# Post Market Monitoring of *In-vitro* Diagnostic Devices for Infectious Disease Near Patient Testing using Quality Assurance

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# Glossary

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| EQA | External quality assessment |
| IFU | Instructions for use |
| IMDRF | International medical device regulators forum |
| IVD | In-vitro diagnostic medical device |
| LMIC | Low- or middle-income countries |
| NAT | Nucleic acid testing |
| NRA | National regulatory authority |
| POC | Point-of-care |
| QA | Quality assurance |
| QC | Quality control |
| QMS | Quality management systems |
| RDT | Rapid diagnostic test |
| WHO | World Health Organization |

## Terminology

| Terms | Definition | Definition Source | Common terms |
|---|---|---|---|
| **batch release** | Means review by regulatory body of documents related to the IVD manufacturer production of each new batch and testing by regulatory laboratory of this new batch to ensure compliance according to required standards | Author's definition | Lot release;<br>Batch verification;<br>Method for testing production batches of IVDs using a standard panel of samples with known reactivity to detect unacceptable differences in IVD batches (lots) |
| **control material** | means a device, solution, or lyophilised preparation intended for use in the Quality Control process to monitor the reliability of a test system and to maintain its performance within established limits | National Pathology Accreditation Advisory Council (Australia): Requirements for Quality Control, External Quality Assurance & Method Evaluation | QC;<br>Quality control sample;<br>Internal quality control sample |
| **external quality assessment** | means a program in which multiple specimens are periodically sent to laboratories for analysis and/or identification, in which each laboratory's results are compared with those of other laboratories in the group and/or with an assigned value, and reported to the participating laboratory and others. | National Pathology Accreditation Advisory Council (Australia): Requirements for Quality Control, External Quality Assurance & Method Evaluation | EQA;<br>EQAS;<br>EQAAS<br>External quality assessment scheme;<br>Proficiency test;<br>Quality assurance program;<br>QAP;<br>PT;<br>Ring test |
| **external quality control** | Means control material sourced outside the laboratory or IVD manufacturer tested periodically to monitor the performance of the test system | Author's definition for the purposes of this document | EQC;<br>Run control;<br>Third party control<br>Proficiency test |
| ***in-vitro* diagnostic medical device** | Means medical device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes | https://extranet.who.int/pqweb/content/glossary | IVD;<br>Test kit;<br>Assay |
| **internal quality control** | means operational techniques and activities at the point of use that are used to fulfil requirements for the quality of Medical Pathology Services. | National Pathology Accreditation Advisory Council (Australia): Requirements for Quality Control, External Quality Assurance & Method Evaluation | IQC;<br>Internal controls |

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| **point of care** | Means testing that is performed near or at the site of a patient with the result leading to possible change in the care of the patient | ISO 22870:2006. Point-of-care testing (POCT) – Requirements for quality and competence. | POC;<br>POCT;<br>Near patient testing;<br>Decentralised testing<br>For the purpose of this document, the term POC is used for all testing performed outside of a well-resourced laboratory setting |
| **post market monitoring** | Means continually monitor and evaluate the safety and, in some cases, the efficacy or performance of therapeutic goods that are available on the market and to manage any risks associated with individual products | https://www.tga.gov.au/postmarket-monitoring | Post market surveillance (performed by manufacturer)<br>Market surveillance (performed by regulatory body) |
| **quality assurance** | "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates good manufacturing practice and other factors, including those outside the scope of this guide such as product design and development. | https://extranet.who.int/pqweb/content/glossary | QA;<br>Overarching set of activities and processes performed to ensure that the testing meets predefined quality requirements |
| **quality control** | All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics. | https://extranet.who.int/pqweb/content/glossary | The use of measurements to ensure that the product or service maintaining a predefined quality requirement |

# Executive Summary

Point-of-care or near-patient testing for infectious diseases is commonplace and rapidly expanding. This testing is increasingly performed outside the conventional laboratory settings and in testing facilities lacking infrastructure and is performed by operators who are not health professionals. To maintain high quality products, most *in-vitro* diagnostic devices (IVDs) are manufactured in facilities accredited to ISO 13485; have strict product design and manufacturing protocols; undergo stringent manufacturing quality controls and are registered with one or more stringent regulatory authorities. IVD manufacturers must implement post-market monitoring of the safety and performance of their products. IVDs are usually delivered to procurement sites using validated shipping protocols. Therefore, the quality of IVDs is well controlled to the point of delivery of the products to the warehouse in the country of use. However, the monitoring of quality of transportation, storage and use of the IVDs on leaving the centralised warehouse is lacking.

Ideally, all testing facilities should undergo quality assurance programs to ensure the accuracy of test results over time. When IVDs are used outside a laboratory setting, post market monitoring and quality assurance of the testing facilities are poorly implemented. Application of traditional laboratory-based quality assurance processes encounter several barriers including use of inappropriate sample types, difficulty in cold-chain shipping, cost of regulated quality assurance materials, loss of quality assurance data and lack of guidance by authorities. Most point of care testing sites do not participate in a regular, external quality assurance program. Manufacturers have difficulty in accumulating the evidence of IVD performance in the field to fulfil their regulatory requirements. Organisations funding the procurement and use of IVDs, such as WHO and Global Fund, as well as national regulatory bodies, rely on post market performance data to ensure testing is accurate and reliable.

**This document seeks to define quality assurance processes that are suitable for use in non-laboratory, point of care settings and contribute data for real-time post market surveillance of IVDs.**

The programs outlines in this document are designed to overcome the barriers encountered by point of care testing facilities. Low cost, standardized sample sets, which have been validated as being stable at ambient temperature over a long period of time and mimic the sample type used in the IVD, are promoted. The cost of these samples should be sufficiently low to allow equitable access to all users. Whereas all testing facilities will engage in some level of quality assurance, selected sentinel sites within regions will test a broader range of quality assurance materials. The proposed quality assurance process encourages the use of IVD manufacturers' distribution channels for the supply and delivery of quality assurance samples. Testing of samples should not be tied to "test events" of set dates in a quality assurance calendar, as many point of care test facilities suffer from expired or out of stock reagents. Importantly, as most point of care tests, in particular rapid test devices, report qualitative test results, traditional quantitative quality control principles do not apply. It is envisaged that all data are submitted to a centralised database and novel acceptance criteria are developed to detect any unexpected trends in results. These data will be used for post market surveillance by the manufacturer, regulators, ministries of health and the funders such as Global Fund and WHO.

By implementing a standardised quality assurance format for point of care testing, using the same samples for each test kit globally, a large dataset of quality assurance results can be accumulated and analysed. Test kit-specific acceptance criteria can be established. The data generated from these quality assurance programs can then be used by manufacturers, regulatory bodies and test kit procurers to monitor the performance of IVDs in real time.

# Introduction

Global efforts for the control on HIV, Malaria and TB are progressing positively but are not expected to meet the established targets (1). The advent of the COVID-19 pandemic adds a significant risk to further limiting progress or reversing this trend, by disrupting health systems and diverting attention, resources and funding from the HIV, TB and Malaria intervention programs. It is critical that funding, aimed at disease intervention programs are effective. Access to quality-assured *in-vitro* diagnostic medical devices (IVDs) underpins clinical efficacy in the diagnosis, treatment and management of HIV, tuberculosis, Malaria, viral hepatitis, sexually transmitted diseases and COVID-19, and supports epidemiological studies and programmatic monitoring and evaluation. IVDs procured for or by national authorities must therefore show adequate analytical and clinical performances at the time of procurement and maintain this level of quality through their shelf-lives when deployed in their intended-use settings. IVD quality, safety and performance should be monitored through a cost-effective quality assurance (QA) framework. This can be a challenge for IVDs used at point-of-care (POC) and nearer to the patient/client testing, and in laboratory settings in low-resourced countries as traditional QA programs are designed for well-developed, regulated laboratory settings. This document seeks to present a QA framework that is suited for IVDs used at POC and near-patient testing and in low resourced laboratories that use rapid testing.

