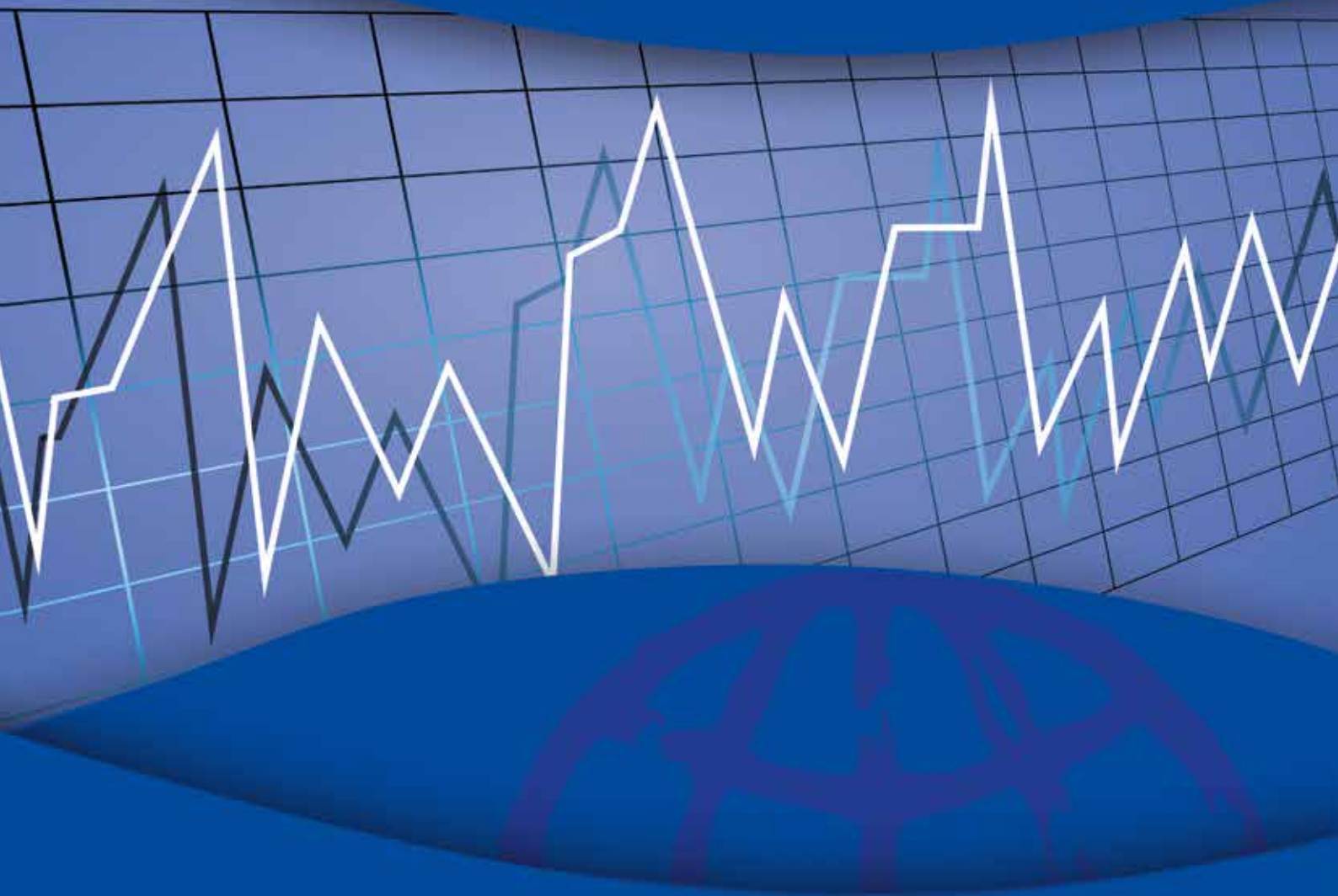


POST-MARKET SURVEILLANCE OF IN VITRO DIAGNOSTICS



POST-MARKET SURVEILLANCE OF IN VITRO DIAGNOSTICS

POST-MARKET SURVEILLANCE OF IN VITRO DIAGNOSTICS

WHO Post-market surveillance of in vitro diagnostics

WHO Library Cataloguing-in-Publication Data

Post-market surveillance of in vitro diagnostics.

1. In Vitro Techniques. 2. Product Surveillance, Postmarketing. 3. Equipment Safety. 4. Equipment Failure. I. World Health Organization.

