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Policy Analysis

Policy analysis: User monitoring of *in-vitro* diagnostic medical devices used for near-patient testing of infectious diseases

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Abstract

Background: All individuals should have equitable access to accurate and timely testing for infectious diseases, which underpins diagnosis and treatment, safeguards blood supplies, and is used to determine disease prevalence. Disadvantaged populations have limited access to laboratory-based testing, so near-patient or point-of-care testing (PoCT) has been developed and implemented. Unlike laboratory-based testing, PoCT is often performed by non-laboratory staff and outside regulatory frameworks. Quality assurance (QA) of PoCT is often lacking or inappropriate, meaning inaccurate testing can go undetected, leading to poor patient outcomes.

Objective: To review the application of QA of PoCT use to detect infectious diseases and propose fit-for-purpose alternatives.

Method: A review of the current QA of PoCT was undertaken by experienced QA providers by mapping the points of failure. Barriers to providing PoCT QA include inappropriate and unstable sample types; expensive shipping to remote sites, including dry ice shipment; cost of international QA programmes; regulatory costs; fixed test events; and a lack of technology for simple, centralized data collection facilitating rapid analysis and reporting of test results. Based on these findings, a novel, fit-for-purpose model of QA for PoCT for infectious diseases is described.

Results: The new model for QA for PoCT identifies and describes novel sample types, including dry tube samples, dried swabs, or liquid-stable clinical samples that are inactivated and stable at ambient temperature; modified distribution channels; and a method for data collection and analysis using mobile phone technology.

Conclusion: The findings of this paper seek to describe a fit-for-purpose process, which aims to improve the quality of testing for infectious diseases at PoCT, globally.

Key words: User monitoring, near-patient testing, point-of-care testing infectious diseases, quality assurance

Key Messages

- PoCT should be subject to quality assurance to minimize false test results.
- There are barriers to applying traditional, laboratory-based QA to infectious disease PoCT.
- A novel, fit-for-purpose approach to conducting QA for infectious disease PoCT is described.

Introduction

Testing for infectious diseases informs the diagnosis and treatment of patients, safeguards the blood supply from transfusion-transmitted infections, and informs epidemiology and disease surveillance programmes [1–4]. Therefore, it is vitally important that laboratory and near-patient testing minimize the risk of incorrect results by monitoring the quality, safety, and performance of the *in vitro* diagnostic medical devices (IVDs) [1]. Systematic, fit-for-purpose quality assurance (QA) of testing minimizes the risk of inaccurate results [4].

All individuals should have equitable access to accurate and timely testing services. Disadvantaged populations, including those living with stigma, socially disadvantaged, remote populations, and at-risk groups, have limited access to laboratory-based infectious disease testing. Immunochromatographic rapid diagnostic tests (RDTs) and portable nucleic acid testing (NAT) technologies help overcome this situation. Testing at or near to point-of-care (POC) has been adopted in both well-resourced and low-middle-income

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countries (LMIC) and can be performed outside laboratory settings by non-healthcare professionals [5]. To assure high quality, IVD POC tests are manufactured in facilities accredited to ISO 13485 [6, 7]. This standard requires manufacturers to monitoring IVD performance and conduct post-market surveillance of the safety, quality, and performance of their products [8–10]. IVDs are usually delivered by the manufacturer to centralized warehouses using validated shipping and storage conditions. Onward distribution to testing sites may be out of the control of the manufacturer, so monitoring the quality of near-patient or point-of-care testing (PoCT) IVDs is difficult. Therefore, poor performance may go undetected.

To ensure accurate and reliable results, all IVDs should have QA measures implemented [4, 5, 11]. When used outside laboratory settings, QA and post-market monitoring are infrequently and/or poorly implemented. PoCT providers have often not considered QA framework at implementation. Laboratory-based QA processes are mature but experience barriers when applied to POC sites, including inappropriate specimen types, expense of cold-chain shipping, cost of regulated external quality control (EQC) materials, and a loss of QA data. Therefore, a QA framework appropriate for POC IVDs is essential, so deterioration in the safety, quality, or performance of the IVD can be detected quickly and corrective actions are implemented. Failure to implement an appropriate QA framework for POC IVDs potentially leads to waste of resources but more importantly, poor patient outcomes [2, 5, 12]. There is a general lack of guidance by authorities on how to apply QA to POC settings. Therefore, most PoCT sites do not participate in a regular external quality assessment (EQA) or EQC programmes. Consequently, IVD manufacturers report difficulties ensuring timely feedback from their users and accumulating evidence of IVD safety, quality, and performance.