# Importance of IVDs for clinical decision making

Testing for infectious diseases informs the diagnosis and treatment of patients; safeguards the blood supply from transfusion-transmitted infections; and provides critical data for epidemiology and disease surveillance programs. Incorrect test results can lead to clinical mismanagement and ongoing transmission of disease; to inappropriate and unnecessary treatment; to contaminated blood supplies and misleading epidemiological data and ultimately undermine the confidence of testing by users. Therefore, it is vitally important that testing sites and laboratories minimise the risk of incorrect test results by monitoring the quality, safety and performance of IVDs used. QA is the foundation of risk minimisation.

All individuals should have equitable access to accurate and timely diagnostic test results. Some of the most disadvantaged populations, including those living with stigma; the poor and socially disadvantaged; remote and regional populations; and many at-risk populations have limited or no access to laboratory-based testing. To overcome this impediment to equity, POC IVDs, such as immunochromatographic rapid diagnostic tests (RDTs) and more portable and robust nucleic acid testing (NAT) technologies have been developed and are widely used. It is important that these IVDs are selected and used in a manner which ensures accurate and reliable test results. Therefore, a QA framework for POC tests is essential as malfunction or deterioration in the safety, quality or performance of all IVDs are a constant risk (2). Failure to implement a comprehensive QA framework potentially leads to waste of resources, but more importantly, poor patient outcomes.

# Regulating quality, safety and performance of IVDs

IVDs are designed, manufactured and distributed for use in medical laboratories; health facilities, such as primary care sites; and in community settings by trained or lay users (including self-testers or peer testers). Countries with well-developed and implemented regulations will conduct pre-market assessment to evaluate the IVDs prior to their introduction within their jurisdiction. The aim of the assessment is to assure the quality, performance and safety of the IVD throughout the product's lifetime. Manufacturers are expected to be compliant to globally-recognised standards such as ISO 13485 or equivalent (3); have a documented product design dossier; and provide comprehensive evidence of clinical and analytical performance for the IVD. The manufacturer's instructions for use (IFU) must be complete and unambiguous; product labelling meet accepted standards and the product comply with safety requirements established by the regulator in the country of origin and use.

A series of quality control activities is undertaken by the manufacturer during and after the manufacturing process. Each new IVD reagent lot is usually tested by the manufacturer using predefined, validated and approved quality control processes including quality control steps. Some regulatory jurisdictions, notably EU and FDA, require batch verification of new lot of certain high risk IVDs by a testing laboratory that is independent of the manufacturer (4). The new lot cannot be supplied to the market until the IVD passes the acceptance criteria set by the manufacturer and assessed by the national regulatory authority (NRA). Once released by the NRA, the new lot can be supplied to the market within that jurisdiction. Regulatory authorities in most other countries do not require lot release as the risk is balanced through accreditation of medical testing facilities and requirement to participate in national External Quality Assessment (EQA) and quality control (QC) programs.

The International Medical Device Regulators Forum (IMDRF) publishes guidance on aspects related to regulation of medical devices that can be adopted by regulators. These include Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices (5), Assembly and Technical Guide for IMDRF Table of Contents Submissions, Medical Device Single Audit Program, and Terminologies for Categorized Adverse Event Reporting as well as others (6).

World Health Organization (WHO) Prequalification of IVDs, coordinated through the Department of Regulation and Prequalification, focuses on assessment of IVDs for priority diseases. The performance and operational characteristics of these IVDs are assessed by an authorised Prequalification Evaluating Laboratory using defined protocols and sample panels (7). If a product meets the requirements for prequalification, it becomes eligible for inclusion in UN procurement tenders. Manufacturers of prequalified IVDs are obliged to report certain incidents to WHO within agreed timelines and their investigation of these incidents must be forwarded to WHO for review. The manufacturer must also submit an annual report of all complaints to WHO for risk assessment purposes.

Slated to come into force in 2022, the European Union will implement new IVD regulations (8) aligned with IMDRF guidance, which will include new requirements for post market surveillance, amongst other changes. Manufacturers are required to "*institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions*." Other IMDRF member NRAs have similar requirements of manufacturers.

## Post market surveillance of IVDs

Although medical devices are designed, developed, manufactured and distributed on the global market after thorough pre-market evaluation, residual risks regarding safety and performance will remain throughout the product's lifetime. Changes to IVD's design or manufacture; changes to raw materials or their suppliers (9) or compromised equipment or consumables (10) can all contribute to malfunction or failure. Test kits are distributed globally and may be stored for some time in warehouses at country level, often in climates not conducive to specified storage conditions. In use, operators may not always follow manufacturer's IFU. Therefore, it is critical to gather and analyse adverse incidents associated with the use of the product and to determine if any action is required. Such actions may include return/destruction or exchange of product; modification of the product or changes to the labelling or IFU; software upgrades; retesting of affected patients' specimens or the review of previous results. Advice on a change in the way the IVD is used, such as revised QC procedure, use of third-party controls or more frequent calibration, may also be required.

Post-market surveillance by manufacturers is a regulatory obligation. Users should report their feedback on the use of the IVD to the manufacturer, often via their economic operator (agent, distributor or authorized representative). Certain incidents must be reported to the NRA according to the specified

timelines. In some jurisdictions and only for certain high risk IVDs, the regulator requires the manufacturer to demonstrate evidence that each new lot of reagent meets acceptable criteria (4). In other circumstances, the performance of the IVD is assessed through a review of the quality assurance (EQA and QC) data. An incident reporting portal allows for incidents to be reported directly to the regulator, who then forwards information onto the manufacturer. Manufacturers are obliged to notify users of any field safety corrective actions that might arise as a result of the analysis of reported incidents.

## Post-production testing of IVDs

Post-production testing of IVDs to determine they meet requirements for safety, quality and performance is conducted by a variety of stakeholders (Table 1).

**Table 1 – Purpose of quality testing conducted by various stakeholders**

| Stakeholder | Purpose of testing |
|---|---|
| ***Manufacturer***  | • Verification and validation studies generate analytical and clinical evidence included in a IVD technical file.<br>• Manufacturers sub-contract other investigators/laboratories to generate clinical evidence on their behalf.<br>• IVD technical file containing data generated both directly by the manufacturer and their subcontracted laboratories is compiled.<br>• Study data are included in the IFU and the technical file.<br>• IFU reviewed by the NRA (or other conformity assessment body).<br>• Each IVD lot is tested by manufacturer as part of the final QC lot release procedure.<br>• Certificate of analysis is created. |
| ***National Regulatory Authorities***  | • NRAs do not conduct testing for marketing authorization purposes, i.e.do not re-confirm performance (e.g. sensitivity, specificity).<br>• NRAs rarely conduct testing (without cause) in the post-market phase, unless indicated by changes in risk, due to other risk mitigation being in place (e.g. testing in accredited sites only, providers are trained and certified, mandatory participation in EQA, stringent IVDs regulations).<br>• If the NRA requires post-market testing due to changes in previously identify risks, a designated laboratory with appropriate expertise to conduct testing is engaged and report generated.<br>• NRA considers the report and decides on actions as required. |
| ***Users***  | • Users verifies new product/test method, using various methodologies, before introduction to testing service/laboratory.<br>• Instruments associated with the IVD require commissioning, maintenance and calibration.<br>• Testing of quality controls, using appropriate QC materials at specified intervals implemented.<br>• Additional validation for specific purposes e.g. each new lot, any new operator (or latent operators), any new lot and/or new shipment, or when the recommended storage conditions are not met.<br>• Users report to manufacturer, and to NRA if national regulations permit, any nonconforming results for their product. |

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| ***Procurers or implementing partners***<br>  | • Procurers may request laboratories with appropriate expertise to conduct testing on receipt of consignments of IVDs.<br>• For cause testing by reference laboratories may be required by Procurers.<br>• Procurer's QA activities are not generally link to the NRAs market surveillance function. |

## Quality assurance of IVDs used in laboratory settings

The term quality assurance invokes different meaning to different people. In its truest sense, QA is just what it says – to assure the quality of the products and the way they are used. It is applied as a set of activities that are ideally, but rarely implemented in a systematic and scientifically robust manner. To implement a comprehensive QA process, the products used must be validated and verified by the manufacturer and should be reviewed by regulatory authorities based on their intended use, using risk management principles. However, once sold into the market, it is imperative that the product is used according to the manufacturer's IFU and that there are systems in place, not only to systematically monitor testing results, but to report any feedback about the use of the product to the manufacturer.