ISBN 978 92 4 150921 3

(NLM Classification: WA 289)

© World Health Organization 2015

All rights reserved. Publications of the World Health Organization are available on the WHO website (www.who.int) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int).

Requests for permission to reproduce or translate WHO publications –whether for sale or for non-commercial distribution– should be addressed to WHO Press through the WHO website (www.who.int/about/licensing/copyright_form/en/index.html).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Printed in France

Contact:

Irena Prat, Essential Medicines and Health Products - WHO - 20, Avenue Appia - 1211 Geneva 27- Switzerland

This document is available on the internet at: www.who.int/diagnostics_laboratory/en/

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	5
DISCLAIMERS	5
INTRODUCTION	6
1 BACKGROUND	6
2 SCOPE AND INTENDED AUDIENCE OF THIS GUIDANCE	6
3 REFERENCE DOCUMENTS, DEFINITIONS AND ACRONYMS	8
4 BASIC PRINCIPLES	12
5 STAKEHOLDERS' ROLES IN POST-MARKET SURVEILLANCE FOR IVDS	15
PART I: END USERS	17
▶ OVERVIEW OF RESPONSIBILITIES	17
1 IDENTIFY COMPLAINTS	18
2 DOCUMENT COMPLAINTS	19
3 VERIFY COMPLAINTS	20
4 REPORT CONFIRMED COMPLAINTS	21
5 COOPERATE IN LOT VERIFICATION TESTING	22
PART II: MANUFACTURERS	24
▶ OVERVIEW OF RESPONSIBILITIES	24
1 UNDERTAKE ROOT CAUSE ANALYSIS	25
2 CLASSIFY COMPLAINTS	26
3 TAKE CORRECTIVE ACTION	26
PART III: NATIONAL REGULATORY AUTHORITIES	31
▶ OVERVIEW OF RESPONSIBILITIES	31
1 COLLECT COMPLAINT REPORTS, INCLUDING FOR WHO-PREQUALIFIED IVDS	32
2 OVERSEE LOT VERIFICATION TESTING	34
3 COLLECT OTHER POST-MARKET INFORMATION	36
4 TAKE REGULATORY ACTION	36
PART IV: NATIONAL REFERENCE LABORATORIES	37
▶ OVERVIEW OF RESPONSIBILITIES	37
EXAMPLE: PROTOCOL FOR HIV RDT LOT VERIFICATION TESTING (PRE- OR POST-DISTRIBUTION)	38
1 RECEIVE AND STORE SAMPLES OF TEST KITS	38
2 PREPARE AND MAINTAIN LOT VERIFICATION TESTING PANELS	38
3 CONDUCT TESTING AND RECORD DATA	41
4 ANALYSE DATA AND REPORT RESULTS	43
ANNEXES	45
ANNEX 1 – LOT TESTING DATA COLLECTION FORM	45
ANNEX 2 – TESTING REPORT FORMAT FOR LOT VERIFICATION TESTING	46
ANNEX 3 – IVD COMPLAINT REPORTING FORM	55
ANNEX 4 – ADVERSE EVENT MANUFACTURER INVESTIGATION REPORTING FORM	52
ANNEX 5 – FIELD SAFETY CORRECTIVE ACTION REPORT FORM	55
ANNEX 6 – EXAMPLE FIELD SAFETY NOTICE	57
ANNEX 7 – POST-MARKET INFORMATION EXCHANGE REPORTING FORM FOR NRAS	58

LIST OF TABLES

TABLE 1 – STAKEHOLDERS’ ROLES IN POST-MARKET SURVEILLANCE FOR IVDS	15
TABLE 2 – STEPS IN VERIFYING COMPLAINTS	20
TABLE 3 – RATIONALE AND PROCESSES FOR LOT VERIFICATION TESTING	22
TABLE 4 – EXAMPLES OF ADVERSE EVENT CLASSIFICATIONS	25
TABLE 5 – LOT VERIFICATION SPECIMEN PANEL FOR RDTs THAT DETECT ANTIBODIES TO HIV-1/2	39
TABLE 6 – LOT VERIFICATION SPECIMEN PANEL FOR RDTs THAT DETECT ANTIBODIES TO HIV-1/2 AND HIV-1 P24 ANTIGEN	40
TABLE 7 – ACCEPTANCE CRITERIA FOR HIV-1/2 RDTs	44