By understanding and documenting the barriers to participation in QA programmes by PoCT sites, QA processes can be re-defined. This document describes 'User Monitoring System', which removes barriers to participation in QA for PoCT sites and allows stakeholders access to post-market surveillance data, and facilitates remedial activities when testing errors are detected.

Regulatory environment for IVDs

IVDs may be designed for use in medical laboratories by laboratory professionals or in community settings by non-professional self- or peer-testers. Countries with mature regulatory systems approve IVDs for use in their market, conducting risk-based pre-market assessment of IVDs to assure the quality, performance, and safety of the IVD throughout the product's lifetime [7, 8, 10, 13]. This assessment reviews clinical and analytical evidence. Regulators require compliance with globally recognized quality standards such as ISO 13485 [6]. The manufacturer's instructions for use (IFU) must be complete and unambiguous, product labelling must meet accepted standards, and the product complies with safety requirements established by the regulator. Manufacturing quality control activities monitor IVD components and raw materials and the manufacturing process. Each new reagent lot is released using predefined and approved quality control processes [9]. In certain regulatory jurisdictions, new reagent lots must pass pre-market lot release by the relevant regulatory authority. Universal lot release at testing sites is not recommended.

The European Union is implementing new IVD regulations aligned with International Medical Device Regulators Forum guidance, which will include requirements for post-market surveillance [7]. Manufacturers should 'play an active role during the post-market phase by systematically and actively gathering information from post-market experience with their devices.... To this end, manufacturers should establish a comprehensive post-market surveillance system' [14]. World Health Organization (WHO) issued updated guidance on post-market and market surveillance of IVDs in 2020 encouraging users of IVDs to monitor IVDs and report any concerns (quality, safety, or performance) to the manufacturer via their local economic operator (supplier, agent, and authorized representative) [8].

WHO Prequalification assesses the performance characteristics of IVDs for selected priority diseases, focusing on POC IVDs [10]. Products meeting the requirements for prequalification become eligible for inclusion in United Nations procurement tenders. Manufacturers of prequalified IVDs are obliged to report adverse events and subsequent investigations to WHO for review, including an annual report of all incidents to WHO for risk assessment purposes.

Therefore, IVDs have acceptable quality, performance, and safety at the point of manufacture and distribution to warehouses. The storage, transport conditions, and the usage of the test kits are less well controlled from that point. Variation in performance can be introduced by adverse storage and transport temperatures and humidity [15, 16]. Users of the IVDs may not strictly follow the IFU or inappropriately use expired product [1]. Wrong specimen types or incorrect volumes of the specimen may be tested. Incorrect incubation time and variation in subjective reading can adversely results. Each variation may compromise the accuracy of the test, leading to inaccurate results and therefore poor patient outcomes [2].

QA of IVDs

To monitor laboratory testing, QA measures including EQA and EQC programmes are recommended by WHO and required by laboratory licencing/accreditation authorities for compliance with ISO 15189 [4]. An EQA scheme involves sending a blinded panel of well-characterized specimens to the participating testing site several times per year. The participating site tests the panel within a defined period, and the EQA provider analyses the results and issues a report [11]. EQC specimens of known reactivity are tested at predefined intervals. Quantitative test results are plotted on a Levey–Jennings chart and variation is monitored over time [16]. Acceptance limits for EQC test results are established, and any results exceeding the acceptable limits are investigated [16]. EQC specimens are IVDs and undergo regulatory approval. External EQC materials suitable for use on POC IVDs and affordable in LMICs are unavailable.

POC IVDs are designed to be simple, robust, and appropriate for use by non-healthcare professionals. Internal quality control (IQC) built into the assay system through a control line for RDTs, control cartridges, amplification controls in NAT, or instrument software controls can detect risk of device malfunction. RDTs have in-built control lines indicating sufficient flow along/through the nitrocellulose membrane but often do not provide positive and negative kit controls. POC

NAT typically includes electronic controls to assess instrument performance. Manufacturers may provide armoured nucleic acid kit controls, which confirms amplification and detection but does not control for extraction. Human DNA detection can ascertain suitable specimen collection. IQC monitors the mechanical functions of the IVD but does not assess result accuracy or monitor the performance of the IVD over time.