In laboratory-based settings, QA of IVDs and their use is based on the following principles,

- Laboratories are accredited
- Users are well-trained and supported
- EQA is a condition for accreditation and provided by accredited organisations
- External QC is highly recommended for ISO 15189 accreditation
- External QC is primarily designed for quantitative IVDs
- External QC samples are regulated as an IVD

***Accreditation of laboratories***

Increasingly, countries require medical testing laboratories be accredited to international standards such as ISO 15189. Accreditation standards address all aspects of a medical testing laboratory including staff training and competence, occurrence management, including corrective actions, equipment commissioning/control/maintenance and supply chain management. Accredited laboratories are expected to have standardised and documented work instructions and procedures, actively assess and monitor performance against pre-defined criteria, especially those related to customer service, and to respond to identified deficiencies in a systematic manner based on risk mitigation.

***External quality assessment***

In accredited laboratories, it is a requirement for medical laboratories to participate in an EQA scheme for each analyte for which they test. An EQA scheme involves sending a panel of specimens with known reactivity to the participating laboratory/user. The panel is tested and results and associated data reported to the EQA provider. The results of all users are analysed and a report is issued by the EQA provider. Users reporting discordant results are expected to investigate and resolve the root cause of the issue. EQA schemes are usually periodic, with panels sent several times per year; the users having to test the panel within a defined time period. Some EQA providers are accredited to ISO 17043, an international standard that addresses all aspects of the delivery of EQA including sample selection, panel design, homogeneity and stability of samples, distribution management, analysis and reporting of results, customer satisfaction, complaint resolution, staff training, record keeping and overarching work instructions and procedures.

***External quality control (EQC)***

Performing external QC is a quality activity in which users test specimens of known reactivity each time a test if performed. At its most basic, a positive and negative specimen is tested to ensure that the expected reactivity is achieved in qualitative tests. An example would be testing a smear containing *M. tuberculosis* with each Ziehl-Neelsen stain. Routine use of a positive and negative QC is important especially when most specimens tested are expected to be negative (antenatal testing for HIV or syphilis) or positive (screening for anti-rubella IgG).

The control of quantitative testing allows for the monitoring of test results over time. By testing the same QC specimen from day to day, the result can be plotted on a Levey-Jennings chart and the variation over time calculated. Acceptance limits for QC test results can be established and the root cause of any results exceeding the acceptance limits can be investigated and resolved.

The QC specimens used in medical testing are considered IVDs and must undergo regulatory approval after undergoing conformity assessment for stability, labelling, safety, and fitness for purpose. However, frequently laboratories use pooled patient specimens or other clinical specimens for QC purposes, due to costs of IVDs. Here within lies a gap in the current market for external QC materials that are most suited for use on the types of POC or near patient testing IVDs that are used in low- and middle-income countries.

Internal controls are systems manufacturers build into their test, either through a control line for RDTs, control cartridges, validation of application in NAT, or software elements that detect risk of inaccurate results. They assess the operations of the device but not necessarily the analytical performance.

## Provision of quality assurance services

Quality assurance activities, including EQA and QC, are predominantly provided by commercial organisations as a fee-for-service. The providers of EQA report the results to participants (users). In some circumstances, only participants using the same product (IVD peer group) have access to the analysed EQA results. The IVD manufacturer is not always informed on non-conforming EQA results or reports them to NRAs as non-conformances, as the issues are often assumed to be user related. In the same way, results of QC are often monitored by the participant without reference to results obtained by other users. Some QC providers utilise internet-based software, allowing participants to compare their QC results with others within their peer group. However, most QC providers do not systematically monitor the QC test results reported by users. So, although EQA and QC participation is widespread, and conducted at a considerable cost, the process is fragmented and much of the QA data, and the potential benefit to the laboratory, the manufacturer and the NRA, are lost.

## Testing in non-laboratory settings

With the advent of POC technologies, testing for infectious diseases has been introduced to settings outside of well-regulated jurisdictions and well-resourced laboratories. RDTs are used extensively in laboratory settings in low -or middle-income countries (LIMC). Although this testing environment is often within a laboratory setting or hospital outpatient clinics, often the infrastructure is poor, with limited access to stable electricity or pure water, poorly trained staff and a lack of quality procedures and documentation. POC and near patient testing outside a laboratory setting is extensive. In LMICs, POC testing is also conducted in community clinics, remote and regional sites without electricity or refrigeration, village-based outreach programs and regions suffering from conflict and disaster. In well-resourced countries, POC or near patient testing is used to access marginalised or stigmatised groups, high-risk populations such as prisons or drug injecting rooms or outreach programs outside of traditional medical infrastructure. Rarely are comprehensive quality assurance programs implemented in these settings..

***For the purpose of this document, the situations described above are collectively referred to as non-laboratory settings.***

Traditional laboratory-based QA processes are applied onto non-laboratory settings such as primary care and community settings, or at worst, not applied at all. Often, laboratory-based QA processes are inappropriate due to identified deficiencies when applied to POC testing (Table 2). It is possible to re-define the QA processes to meet the quality needs of manufacturers of IVDs and their users in non-laboratory settings and produce a superior outcome compared with traditional QA approaches. A new paradigm suited to testing in non-laboratory settings can be developed. Only then can meaningful approaches to QA and post-market monitoring of IVDs used at or near to point of care testing in a non-laboratory setting be achieved.

## Deficiencies of laboratory-based quality assurance for testing at POC

There are numerous deficiencies when traditional, laboratory-based QA processes are applied to testing at POC or near patient testing in a non-laboratory setting.

**Table 2 – Deficiencies of laboratory-based QA processes when applied to testing at POC in non-laboratory settings**

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| ***Specimen types*** | • Serum/plasma is used for laboratory-based testing, while IVDs for testing at POC often use capillary whole blood or oral fluid.<br>• QA materials are based on serum/plasma rather than actual specimen matrix tested.<br>• Process for adding specimen to the IVD via specimen transfer devices is a likely source of error for IVDs used at POC and this process is not tested in traditional QA.<br>• QA materials should react close to the limit of detection of RDTs; this concentration being assay specific. |
| ***Batched test runs*** | • RDTs and cartridge-based NAT reagents are single use, whereas laboratory-based assays are batched or continuous access.<br>• QA of single-use tests might not detect failure if a lot is not manufactured homogenously. |
| ***Testing facilities*** | • POC IVDs are used in decentralised settings where quality systems can be lacking.<br>• Testing facilities are numerous and sometimes mobile, making QA sample distribution and compliance difficult.<br>• Inadequate information management systems to manage data collection and analysis.<br>• More adverse environmental conditions impact stability of traditional laboratory QA materials.<br>• Poor infrastructure, such as lack of cold storage facilities, for QA samples limit storage capacity. |
| ***Fixed test events*** | • EQA providers have fixed test events throughout the year.<br>• Users are required to test and report results within that fixed time period in order to be included in data analysis.<br>• Shipping/importation difficulties mean shipment of materials are sometime delayed, so test event is missed.<br>• Unavailability of reagents at time of EQA, so users miss the testing window, thereby wasting their EQA purchase. |