LIST OF FIGURES

FIGURE 1 – STEPS FOR POST-MARKET SURVEILLANCE OF WHO-PREQUALIFIED IVDS	13
FIGURE 2 – RISK MANAGEMENT PROCESS FOR MEDICAL DEVICES (INCLUDING IVDS)	14
FIGURE 3 – FLOW CHART FOR USERS TO REPORTING COMPLAINTS RELATED TO IVDS	18
FIGURE 4 – FLOW CHART OF REPORTING COMPLAINTS FOR WHO-PREQUALIFIED IVDS	33
FIGURE 5 – DILUTION SENSITIVITY OF TWO SPECIMENS ON ONE HIV-1/2 RDT	40
FIGURE 6 – STANDARD CURVE FOR HIV-1 P24 ANTIGEN IN 4TH GENERATION HIV-1/2 RDTs	41

ACKNOWLEDGEMENTS

The following people were part of the technical working group who met in Geneva on two occasions (June and October 2014) to develop the guidance. This guidance document was written by Anita Sands and Irena Prat, with overall direction by Irena Prat. Monika Zweggarth provided editorial and layout assistance.

The experts who participated in two rounds of consultative meetings (June 2014 and October 2014) and reviewed the draft guidance were: Sue Best, Patience Dabula, Joelle Daviaud, Dianna Edgil, Martine Guillerm, Jan Jacobs, Deidre Healy, Sandra Incardona, Joel Kuritsky, Victor Muchunguzi, Heiner Scheiblauber, Aisseta Tourè, Elsa Tran, Stuart Turner, Vincent Wong, and Bibiana Zambrano.

The draft guidance was then made available for public comment on the WHO website for the period of one month in early 2015.

The WHO staff who participated in the development and review of the guidance were: Helena Ardura, Jane Cunningham, Shona Dalal, Guy-Michel Gershey-Damet, Cheryl Johnson, Robyn Meurant, Irena Prat, Sabine Ohse, Julie Samuelson, Anita Sands and Willy Urassa.

DISCLAIMER

This guidance was developed based on the in vitro diagnostic (IVD) technology in use at the time, and therefore may require certain adaptation as technology formats develop. The illustrative examples used in this guidance are not an exhaustive list.

INTRODUCTION

1. BACKGROUND

Prequalification of IVDs The World Health Organization (WHO) Prequalification of In Vitro Diagnostics Programme is coordinated through the department of Essential Medicines and Health Products. The aim of the WHO Prequalification of In Vitro Diagnostics Programme is to promote and facilitate access to safe, appropriate and affordable in vitro diagnostics (IVDs) of good quality in an equitable manner. Focus is placed on IVDs for priority diseases and their suitability for use in resource-limited settings.

Comprehensive assessment The WHO Prequalification of In Vitro Diagnostics Programme undertakes a comprehensive assessment of IVDs through a standardized procedure aimed at determining if the product meets WHO prequalification requirements. The prequalification assessment process includes three components:

- Review of a product dossier;
- Laboratory evaluation of performance and operational characteristics; and
- Manufacturing site(s) inspection.

Beneficiaries The findings of the WHO Prequalification of In Vitro Diagnostics Programme¹ are used to provide independent technical information on safety, quality and performance of IVDs, principally to other United Nations (UN) agencies but also to WHO Member States and other interested organizations. The WHO prequalification status, in conjunction with other procurement criteria, is used by UN agencies, WHO Member States and other interested organizations to guide their procurement of IVDs.

Post-market surveillance The purpose of post-market surveillance is to protect individual health and public health through continued surveillance of IVDs once they are placed on the market by reducing any risks. Such activities should ensure the manufacturer's obligations are fulfilled through ensuring they are aware of event which enables them to undertake and assessment of any risks, and as appropriate any suggested steps to risk mitigation.

In the context of the WHO Prequalification of In Vitro Diagnostics Programme, this guidance aims to ensure the ongoing compliance of WHO prequalified IVDs with WHO prequalification requirements once they are placed on the market. Manufacturers of WHO prequalified IVDs are obliged to report regularly post-market information to the relevant national regulatory authorities, and to WHO.

2. SCOPE AND INTENDED AUDIENCE OF THIS GUIDANCE

Scope This document pertains to the objectives and processes of the post-market surveillance **for IVDs that are within the scope of the WHO Prequalification of In Vitro Diagnostics Programme, i.e. WHO prequalified IVDs**². It describes the measures that should be taken to ensure the ongoing compliance of WHO-prequalified IVDs with WHO prequalification requirements for safety, quality and performance after they are placed on the market. Therefore, manufacturers, users, and regulators of WHO prequalified IVDs are suggested to follow this guidance.