Testing in non-laboratory settings

In LMICs, IVDs are used at POC in community clinics and village-based remote sites without electricity or refrigeration, in regions without mature regulatory frameworks. POC IVDs are also used in laboratory settings or hospital outpatient clinics, where infrastructure is poor [17, 18]. In well-resourced countries, PoCT is used to access high-risk, marginalized, or stigmatized populations, such as (prisons or drug injecting rooms) outside traditional laboratory infrastructure and associated regulations. Each of these situations often lacks comprehensive QA processes, and therefore, the quality of testing cannot be assured, errors go undetected and unresolved, and manufacturers have difficulty complying with post-market surveillance requirements [11, 12, 17].

Barriers to applying laboratory-based QA for PoCT

There are numerous deficiencies when traditional, laboratory-based QA processes are applied to PoCT in non-laboratory settings (see Table 1). These barriers reflect the inherent differences in POC compared with laboratory-based testing. By understanding these differences, more appropriate POC QA practices can be developed.

Identifying points of failure of IVDs and their costs

IVDs can fail at multiple points in their transport, storage, and use [1, 2, 12]. Uncontrolled road transport can experience excessive humidity and temperatures. Storage in facilities with noncontrolled temperature in tropical or arid environments can damage IVDs. Compromised IVDs may function appropriately in the short term but exhibit suboptimum performance over time [19]. Monitoring stability of IVDs over the product life is important to confirm expected performance. Human error is the primary source of variation. Test providers use expired test kits, test unvalidated specimen types, ignore pre-analytical steps, use different specimen application methods/devices, or modify the volume of specimen and/or reading time. Without a comprehensive QA programme, these variations go undetected and unresolved [3].

False PoCT results are well documented [1–3, 5, 12, 18, 20–22]. The extent of the percentage of failures varies with location, analyte, and device; the manner of training and competency of the user; and implementation of QA [1, 11, 12, 17]. Although IVDs designed for near-patient testing and registered by a stringent regulatory authority or WHO have relatively high sensitivity and specificity, the performance of test results declines when implemented into routine testing but non-laboratory users [22]. However, there is a paucity of data relating to the cost of QA and the economic cost of misdiagnoses. A significant study indicated that the cost of an early infant diagnosis HIV QA programme was estimated to be US dollars (US$) 400 and US $1500 per site but would save US $500 000 in averted healthcare costs attributable to treating uninfected infants [12], concluding that QA implementation

Table 1 Deficiencies of laboratory-based QA processes when applied to testing at POC in non-laboratory settings

Specimen types	• Serum/plasma is used for laboratory-based testing, while IVDs for testing at POC often use capillary whole blood or oral fluid. • QA materials are based on serum/plasma rather than specimen matrix tested. • Process for adding specimen to the IVD via specimen transfer devices is a likely source of error for IVDs used at POC and is not assessed in traditional QA. • 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. • QA of single-use tests might not detect failure if a lot is not manufactured homogenously.
Testing facilities	• POC IVDs are used in decentralized settings where quality systems can be lacking. • Testing facilities are numerous and sometimes mobile, making QA sample distribution and compliance difficult. • Inadequate information management systems are available to manage data collection and analysis. • Adverse environmental conditions impact stability of traditional laboratory QA materials. • Poor infrastructure, such as lack of cold storage facilities, for QA samples limits storage capacity.
Fixed test events	• EQA providers have fixed test events throughout the year. • Users are required to test and report results within that fixed time period to be included in data analysis. • Shipping/importation difficulties mean shipment of materials is sometimes delayed, so test event is missed. • Unavailability of reagents at time of EQA, so users miss the testing window, thereby wasting their EQA purchase.
Regulation of QC materials	• QC materials are considered IVDs by most International Medical Device Regulators Forum members and must undergo conformity assessment by the NRA, which ensures their quality but increases cost. • Infectious QC materials must be shipped as dangerous goods and often require dry ice, increasing cost and placing administrative burdens, e.g. requirements for valid importation permits. • Traditional QC materials can be cost-prohibitive in resource-limited countries. • Testing facilities use pooled patient samples to reduce cost but introduce variation due to poorer sample types.
Qualitative result outputs	• QC results for qualitative IVDs such as RDTs cannot be plotted on a Levy–Jennings chart to monitor variation. • No suitable alternative to monitoring qualitative data is currently routinely used in the POC setting. • QC results must be collected in a systematic manner to allow for meaningful and statistically relevant data analysis to detect failure, drift, etc. • Large data sets are required to identify patterns of failure in qualitative tests.