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| ***Regulation of QC materials*** | • QC materials are considered IVDs by most IMDRF members and must undergo conformity assessment by the NRA which ensures their quality but increases cost.<br>• Infectious QC materials must be shipped as dangerous goods and often on dry ice, increasing cost and placing administrative burdens e.g. requirements for valid importation permits.<br>• Traditional QC materials can be cost-prohibitive in LIMCs.<br>• Testing facilities use pooled patient samples to reduce cost but introduces variation due to poorer sample type. |
| ***Qualitative result outputs*** | • QC results for qualitative IVDs such as RDTs cannot be plotted on a Levy-Jennings chart to monitor variation.<br>• No suitable alternative to monitoring qualitative data is currently routinely used in the POC setting.<br>• QC results must be collected in a systematic manner to allow for meaningful and statistically relevant data analysis to detect failure, drift, etc.<br>• Large data sets are required to identify patterns of failure. |
| ***Lack of integration to improve quality of testing programmes*** | • Participation in EQA is often a regulatory requirement for users but is only one part of QA.<br>• A well-designed EQA is a snapshot of testing and IVD quality several times per year.<br>• EQA is often conducted by the most senior staff.<br>• Results are not centrally analysed or reported to NRAs and are often lost to follow-up by the testing site and the manufacturer. |
| ***Loss of data*** | • QA users are expected to review the data and perform remedial activities if nonconformities are detected.<br>• Errors are often covered up, the issue go unresolved, which means EQA is often not effective.<br>• Errors identified using QA may not be reported to the IVD manufacturer or NRA by user or EQA provider.<br>• QA programs are conducted by various organisations so systematic collection of QA data is not generally undertaken leading to fragmented data sets. |
| ***Disconnect between QA providers and other stakeholders*** | • Regulators and manufacturers have an interest in the results of QA activities but there are few requirements of QA providers to report issues to NRAs.<br>• WHO has an incident reporting mechanism for issues (product problems) related to WHO recommended IVDs.<br>• Many IVD manufacturers see QA providers as a threat and are often antagonistic to their findings. |
| ***Lack of guidance for QA for POC testing*** | • QA processes are designed for laboratory settings.<br>• They are ill-adapted for POC testing.<br>• Therefore, the cost-benefit of QA is questioned by IVD procurers.<br>• Protocols and associated training for troubleshooting for QA of POC lack development.<br>• QA of POC should be implemented in a coordinated approach, with oversight of key stakeholders.<br>• QA of POC should be a requirement by MOH and regulators. |

## Identifying points of product failure of IVDs used at POC

To better ensure the quality of IVDs used in POC and near patient testing in non-laboratory settings, a framework that uses risk management principles by identifying points of failure can be used to monitor IVD quality.

***Product design changes:***
Most IVDs are manufactured under Quality Management Systems (QMS) principles in facilities that are compliant with ISO 13485 or equivalent. A dossier/technical file is compiled by the manufacturer and is submitted to the NRA in the country where the product is distributed and used at time of registration, demonstrating that the IVD complies with the design specifications and intended use established during its development; confirmed in manufacturer validation and verification studies. The standards ensure that changes made to manufacturing process are well-controlled for risk. Any changes that require modification of the device or its manufacture must be assessed and approved by the NRA prior to their implementation.

***Point of manufacture:***
IVDs can experience variation at during manufacture, sources of antigens and antibodies may change, and different lots of biological components may experience changes in reactivity. Inert components such as buffers, stabilisers or plastics can contribute to variation (9, 10). Any variation that might affect quality, safety or performance of an IVD can be minimised through adherence to QMS and risk management principles, where a design dossier/technical file is updated, new components/suppliers are validated prior to introduction, each new lot is subjected to continual QC through production and at final lot release. However, even with such controls, issues can occur, which require corrective actions to reduce risk of harm to user, patient/client or other people. (9, 10).

***Storage and shipping:***
Once manufactured, IVDs must be held within defined environmental conditions (temperature and humidity) until use. Storage conditions during shipping and long-term storage by the user are less easily traceable, especially for IVDs that are used in remote settings that lack infrastructure such as freezers, refrigerators and climate-controlled facilities. Although many IVDs for use at or near to POC are validated for a range of environmental conditions, deviations from these conditions are not unexpected especially when transported to very hot or very cold geographies using local transportation systems. IVDs that are compromised may function appropriately in the short-term but exhibit suboptimum performance over time (11). Monitoring stability of IVDs over the product life post-distribution is important to confirm expected specifications for performance.

***Instrument commissioning and maintenance:***
Although the IVDs may have been manufactured and shipped within specifications, the appropriate use of the IVDs is essential to ensure correct test results. It is difficult to determine if the IVD, or any associated instrument/platform, is working within specification without appropriate processes for installation/calibration. A formal process of commissioning instrumentation, using calibration materials of known reactivity; documenting the commissioning of instruments/platforms and equipment; and a documented process for training each new user of the instrument, is required. For instrument based IVDs, pre-service training should be conducted by the manufacturer, their economic operator or technical experts who are preferred by the manufacturer. Provision must also be made for on-going training and competency assessments when staff turnover means that new users will operate the instrument. Uncontrolled training of new staff by peers is to be avoided, unless the peer has been adequately trained in a “train the trainer” program preferred by the manufacturer.

Once implemented the user should conduct instrument calibration and maintenance as outlined by the manufacturer. In case of adverse events, the user should have access to timely engineering services.

***User Competence:***
Even after training, users may not follow procedures for various reasons. At times, users may be unaware of the consequences of variation introduced by not following procedures, such as applying insufficient or excessive volume of specimen, use of non-validated specimen types, reading of results in an inappropriate manner or outside the required time period of incubation. On-going assessment of the use of IVDs is a requirement in a laboratory-based setting and is equally important, if not more so, in a testing environment where the IVDs are used by non-laboratory personnel.

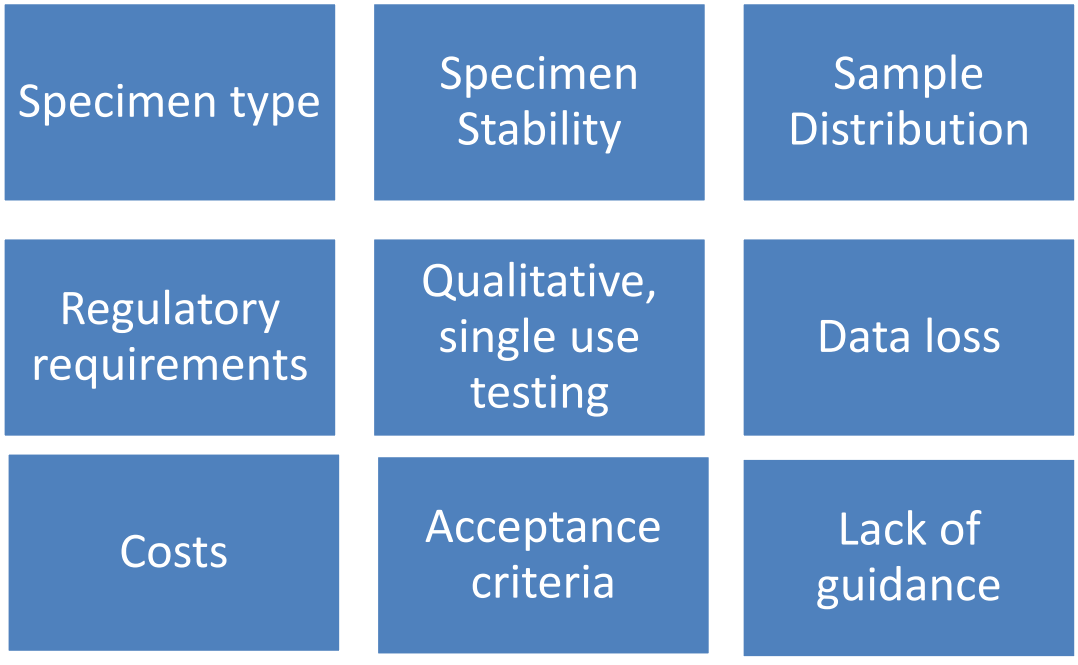
***Changes in risk:***
Previously unidentified risks or increased occurrence of known risks may also occur after a product is placed on the market. Risk is the probability of occurrence of harm; and the consequences of that harm, that is, how severe it might be. Risk management by IVD manufacturers is a continuous and iterative process, during which the hazards associated with the IVD are identified during development. The associated risks are estimated and evaluated, these risks are controlled, and the effectiveness of the controls is monitored through post-market surveillance.