¹ Prequalification does not imply any approval by WHO of the product and manufacturing site(s). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its safety, quality, or performance.

² As of 2015, the scope of the WHO Prequalification of In Vitro Diagnostics Programme includes HIV rapid diagnostic tests, manual HIV enzyme immunoassays, HIV supplemental assays, CD4 enumeration technologies, HIV nucleic acid tests (qualitative and quantitative), malaria rapid diagnostic tests, hepatitis C rapid diagnostic tests, manual HCV enzyme immunoassays, hepatitis B surface antigen rapid diagnostic tests, and manual hepatitis B surface antigen enzyme immunoassays.

However, in light of the current lack of adequate post-market surveillance in many settings, the **principles of this guidance may also be applied to other IVDs** (either analyte or format) that fall outside the scope of the WHO Prequalification of In Vitro Diagnostics Programme.

This guidance was developed with the underlying assumption that adequate pre-market assessment data is available for the national regulatory authorities to determine if post-market information will discern differences in post-market vs. pre-market safety, quality and performance of IVDs. Therefore, this guidance should not be wholly or partially adopted without access to adequate pre-market assessment data, such as the data generated in WHO Prequalification of In Vitro Diagnostics Programme.

For regulatory purposes, IVDs are considered to be a subset of medical devices. Therefore, certain elements of this guidance are adapted from best practices for regulation of medical devices.

Audience

The intended audience of this guidance is:

- Manufacturers of IVDs;
- End users of IVDs in laboratories and other testing sites;
- Programme implementers and procurers, including procurement agencies and central medical stores; and
- Staff responsible for post-market surveillance within national regulatory authorities and national reference laboratories.

Comprehensive guidance

This document provides an overview of procedures for:

- proactive post-market surveillance through in-country lot verification testing, both pre-distribution and post-distribution of test kits to testing sites; and
- reactive post-market surveillance through reporting and evaluation of complaints, including adverse events, and any required actions to correct and prevent recurrence.

Build on existing systems

This document is intended to supplement, and not substitute the internal procedures for post-market activities which are expected to be an integral part of the manufacturer's quality management system.

National regulations might require manufacturers and/or end users of IVDs to perform post-market activities and submit relevant post-market information to national regulatory authorities. WHO recognises that certain jurisdictions have implemented regulatory requirements for post-market surveillance of IVDs. This guidance does not intend to replace any requirements that might already be in place, and aims to be harmonized with their processes and procedures.

However, the principles laid down in this document should be considered by national regulatory authorities when developing or amending existing national post-market surveillance regulations. It can also be used by procurement agencies and other entities that procure IVDs and wish to be assured of their continued quality, safety and performance.

Guidance for adaptation

This document intends to give an overview of the technical aspects of post-market surveillance for IVDs, in particular for those IVDs that fall within the scope of the WHO Prequalification of IVDs Programme.

Manufacturers of WHO prequalified IVDs are obliged to follow these guidelines as part of their on-going commitment to WHO prequalification.

Other stakeholders are invited to adopt these guidelines in relation to the resources available, *i.e.* a phased implementation may be most appropriate. For instance, stakeholders may choose to begin with pre-distribution lot testing and later add post-distribution lot testing, or to start with complaint reporting and later add lot verification testing.

3. REFERENCE DOCUMENTS, DEFINITIONS AND ACRONYMS

3.1 REFERENCE DOCUMENTS

The following reference documents have been used in preparing this guidance.

POST-MARKET SURVEILLANCE

- ISO 9000:2005 Quality management systems - Fundamentals and vocabulary
- ISO 9001:2008 Quality management systems - Requirements
- ISO 13485:2012 Medical devices - Quality management systems - Requirements for regulatory purposes
- ISO/TR 14969:2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485:2003
- ISO 14971:2007/2007 Medical devices -- Application of risk management to medical devices
- World Health Organization, PQDx_152, *A risk based approach for assessment of in vitro diagnostics (IVDs)*. Accessed 31 October 2014 at http://www.who.int/diagnostics_laboratory/evaluations/140513_risk_based_assessment_approach_buffet.pdf?ua=1

LOT TESTING

- EN 13612:2002 Performance evaluation of in vitro diagnostic medical devices
- BS EN 13975:2003 Sampling procedures for acceptance testing of in vitro diagnostic medical devices- Statistical aspects
- ISO 2859-10:2006 Sampling procedures for inspection by attributes - Part 10: Introduction to the ISO 2859 series of standards for inspection by attributes