(continued)

Table 1 (Continued)

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. • A well-designed EQA is a snapshot of testing and IVD quality several times per year. • EQA is often conducted by the most senior staff. • 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. • Errors are often covered up, and the issues go unresolved, which means EQA is often not effective. • Errors identified using QA may not be reported to the IVD manufacturer or NRA by user or EQA provider. • QA programmes are conducted by various organizations, so systematic collection of QA data is not generally undertaken leading to fragmented data sets.
Disconnection 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. • WHO has an incident reporting mechanism for issues (product problems) related to WHO-recommended IVDs. • Many IVD manufacturers see QA providers as a threat and are often antagonistic to their findings.
Lack of guidance for QA for PoCT	• QA processes are designed for laboratory settings. • They are ill-adapted for PoCT. • Therefore, the cost-benefit of QA is questioned by IVD procurers. • Protocols and associated training for troubleshooting for QA of POC lack development. • QA of POC should be implemented in a coordinated approach, with oversight of key stakeholders. • QA of POC should be a requirement by MOH and regulators.

of PoCT was cost-effective. The model proposed below seeks to reduce the cost of delivery of QA for PoCT and therefore increase the cost-effectiveness of the programmes.

Establishing fit-for-purpose QA for POC IVDs

A more suitable model for providing QA to PoCT can be developed using the following principles.

- **Specimen types**—The dried tube specimen (DTS) format has been used for QA for both serology and NAT assays [23–25]. DTSs are sufficiently stable at ambient temperature for transportation and retain stability for long periods of time when frozen. Foundation for New Innovative Diagnostics (FIND) and WHO have developed lyophilized recombinant proteins of the two antigens commonly detected by Malaria RDTs [26]. Swabs and viral culture media, containing inactive or non-viable organisms, have also been used for EQA and EQC programmes. Dried plasma specimens are appropriate for use in EQC programmes [27, 28]. Commercial collection devices have been validated for the transport of plasma for NAT [29, 30]. Use of specimens containing whole virus allows the monitoring of the NAT extraction process.
- **Stability and homogeneity of materials**—Materials can be manufactured in bulk and stored for long periods of time. Manufacture at scale is the cheapest option and ensures homogeneity, so participating sites test the same batch of materials. Results obtained from the same batch can be combined for analysis and be monitored over time. Methods for transportation and storage of the materials can be validated and applied universally.
- **Panel distribution**—To overcome the cost of resource-intense distribution processes, concurrent consignments of QA materials with the IVDs are suggested. QA materials shipped to the centralized warehouse can be distributed to the testing sites with the test kits. This removes the additional cost of shipping from the QA provider to individual participants.
- **Removal of fixed test period for EQA**—Removing the requirement of testing EQA specimens within a specified period allows non-laboratory testing sites to participate in quality activities when they have test kits or when testing is active. Mechanisms to minimize collusion, such as checking results with other laboratories prior to submission, are required.
- **Data collection and analysis**—QA results should be stored in a global database, and automated messaging of result accuracy is sent to the participant. Preferably, the EQA and the EQC results would be stored within the same global database, to facilitate cross-programme analysis. A data manager, preferably an accredited QA provider, can analyse results and monitor for signals or unacceptable variations over time. Issues are reported to the IVD manufacturer, the regulator, and other stakeholders who might initiate 'for-cause' testing. As an example, National Serology Reference Laboratory, Australia provides a run control programme using internet-based quality control peer-to-peer software EDCNet™ [16, 31, 32].

Proposed QA framework for PoCT

Monitoring POC IVDs should be based on risk, so a tiered QA framework is proposed (see Table 2) focusing on the delivery of IVDs from the warehouse to the testing site and their subsequent use.

- **User monitoring**—There should be evidence that new operators are trained appropriately, instruments are installed successfully, and ongoing operator competency is monitored by testing small numbers of specimens with known reactivity over time. This competency assessment may be combined with a short questionnaire to assess the test provider's knowledge.
- **EQA**—Participation in the EQA scheme is conducted by a provider accredited to ISO 17043, by testing inactivated specimens stable at ambient temperatures. Programme consists of at least two challenges per year not restricted to specific dates.