## Removing barriers to a quality framework for IVDs used at or near to POC

Having identified the potential points of failure of IVD used at POC and understanding the limitations of laboratory-based QA (QC and EQA) as applied to testing at POC in a non-laboratory setting, a novel and more appropriate QA framework is proposed. The aim of this novel approach is to develop targeted but functional processes to assess the safety, performance and quality of the IVDs as they transition through these points of failure; collect the data and develop statistical and analytical QA processes that have acceptance criteria for each assessment. By utilising a centralised database and metrics, all stakeholders, including Global Fund, WHO, implementing partners, MOH, IVD manufacturers and QA providers can have access to the same data and coordinate any intervention or remedial activities. They can also share a sense of comfort when testing quality is maintained.

There are several elements that need to be addressed before a comprehensive quality framework for IVDs used at POC can be developed (Figure 1).

**Fig 1 – Barriers presented by current QA approaches**



***Preferred specimen types:***

**Serology:** The dried tube plasma specimen, as a surrogate for liquid serum or plasma, was first described by USA CDC and has used been used successful in both EQA and QC programmes (12-14). Dried plasma or whole blood spots have also been utilised for QA purposes. NRL, Australia has developed an artificial whole blood serology EQA specimen type that detects multiple markers/diseases (unpublished data). FIND and WHO have developed lyophilized recombinant proteins of the two antigens commonly detected by Malaria RDTs (15). These sample types can potentially be used by the testing facility as a single-use positive controls or as prediluted panels to assess the performance of RDT in a reference laboratory and to identify any significant change in analytical performance when compared to reference values and acceptance criteria. The use of stabilized whole blood has been investigated, however to date, the length of time the red blood cells remain intact is insufficient for routine QA use. Lysed red blood cells mask the reaction in RDTs.

The appropriate dilution of serum/plasma specimens best suited for use for QA on serological RDTs should be determining prior to implementation, as IVDs have different analytical sensitivity.

**NAT (plasma):** Dried plasma specimens have been validated for use in NAT QA (12), with EQA programs accredited to ISO 17043 incorporating these specimens being available. These samples are inactivated and therefore non-infectious; have a storage life at -20°C prior to shipping of many years, can be shipped ambient and stored at 4°C for periods of time. Dried tube samples are UN3373 and customs and importation permit exempt reducing the cost and complexity of shipping. Recently, dried plasma specimens have been shown to be appropriate for use in QC programmes (16, 17). Commercial collection devices have been validated for the transport of plasma for NAT, and these may be suitable for QA purposes (18, 19).

**NAT (whole blood):** A dried tube specimen type comprised of washed, packed red blood cells reconstituted with human plasma infected with a known viral load has been developed and validated for use in QA (unpublished data). It is expected that this specimen type will have similar stability to dried plasma and therefore be used in EQA and QC programmes.

**NAT (sputum):** Inactivated bacterial culture of *M. tuberculosis* diluted in buffer have been used in QA programs. This sample type has been shown to be stable with long term storage at -20°C and for periods of time suitable for QA purposes when stored at 4°C.

**Swabs (NAT):** Dried swabs containing organism DNA or RNA have been utilised for EQA programmes. This sample type is appropriate for testing of analytes where swabs are routinely collected as clinical samples, including naso-oral swabs (respiratory viruses) and sexually-transmitted infections such as *N. gonorrhoea, C. trachomatis, T. vaginalis*.

**Transport Media**: After an initial decrease of copy numbers, organism RNA and DNA are surprisingly stable. Ambient transport and refrigerated storage of organisms in media such as PBS, viral transport media or cytology media has been validated for a range of analytes such as *M. tuberculosis*, Leptospira and HPV.

***Preferred stability of QA materials:*** Specimen type must be optimised and validated for the specific assays being monitored and homogeneity and stability of the specimens validated prior to use. The length and period of storage post-production; the period and required temperature range during transportation and the temperature and time of storage after receipt must be validated and communicated to the user via the IFU (Table 3). The specimens can be manufactured in bulk and stored at the validated temperature prior to shipping. The bulk can be stored by the manufacturer in temperature-controlled environments prior to shipping and should be stable for long periods of time post-manufacture. The QA materials should have an acceptable remaining shelf-life post-distribution. Preferably, shipping should be as cool cargo,

but room temperature distribution is acceptable, as long as the shipping conditions are validated. Where possible, in-use stability should not alter the expiry date of the product.

***Preferred distribution channels:*** Distribution of QA materials has a significant cost, especially when transported to remote regions. To overcome the cost and resource-intense shipping processes, concurrent shipment of QA materials with the IVD is suggested. The QA materials can be shipped to the manufacturer's warehouse and distributed to the testing sites with the test kits. If this is not possible, bulk shipment to central medical stores or other economic operators may be considered. This removes the additional cost of shipping from the QA provider to individual participants and therefore reduces the overall cost of the QA program.

**Table 3 – Optimum and minimum criteria for storage and transport of quality assurance samples for POC or non-laboratory infectious disease testing**

| Time after manufacture | Validated storage temperature Optimum (Minimum) | Validated time period Optimum (Minimum) |
|---|---|---|
| **Post-production Pre-distribution** | 2-8°C (-80°C) | > 5 years (6 months) |
| **Transportation** | Ambient (Cold shipments (ice packs)) | 14 days (5 days) |
| **Post distribution** | Ambient (2-8°) | 12 months (2 months) |

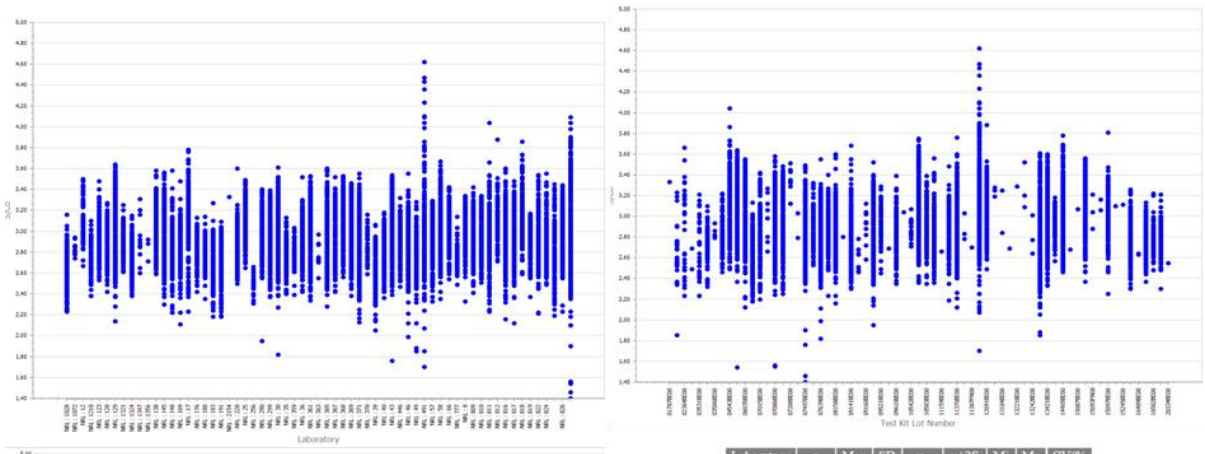
***Preferred way to use QA to improve quality***: By optimising and standardising the specimens used in QA activities, the data obtained from each activity can be integrated, analysed and compared. The same specimen sets can be included in the manufacturer's final QC lot release, as well as being tested by the user, as part of overarching QA activities. Common reporting criteria, based on data collected, can be established. If unexpected results are obtained, identification of the root cause would be more easily identified.