VIGILANCE

- GHTF/SG2/N54R8:2006 Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices
- GHTF/SG1/N045:2008 Principles of In Vitro Diagnostic (IVD) Medical Devices Classification
- GHTF/SG1/N046:2008 Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices
- GHTF/SG2/N008R4:1999 Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices
- GHTF/SG2/N57R8:2006 Medical Devices Post Market Surveillance: Content of Field Safety Notices
- GHTF/SG3/N15R8:2005 Implementation of risk management principles and activities within a Quality Management System
- MEDDEV 2.12-1 rev. 8 Vigilance, European Commission guidelines on a medical devices vigilance system

3.2 DEFINITIONS

Abnormal use	Act or omission of an act by the operator or user of a medical device as a result of conduct that is beyond any reasonable means of risk control by the manufacturer. ³
Adverse event (incident)	Defined as a product defect (<i>i.e.</i> malfunction or failure, deterioration in characteristics or performance, or inadequacy of labelling or of instructions for use) that, directly or indirectly, might lead to or might have led to serious medical consequences, namely death or serious deterioration in the state of health of the patient, user or another person. Also called an incident. ⁴
Analytical sensitivity	Analytical sensitivity measures a test's ability to detect a low concentration of a given substance. Sometimes used interchangeably as limit of detection ⁵ or detection limit. ⁶
Accuracy	The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. ⁷

³ IEC 60601-1-6:2004 Medical electrical equipment. General requirements for safety - Collateral standard: Usability.

⁴ GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

⁵ CLSI, EP17-A, 24, 34, Oct 2004. Protocols for Determination of Limits of Detection and Limits of Quantitation.

⁶ ICH guideline Q2(R1), Nov 2005. Validation of Analytical Procedures: Text and Methodology.

⁷ CLSI, EP17-A, 24, 34, Oct 2004. Protocols for Determination of Limits of Detection and Limits of Quantitation.

Become aware	Manufacturers are considered to have “become aware” of a reportable event when: (1) any employee becomes aware of a reportable event or (2) any employee who is a person with management or supervisory responsibilities over persons with regulatory, scientific or technical responsibilities, or a person whose duties relate to the collection and reporting of adverse events, becomes aware that a reportable event, from any source, including any trend analysis, necessitates remedial action to prevent an unreasonable risk of substantial harm to public health. ⁸
Clinical sensitivity	The number of true positive specimens identified by a given assay as positive divided by the number of specimens identified by the reference assays as positive, expressed as a percentage. ⁹
Clinical specificity	The number of true negative specimens identified by a given assay as negative, divided by the number of specimens identified by the reference assays as negative, expressed as a percentage. ¹⁰
Conformity	Fulfillment of a requirement. ¹¹
Conformity assessment	The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the national regulatory authority (NRA), to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles of Safety and Performance of Medical Devices. ¹²
Component	Any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device. ¹³
Complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. ¹⁴ Complaints may be administrative (<i>i.e.</i> contractual) in nature or technical.
Correction	Action to eliminate a detected nonconformity. ¹⁵
Corrective action	Action to eliminate the cause of a detected nonconformity or other undesirable situation and to prevent recurrence. ¹⁶
External quality assessment	Monitoring of performance through either direct observation and supervision or inter-laboratory comparisons made possible by participation in an external quality assessment scheme (sometimes known as proficiency testing). ¹⁷
Field safety corrective action (FSCA)	Action taken by the manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. ¹⁸
Field safety notice (FSN)	A communication sent out by the manufacturer or its representative to the device users in relation to a field safety corrective action. ¹⁹

8 US Food and Drugs Administration, CFR - Code of Federal Regulations Title 21, 21CFR803.3

9 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

10 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

11 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

12 Essential Principles of Safety and Performance of Medical Devices are described in the GHTF/SG1/N41R9:2005 document.

13 US Food and Drugs Administration CFR – Code of Federal Regulations Title 21, 21CFR820.3

14 US Food and Drugs Administration CFR – Code of Federal Regulations Title 21, 21CFR820.3

15 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

16 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

17 WHO Laboratory Quality Management Systems Handbook, accessed 25 March 2014 at http://whqlibdoc.who.int/publications/2011/9789241548274_eng.pdf?ua=1