Table 2 Proposed QA mechanisms for PoCT for infectious diseases

QA programme	Number of samples	Frequency	Additional information
User monitoring	One to two per analyte	Weekly–monthly	• Training new operators • Periodic competency assessment • Assessment of new reagent lots • Post-instrument commission or maintenance
EQA	Minimum five per challenge	Two to three challenges per year	• Specimens in challenge represent all variations of analytes over time • Number of specimens per challenge depends on number of analytes being tested • Alternate test providers for each challenge • Minimum two challenges per year
EQC	One to two per analyte	Weekly–monthly	• Frequency depends on number of specimens tested per week • Could be replaced with user monitoring if specimens are appropriately regulated for use as controls
Sentinel site testing	Twenty specimens per analyte	Predefined periods (e.g. monthly or quarterly) throughout life of IVD	• Sites selected by Ministry of Health, Regulator • Sites should have high throughput and be geographically distributed through urban and rural settings • Well-characterized specimens representing positive, negative, and low positive reactivity. • Mixture of geno/serotypes was relevant • Specimen panel is designed to be IVD-specific • Established acceptance criteria
For-cause testing	Specimen panel created to address particular issue using stored, previously prepared sample bank	In response to identified issues	• Specialized laboratory used for testing • Preferably ISO 15189 or 17025 accredited • Report directly to regulatory authority • Regulator reports to manufacturer and procurer

- **EQC**—A positive control, optimized for the IVD, is tested weekly. Competency Panel may be used for that purpose. The test results and associated metadata are collected into a centralized database [16]. Quantitative results can be monitored using a Levey–Jennings chart. Results outside the acceptance criteria should be reported to the IVD manufacturer by the QA provider for post-market surveillance [31]. Qualitative results are reviewed for signals, including adverse events such as misdiagnosis.
- **Sentinel site testing**—Where all POC test sites cannot conduct independent QA, monitoring the performance of IVDs at selected sites is an alternative. Sentinel sites are selected by Ministries of health (MOH) and/or national regulatory authority (NRA) to monitor IVDs used in that area. This approach can contribute to market surveillance activities of the NRA and trigger for-cause testing. The sentinel sites would test the sentinel panel (Table 2) at predefined periods for the shelf life of the product and report results into a centralized database.
- **For-cause testing**—Specialized laboratories, competent in specific disease testing (e.g. HIV, malaria, and tuberculosis) and ideally accredited to ISO 15189 or ISO 17025, perform for-cause testing. International laboratories may be used to test for a specific analyte. For-cause testing should be requested by the NRA in response to adverse events. For-cause sites would analyse and report data derived from IVD incidents. The manufacturer would provide a root cause analysis, including impact of the issue back to the NRA. For-cause testing coordinated by the NRA should be considered as an element of market surveillance.

Conclusion

Serological testing using RDTs has been universally applied as a tool to reduce the burden of HIV, malaria, viral hepatitis, and syphilis. NAT used at or near to POC is used to diagnose and then determine eligibility for, and response to, treatment for HIV, viral hepatitis, TB, and cervical cancer and to address the high burden of sexually transmitted infections. Therefore, testing for infectious diseases, outside the laboratory setting, is well established and increasing in both well-resourced and LMICs, supporting equitable access to testing for all. It is envisaged that this model can be used within a geographical region, across multiple regions, or internationally.

However, unlike laboratory-based testing, QA for IVDs used at or near to PoCT has not been adapted to suit the needs. Traditional, laboratory-based QA programmes are cost-prohibitive and are not designed for POC IVDs. By recognizing these barriers and designing a QA framework that is more appropriate for POC IVDs, a comprehensive and fit-for-purpose model can be developed that will meet the needs, of not only the QA of testing sites, but fulfil the post-market requirements of manufacturers and regulators. A well-designed and implemented QA approach can generate real-time and detailed data, which can be analysed to establish acceptance criteria. By reducing the cost of sample manufacturing and logistics, removing the impediment of set test events, and implementing an internet-based but mobile phone-enabled data collection and storage into a centralized database, the proposed model can be rolled out to any interested party at a fraction of the cost of a laboratory-based QA programme. The findings of a POC QA programme can trigger a more detailed review and, where required, action

by manufacturers and by regulators. Without such a model, poor quality for results from IVDs used at POC often goes undetected, resulting in adverse clinical events. The potential of inaccurate test results and the associated consequences will continue, leading to misdiagnosis, delayed diagnosis and treatment, continued onwards transmission of disease, waste of resources, and a loss of confidence in testing.

Data availability

This paper is an analysis of policy. No data were collected or analyzed.

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