***Preferred data collection and analysis:***
It is suggested that an organisation be a designated data manager. Using a common database, the performance of products can be monitored by Global Fund. Users can report QA results into a common database for assessment by an independent scientific organisation. The results can be reviewed against pre-determined acceptance criteria (established in collaboration with the QA provider and IVD manufacturers). Certificates can be sent to the user on successful completion of each activity as evidence of performance. Automatic feedback will be sent to interested parties such as the IVD manufacturer and MOH. NRAs will be informed when results are outside acceptance criteria or meet pre-defined triggers. Manufacturer can be provided electronic access to the reports and use these data to strengthen their mandatory post-market monitoring requirements. Periodic reports could be developed, or an electronic control dashboard, using a data visualisation module could be developed to review performance of all devices globally.

As an example, NRL, Australia provides a run control program for infectious diseases using internet-based quality control peer-to-peer software where global data are collected, analysed and reported centrally and NRL staff provide oversight of results, initiating and conducting root cause analyses. In this way, significant findings of IVD failures have been detected and addressed before causing adverse patient outcomes (9). (**Figure 2**)

***Removal of fixed test period for EQA:*** Laboratory-based EQA relies on the user testing the EQA specimens within a specified time period. By removing this requirement, non-laboratory testing sites can participate in the QA activities when they have test kits, or when testing is active. Mechanisms to minimise collusion are required.

**Figure 2. Examples of quality control data output. QC results from more than 60 laboratories testing the same QC sample on the same test system, presented by laboratory, instrument and reagent lot number in graphical and tabular form.**



| Laboratory | n | Mea | SD | x- | x+2S | Mi | Ma | CV(% |
|---|---|---|---|---|---|---|---|---|
| NRL : 1028 | 272 | 2.60 | 0.1 | 2.30 | 2.90 | 2.2 | 3.1 | 5.78 |
| NRL : 12 | 56 | 3.10 | 0.2 | 2.68 | 3.52 | 2.6 | 3.5 | 6.77 |
| NRL : 1210 | 112 | 2.76 | 0.1 | 2.48 | 3.05 | 2.3 | 3.1 | 5.21 |
| NRL : 123 | 412 | 2.96 | 0.1 | 2.66 | 3.27 | 2.5 | 3.4 | 5.16 |
| NRL : 128 | 227 | 2.90 | 0.1 | 2.60 | 3.20 | 2.4 | 3.2 | 5.21 |
| NRL : 129 | 410 | 2.98 | 0.2 | 2.41 | 3.54 | 2.1 | 3.6 | 9.47 |
| NRL : 1321 | 121 | 2.89 | 0.1 | 2.64 | 3.15 | 2.6 | 3.2 | 4.46 |
| NRL : 1324 | 147 | 2.74 | 0.1 | 2.43 | 3.05 | 2.3 | 3.1 | 5.58 |
| NRL : 1347 | 12 | 2.95 | 0.2 | 2.50 | 3.40 | 2.6 | 3.3 | 7.67 |
| NRL : 1356 | 3 | 2.84 | NA | NA | NA | 2.7 | 2.9 | NA |
| NRL : 138 | 611 | 3.00 | 0.1 | 2.63 | 3.38 | 2.5 | 3.5 | 6.19 |
| NRL : 145 | 386 | 2.94 | 0.2 | 2.49 | 3.39 | 2.3 | 3.5 | 7.62 |
| NRL : 148 | 307 | 2.86 | 0.1 | 2.50 | 3.22 | 2.2 | 3.5 | 6.29 |
| NRL : 169 | 300 | 2.86 | 0.1 | 2.51 | 3.22 | 2.1 | 3.4 | 6.25 |
| NRL : 17 | 168 | 3.07 | 0.3 | 2.46 | 3.69 | 2.2 | 3.7 | 10.03 |
| NRL : 176 | 159 | 2.82 | 0.1 | 2.57 | 3.07 | 2.4 | 3.1 | 4.46 |
| NRL : 180 | 131 | 2.78 | 0.1 | 2.54 | 3.01 | 2.3 | 3.1 | 4.22 |
| NRL : 183 | 603 | 2.68 | 0.1 | 2.41 | 2.95 | 2.1 | 3.2 | 5.03 |
| NRL : 191 | 178 | 2.70 | 0.1 | 2.32 | 3.09 | 2.1 | 3.0 | 7.17 |
| NRL : 220 | 264 | 2.84 | 0.1 | 2.53 | 3.15 | 2.5 | 3.6 | 5.50 |

## Implementing a quality framework for non-laboratory settings

Having identified the points of failure and implementing processes to overcome barriers to quality for testing near to patient, a novel QA framework which is suited to testing at or near POC can be developed (Annex 4).

Global Fund's QA policy recommends procurement of IVDs that have undergone stringent regulatory review or WHO prequalification. Products that are WHO prequalified have been assessed to be manufactured in a manner that complied with the requirements for safety, quality and performance to fit the criteria for procurement. When transporting IVDs the use of validated shipping containers, shipping processes, as well as temperature and humidity loggers, is encouraged to avoid risks of failure of the devices. Given the controlled manufacturing and transportation of IVDs, ***universal lot-release testing is not recommended***.

However, a practical post-market monitoring process alternative would be to use sentinel sites in different geographical regions to monitor the post-market quality of IVDs, assessing the quality at the point of delivery to the sites in a systematic and measurable manner. This activity will assess both shipment as well as manufacturing integrity.

Therefore, a tiered quality assurance algorithm is suggested –

- **User Monitoring** conducted by all near-patient test sites routinely perform QA testing on small sample sets (2-3 samples) approximately weekly for relatively high throughput testing sites but no less frequently than monthly; when commissioning or moving instruments or equipment; for staff training and competency assessment and, where deemed important, validating new reagent lots.

- **Sentinel test sites** perform a larger, well-designed panel of samples used to perform post-market monitoring of IVDs and assess the quality of the test sites.
- **For-cause testing** performed at nominated reference laboratories testing IVDs identified by the sentinel test sites or routine test sites as having unexpected results, using well-designed panels of samples.
- **External Quality Assessment** conducted by all sites no less frequently than twice per year.

***User Monitoring Panel (for qualitative tests):***
A User Monitoring Panel, consisting of a low and high positive specimen (being two of the specimens in the Sentinel Site panel) would be made available for all testing facilities as a low cost. Ideally, they would be distributed with the reagents by the manufacturer. Users can choose to test the monitoring panel periodically (e.g. weekly or with each new lot), depending on their site throughput. The panel could be used for commissioning of instruments, training of new staff or assessment of competency of existing staff. A portal for the collection of the test results should be made available.

***Sentinel site testing:***
Specified Sentinel Sites, at a provincial and district level of testing can be selected to perform sentinel site testing of test kits used in that region. The number of sites per test kit will be determined by Global Fud, MOH and the NRA. The Sentinel Sites should be relatively high throughput facilities, be located throughout the geographical region rather than just in urban areas and have a demonstrable level of competence for the specific disease testing. Specific training of these sites against a standard curriculum is encouraged. The Sentinel Sites would test the Sentinel Panel of samples in predefined, regular periods e.g. monthly for the shelf life of the product. The results would be reported via a portal into a common database. In this way, the data can be compared and analysed against set acceptance criteria and the test kit quality can be monitored over time. The regional, for-cause testing site may be employed to support and mentor the Sentinel Sites in that region.