18 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

19 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

Harm	Physical injury or damage to the health of people or damage to property or the environment. ²⁰
Hazard	Potential source of harm. ²¹
In vitro diagnostic (IVD)	A 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. This includes reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles. ²²
Lot	Defined amount of material, either starting material, intermediate or finished product which is uniform in its properties and has been produced in one process or series of processes. ²³
Manufacturer²⁴	The natural or legal person responsible for design, production, assignment of intended purpose, packaging and labeling of the diagnostic product - whether these tasks are performed by that person or on their behalf - and who represent themselves as the manufacturer on the diagnostic product labeling.
National Reference Laboratory (NRL)	A testing laboratory which - in agreement with a specified laboratory community or through appointment by a competent organization - provides reference values ²⁵ in a specific technical field, <i>i.e.</i> property values of materials or products to which test results can be related or traced back and whose quality is fit for the purpose. ²⁶
National Regulatory Authority (NRA)	A government body or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and that may take enforcement actions to ensure that medical products marketed within its jurisdiction comply with legal requirements. ²⁷
Nonconformity	Non-fulfillment of a requirement. ²⁸
Preventive action	Action to eliminate the cause of a potential nonconformity or other undesirable situation and to prevent occurrence. ²⁹
Requirement	Need or expectation that is stated, generally implied or obligatory. ³⁰
Risk	Combination of the probability of occurrence of a harm and the severity of that harm. ³¹
Sample	One or more units of product, either components or finished devices, drawn from a lot without regard to the quality of the units. ³²
Sample size	Number of units of product in the sample.
Surveillance	Continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. ³³

20 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

21 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

22 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

23 EN 13975:2003 Sampling procedures used for acceptance testing of in vitro diagnostic medical devices – statistical aspects.

24 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2). WHO has adopted this internationally accepted approach of defining a manufacturer to ensure that there is a clear understanding of the term "manufacturer" for this product across international markets.

25 A reference values is a property value of a specified material or product that has been determined with an accuracy fit for use as a source of traceability of test results obtained on comparable materials or products.

26 EUROLAB Position paper No. 1/2007, March 2007 on reference laboratories in the field of testing

27 GHTF, Principles of Conformity Assessment for Medical Devices GHTF/SG1/N78:2012

28 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

29 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

30 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

31 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

32 British Standard, Sampling procedures used for acceptance testing of in vitro diagnostic medical devices – statistical aspects, BS EN 13975:2003.

33 Adapted from the WHO website. Accessed on 19 November 2014 http://www.who.int/topics/public_health_surveillance/en/

Test kit	Commercially prepared reagent sets, with accessory devices, containing all of the major components and literature necessary to perform one or more designated diagnostic tests or procedures.
Testing algorithm	A testing algorithm describes the combination and sequence of specific HIV assays used within a given HIV testing strategy. ³⁴
Testing strategy	Generic description of a testing approach for a specific need (for example, blood transfusion and transplantation safety, HIV surveillance, and/or diagnosis of HIV infection in both client-initiated and provider-initiated testing and counselling), taking into consideration the presumed HIV prevalence in the population being tested. ³⁵
Trend reporting	A reporting type used by the manufacturer when a significant increase in the events not normally considered to be incidents occurred and for which pre-defined trigger levels are used to determine the threshold for reporting. ³⁶
Unanticipated	A death or serious injury is considered unanticipated if the condition leading to the event was not considered in a risk analysis performed during the design and development phase of the device. There must be documented evidence in the design file that such analysis was used to reduce the risk to an acceptable level. ³⁷
Use error	An act, or omission of an act, that has a different result to that intended by the manufacturer or expected by the operator. ³⁸
Verification	Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled. ³⁹
Vigilance	One of the post-market activities undertaken by the manufacturer to protect the health and safety of patients, which relates to monitoring of adverse events (according to the definition of an adverse event given above), investigation of adverse events to determine root causes and the consequent corrective and preventive action. ⁴⁰

3.3 ACRONYMS

ART	Antiretroviral therapy
CAPA	Corrective and preventive action
EIA	Enzyme immunoassay
EQA	External quality assessment
FSCA	Field safety corrective action
FSN	Field safety notice
GHTF	Global Harmonization Task Force (now known as IMDRF)
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
IVD	In vitro diagnostic
NRA	National Regulatory Authority
NRL	National Reference Laboratory
PMS	Post-market surveillance
RDT	Rapid diagnostic test
WHO	World Health Organization

34 WHO Service delivery approaches to HIV testing and counselling (HTC): a strategic framework, accessed 25 March 2014 http://www.who.int/hiv/pub/vct/htc_framework/en/

35 WHO Service delivery approaches to HIV testing and counselling (HTC): a strategic framework, accessed 25 March 2014 http://www.who.int/hiv/pub/vct/htc_framework/en/

