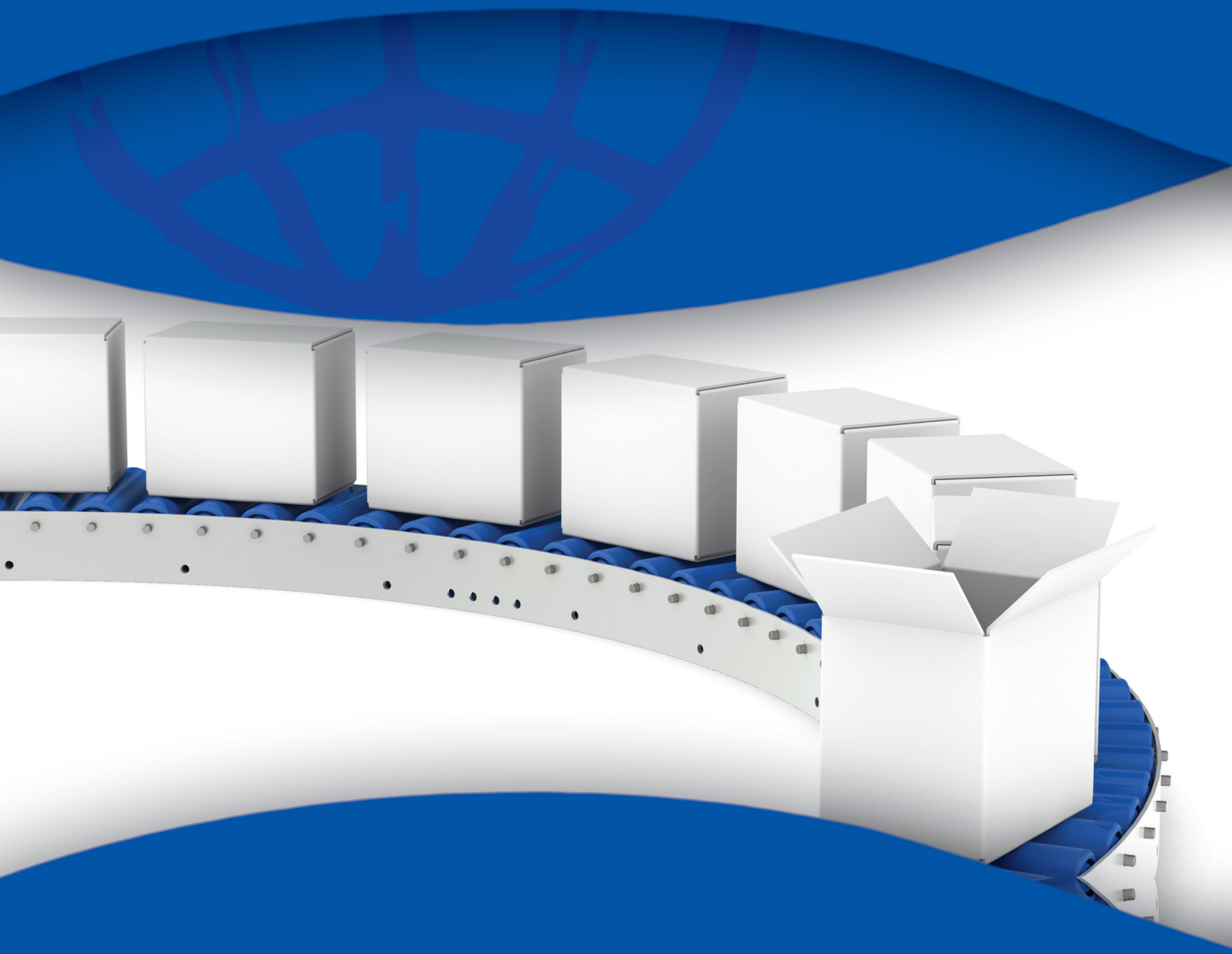

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