The Sentinel Panel of specimens would be relatively small. As an example only, an HIV serology panel may comprising approximately 20 specimens, including about 5-10 negative specimens, 5 specimens known to be positive and a dilution series of at least two separate specimens, and at concentrations known to be around the limit of detection of the test kit being assessed (Annex 1 to 3). The sample type will be determined for each test kit/disease/technology but must fulfil the criteria discussed above; being cheap, stable and fit for purpose. It is recommended that the Sentinel Panel be product-specific, designed, validated and manufactured by a single entity rather than multiple sources of QC specimens. Any variability in test kit performance must be due to the test kit rather than the QA specimens. Reporting of test results by the Sentinel Sites should be standardised, ensuring that standard data are collected. However, the Sentinel Panel test results should not be used as "Go-No Go", but as a mechanism to systematically monitor qualitative IVD performance over time.

***For-cause testing:***
The data collected from sentinel sites may not be conclusive and further testing on the implicated product may need to be undertaken. Specialised laboratories should be selected to conduct for-cause testing. These laboratories should be selected to cover all geographies and ideally be accredited to ISO 15189 or ISO 17025. The selected laboratories should have competent in specific disease testing (e.g. HIV, Malaria, TB***). Testing for cause should be triggered by the NRA.*** If issues related to an IVD are detected e.g. increase in misdiagnosis (false negative, false positive or indeterminate/invalids), either by users or the results of sentinel site testing, collected data can be analysed to document the incident for reporting to the manufacturer, who would refer the incident to the NRA. In some cases, the user may report the incident directly to the NRA via the reporting portal.

QA specimens designed to assess certain performance characteristics are recommended. The For-cause Panels will be created by the specialised laboratory. The panel samples should be representative of the patient sample type i.e. plasma/serum samples for serology assays. They should be stored as liquid frozen in single use aliquots. It is suggested that these panels are compiled by the sites and stored for use so

there is no delay in for-cause testing. As an example only, a panel for HIV serology may consist of approximately 50 specimens, comprising about 20 negative and 20 positive specimens, as well as a dilution series (being the same as that used in the sentinel site panel). Acceptance criteria for these specimens will be established by testing the specimens on all Global Fund-procured test kits. However, it is noted that different analytes and technologies, as well as non-standard issues, may require bespoke panels being produced. The specialised laboratory would be responsible for the creation of panels to meet each specific need.

If the results of for-cause testing do not meet the acceptance criteria, the NRA will be notified and may direct the manufacturer to perform a root cause analysis, under the control of their QMS. Additional testing by the manufacturer is likely and so the user must have quarantined an appropriate number of tests and return to the manufacturer. The manufacturer must notify WHO and Global Fund of the outcome of the investigations and demonstrate the IVD remains fit for purpose before use of that reagent is reinstated. In this way, the for-cause testing can link into post market surveillance.

***Quality control (for quantitative tests):***
For quantitative assays, dried tube specimens can be used to monitor variation over time (12). A panel of two specimens (high and low) would be designed and manufactured specifically for each test kit. Where possible and appropriate, the same panel design would be used across different test kits and a list of test kit/panel combinations published. Results from samples would be reported into an internet-based software or equivalent, and results collected and analyse data in real time. Reporting criteria would be established, and an electronic portal made available to provide feedback to the WHO, manufacturer and other stakeholders, again in real time.

***External quality assessment:***
Traditional EQA, confined by set deadlines, can be replaced by EQA panels distributed to participants by the manufacturer through their distribution channels at the same time as reagents. By randomising the EQA panels, collusion can be minimised. Panels can be distributed by the manufacturer at specified, pre-determined points in time, dependent on the usage of the test system. For example, if an intervention program is being developed for a region, the quality framework should be part of the planning. Participating testing sites could receive EQA panels at pre-defined period throughout the programme.

The samples in the EQA panel would comply with the criteria of being cheap, stable and fit for purpose. They could be subsets of the Sentinel Site Panels, or be more challenging incorporating different concentrations, geno/serotypes or disease states. However, it is noted that to achieve universal coverage, the panels will be less comprehensive than laboratory-based EQA. Ideally, the EQA program would be conducted by an organisation(s) accredited to ISO 17043 and the program come under their scope or accreditation.

## Distribution of Panels

The cost of logistics has been identified as a major impediment to participating in traditional QA programmes. Given that many near-patient testing sites in LMICs are in geographically remote regions, lacking logistics infrastructure and often subject to adverse conditions (flooding, snow, conflict), traditional logistics processes are often unsuccessful in delivering the EQA panels. When successful, the cost is often prohibitive. However, the manufacturers have existing distribution channels for the supply of reagents. By utilizing these channels, both the cost and difficulty of distribution can be overcome. By working with the manufacturer, the panels could be assigned a product code and link directly into their warehouse, pick and pack and delivery services. A set number of each different panel type could be determined for each recipient based on their testing frequency, and their status as a routine testing facility, sentinel site, etc.

## Database

The results of testing of each of the panels described above should be submitted into a central database. The data fields collected and the relations of each field to each other must be established. It is beyond the scope of this document to describe the requirements in detail. However, some suggestions are provided. To facilitate the analysis of the QA results, all data collected must be in a standard, well-documented format. Mandatory fields must be identified (e.g. site identification, panel type and lot number, date of testing, IVD product code and lot number). The manner of reporting results of qualitative subjective tests must be standardised. Categorical data (e.g Strong=3, Mod=2, Weak=1, Negative=0) could be employed. If quantitative data are collected, then the unit of measure for each test kit needs to be standard (e.g. Ct value, index, Sample to cut-off). The relationship between fields needs to be established. For example, results from specific instrument serial numbers need to be captured and traceable for future analysis. A database business analysis will be required to develop the requirements with the responsible bodies.

There are several potential options for the collection and analysis of data. As an example only, two possibilities are discussed, although other possibilities could be considered.

**Relational databases:** There are several examples of relational databases that have been used to manage the results of laboratory-based quality assurance. Providers of quality control have established internet-based data management and analysis tools such as EDCNet (NRL, Australia), IAMQC (Technopath Diagnostics), LabLinks (Thermo Fisher) and Unity (BioRad). Results from each testing facility are entered into a central relational database, usually MS Sequel, and analysis and graphic functionality allows the user to review its test results and compare their performance with other participants using the same sample/test kit combination. All major EQA providers have developed bespoke software for the collection, analysis and reporting of EQA results, using a relational database system.

**Distributed ledger technology:** Blockchain technology makes possible the decentralisation of data storage so the data is not stored by any one entity. Instead, users could store files on any computer that met the rules of the protocol on a decentralised file storage network that protect the user's community. The key cryptographic ingredient used in blockchain is known as a cryptographic hash function, represented as a string of 64 hexadecimal characters, making it impossible to decrypt and allowing for an online, decentralized, and transparent record of every transaction undertaken on the network since its inception, also known as decentralised, public ledger (20, 21). This means the secure database could be accessible across different sites, without the need of third parties that retain administrative rights over the database. The data is immutable and cannot be tampered with, all transactions are recorded. Each participant maintains a copy of the records, blockchain technology will immediately identify and correct any unreliable information. Data can automatically identify and correct itself based on coded business logic (smart contracts) and consensus, participants are intrinsically able to trust it, and it creates opportunities for more participants to join the blockchain network and increase the visibility into the data.