36 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

37 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

38 Definition taken from AAMI HE 74:2001² and IEC/CD2 60601-1-6:2002

39 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

40 GHTF, Glossary and Definitions of Terms Used in GHTF Documents, GHTF/SC/N4:2012 (Edition 2)

4. BASIC PRINCIPLES

4.1 RATIONALE FOR POST-MARKET SURVEILLANCE

Many countries lack effective IVD regulation	The lack of regulatory oversight of IVDs in many countries, both for pre-market assessment and post-market activities, has widely been acknowledged as a shortcoming for assuring the safety, quality and performance of IVDs. The type of IVDs that are most appropriate and well adapted for use in resource-limited settings are often used in jurisdictions without existing comprehensive regulatory control; thus they may escape any stringent pre-market and post-market regulatory oversight.
Pre-market assessment as a basis	A degree of pre-market assessment of IVDs is recommended for any product prior to entry into the marketplace in each country of intended use. While pre-market assessment of IVDs can provide information on a product's safety, quality and performance, there might be questions that cannot be answered in the pre-market stage or issue that may arise after the product is marketed.
Post-market surveillance to protect public health	The safety, quality and performance of IVDs should be further verified upon delivery and before distribution to laboratories and other testing sites. Post-market information on IVDs empowers NRAs and WHO to detect, investigate, communicate and contain events that threaten public health security and to take appropriate action.

4.2 POST MARKET SURVEILLANCE MECHANISMS

Post-market surveillance can be divided into reactive and proactive measures,

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

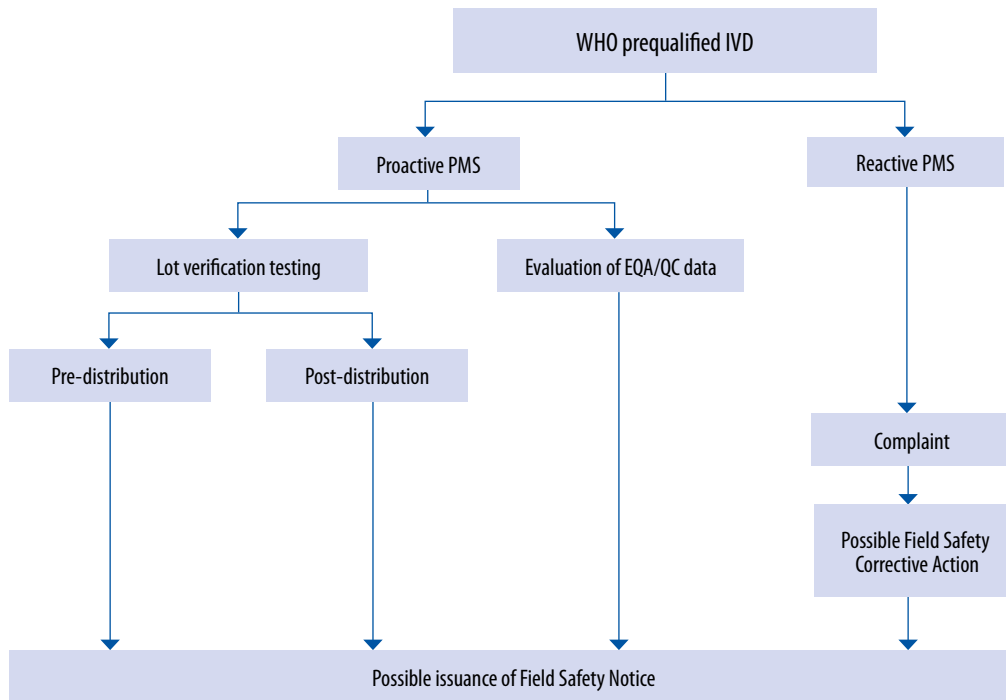
Proactive PMS Additional information on quality, safety or performance may also be collected proactively through **lot verification testing**. This relates to proactively trying to identify a problem before it affects a clinical decision. Lot verification testing is conducted after shipment to the buyer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

Manufacturers should also collect post-market surveillance through actively gathering evidence from the literature on their product or similar products, through seeking feedback from customers, and post-market clinical follow up. This is a critical aspect that will not be widely covered in this guidance as has been published elsewhere.⁴¹

⁴¹ GHTF, Post-Market Clinical Follow-Up Studies, GHTF/SG5/N4:2010

Figure 1 illustrates the post-market surveillance processes for WHO-prequalified IVDs as an example, excludes the manufacturers own responsibilities for post-market surveillance.