**Data Management**: The collection of data must be well documented, and users trained. Validation protocols must be included at result entry to minimise data entry errors. Ideally, a body should be responsible for the maintenance of the database, reviewing data for inconsistencies, reporting unusual events to stakeholders and communicating with users for technical issues. This body may also liaise with the software developers to manage de-bugging the system and creating additional functionality. Data entry of result scan be onerous and subject to errors. Where possible, partnering with the manufacturer of instrument-based IVDs could allow for the direct electronic transmission of data directly from instrument to database.

**Analysis and reporting**: Once validated data are received into the database, a process for the analysis and reporting of results to stakeholders is required. Participating testing facilities will require reports of their results and a comparison of their results with their peers, usually as summary statistics. WHO and Global Fund may require exception reports; notification when results exceed pre-determined criteria.

Manufacturers can acquire access to all data reported from the use of their test kits. They can use these data to demonstrate post market monitoring compliance, detect issues and confirm resolution. Standard reports for each stakeholder can be created and scheduled for delivery at specific period of time.

## Benefits of a quality framework for testing at POC

Traditional QA programs have been designed for laboratories in well-resourced setting and in a regulated environment. These QA programs encounter significant barriers when applied to infectious disease testing in non-laboratory settings, including POC or near-patient facilities or in resource-limited laboratories. QA programs can be redesigned to overcome these barriers and to meet certain QA needs such as verification of test procedures, competency of operators, shipping integrity and monitoring of test kit performance. By implementing a systematic, comprehensive and novel approach to quality assurance for POC, QA data can be collected in a standardised manner allowing the establishing of acceptance criteria. These criteria can be used to trigger incidence reporting to NRAs and IVD manufacturers, supporting into post market monitoring systems. The data collected will allow the manufacturer to demonstrate to regulatory bodies an on-going, independent and robust post-market monitoring process. Outsourcing the QA materials production and data management to an independent organisation that has established infrastructure will reduce costs, increase effectiveness and provide the testing community confidence in the results reported in a POC or non-laboratory setting. The program will also underpin the effectiveness of programs supported by Global Fund and other procurers of IVDs.

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## Annex 1: Quality Assurance framework for rapid diagnostic lateral flow devices.

| Near-Patient Testing Quality Assurance Framework | | |
|---|---|---|
| **Test Information** | | |
| Test System | Lateral Flow Antibody Test | |
| Specimen Type | Capillary Whole Blood | |
| **Quality Assurance Information** | | |
| QA sample type | Dried serum sample<br>Dried whole blood sample<br>Dried blood spot | |
| QA sample stability (validation criteria) | Long term storage – more than 12 months at less than -20$^{o}$C<br>Shipping temperature – 2 weeks at less than 25$^{o}$C<br>Pre-testing storage – 2 months at less than 25$^{o}$C or<br>– 6 months at 2 -8 $^{o}$C | |
| Distribution process | Bulk shipment to Global Fund Recipient Warehouse or<br>In collaboration with IVD shipment to recipient sites | |
| **Quality Assurance Programmes** | | |
| Sentinel Site Testing | 20 sample panel | 10 negative<br>5 positive<br>5 member dilution series (assay specific) |
| | **Testing performed at nominated sentinel sites** | |
| Monitoring Panel | 2 sample panel | 1 negative<br>1 low positive (assay specific) |
| | **Testing performed at all sites** | |
| External Quality Assessment | 5 sample panel | 1 negative<br>2 low positive (assay specific)<br>2 positive |
| | **Testing performed at all sites** | |
| **For-cause Testing** | | |
| Sample panel (liquid frozen plasma) | 50 sample panel (assay specific) | 20 negative<br>20 positive<br>5 member duplicate dilution series |
| | **Testing performed at national reference laboratory** | |

## Annex 2: Quality Assurance framework for point of care malaria testing

<table>
<tr><th colspan="3">Near-Patient Testing Quality Assurance Framework</th></tr>
<tr><td colspan="3">Test Information</td></tr>
<tr><td>Test System</td><td colspan="2">Near patient malaria antigen detection rapid diagnostic test</td></tr>
<tr><td>Specimen Type</td><td colspan="2">Capillary or venous whole blood</td></tr>
<tr><td colspan="3">Quality Assurance Information</td></tr>
<tr><td>QA sample type</td><td colspan="2">Dried recombinant antigens<br>Dried culture samples<br>Dried whole blood samples</td></tr>
<tr><td>QA sample stability<br>(validation criteria)</td><td colspan="2">Long term storage – more than 12 months at less than -20$^{o}$C<br>Shipping temperature – 2 weeks at less than 25$^{o}$C<br>Pre-testing storage – 2 months at less than 25$^{o}$C or<br>– 6 months at 2 -8 $^{o}$C</td></tr>
<tr><td>Distribution process</td><td colspan="2">Bulk shipment to Global Fund Recipient Warehouse or<br>In collaboration with IVD shipment to recipient sites</td></tr>
<tr><td colspan="3">Quality Assurance Programmes</td></tr>
<tr><td rowspan="2">Sentinel Site Testing</td><td>20 sample panel</td><td>10 negative<br>5 positive (varying parasitemia)<br>5 member dilution series (assay specific)</td></tr>
<tr><td colspan="2">Testing performed at nominated sentinel sites</td></tr>
<tr><td rowspan="2">Monitoring Panel</td><td>3 sample panel</td><td>1 negative<br>1 low positive P. falciparum<br>1 low positive P. vivax</td></tr>
<tr><td colspan="2">Testing performed at all sites</td></tr>
<tr><td rowspan="2">External Quality Assessment</td><td>10 sample panel</td><td>2 negative<br>4 subclinical positive (varying species)<br>4 positive (varying species)</td></tr>
<tr><td colspan="2">Testing performed at all sites</td></tr>
<tr><td colspan="3">For-cause Testing</td></tr>
<tr><td rowspan="2">Sample panel<br>(liquid frozen plasma)</td><td>50 sample panel<br>(assay specific)</td><td>20 negative<br>20 positive (varying species and parasitemia)<br>5 member dilution series (duplicate)</td></tr>
<tr><td colspan="2">Testing performed at national reference laboratory</td></tr>
</table>

## Annex 3: Quality Assurance framework for point of care viral load testing

| Near-Patient Testing Quality Assurance Framework | | |
|---|---|---|
| **Test Information** | | |
| Test System | Near patient molecular viral load testing | |
| Specimen Type | Plasma or Capillary Whole Blood | |
| **Quality Assurance Information** | | |
| QA sample type | Dried plasma sample<br>Dried whole blood sample<br>Dried plasma or blood spot | |
| QA sample stability (validation criteria) | Long term storage – more than 12 months at less than -20$^{o}$C<br>Shipping temperature – 2 weeks at less than 25$^{o}$C<br>Pre-testing storage – 2 months at less than 25$^{o}$C or<br>– 6 months at 2 -8 $^{o}$C | |
| Distribution process | Bulk shipment to Global Fund Recipient Warehouse or<br>In collaboration with IVD shipment to recipient sites | |
| **Quality Assurance Programmes** | | |
| Sentinel Site Testing | 20 sample panel | 10 negative<br>5 positive (varying genotypes)<br>5 member dilution series (assay specific) |
| | **Testing performed at nominated sentinel sites** | |
| Monitoring Panel | 2 sample panel | 1 negative<br>1 low positive (assay specific viral load) |
| | **Testing performed at all sites** | |
| External Quality Assessment | 5 sample panel | 1 negative<br>2 low positive (assay specific viral load)<br>2 positive (varying genotypes) |
| | **Testing performed at all sites** | |
| **For-cause Testing** | | |
| Sample panel (liquid frozen plasma) | 50 sample panel (assay specific) | 20 negative<br>20 positive (varying genotypes & viral load)<br>5 member dilution series (duplicate) |
| | **Testing performed at national reference laboratory** | |

## Annex 4: Schematic diagram representing the flow of samples and information between parties involved in point of care testing