Figure 1 – Steps for post-market surveillance of WHO-prequalified IVDs



Other data

Data on the quality, safety and performance of IVDs in the post-market phase may also come from on-going external quality assessment schemes (EQAS), also known as proficiency testing. These programmes collect testing results from testing sites that receive the same blinded specimens to test. Lot numbers used to test these specimens should be recorded to make these useful data sets. In resource-limited settings, national reference laboratories usually coordinate this data collection and should provide feedback to WHO.

Quality control (QC) programmes with comparable data sets on particular test kits may also yield important post-market information.

4.3 RISK MANAGEMENT

Risk management is a guiding principle in most aspects of health product manufacture and regulation. Risk management principles have been considered in developing this guidance.

Risks of IVD use depend on the setting

The risk associated with use of an IVD depends among other factors on the intended setting. In high-resource settings, clinical testing typically takes place in accredited laboratories by certified and proficient users using products that have undergone established pre-market assessment for their appropriateness to be used in that intended setting.

However, in many countries, HIV and malaria testing for diagnosis using RDTs is performed outside of the traditional laboratory setting and often by unsupported users with minimal training. In addition, the risk that an incorrect test result will lead to serious consequences (death or serious deterioration in health) for an individual or the population is greater in settings with higher disease prevalence and lower access to diagnosis, care and treatment services.

What is meant by “risk”?

Indeed “*risk management is a complex subject because each stakeholder places a different value on the probability of harm occurring and its severity. It is accepted that the concept of risk has two components: a) the probability of occurrence of harm; b) the consequences of that harm, that is, how severe it might be.*”⁴²

The acceptability of a risk to an individual varies depending upon their cultural and economic background, and many other factors.

How stakeholders manage risks

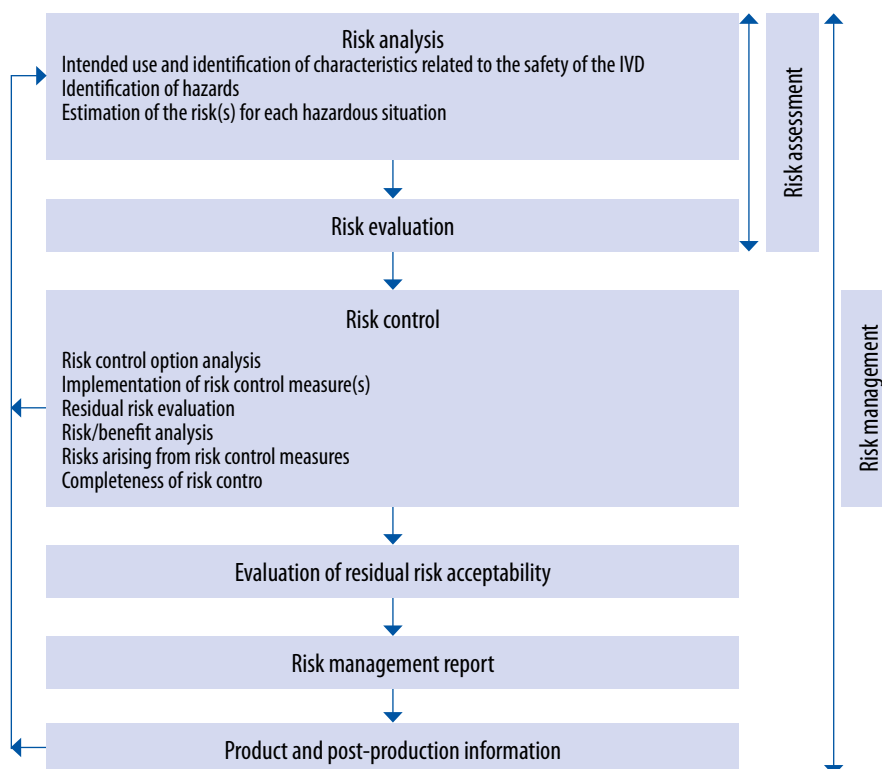
Risk management applies to all stakeholders, including manufacturers, national authorities (regulators and reference laboratories) and end users as well as procurers and implementing partners.

Each manufacturer is obliged to have undertaken risk management and risk assessment with respect to their IVD before placing it on the market, implementing the most stringent controls to those aspects of design, and manufacturing and control steps where the risk is greatest. When a complaint is received, the manufacturer should review and update the risk management file for the IVD accordingly.

Manufacturers, regulators and procurers will use the information that comes from complaints and any other information and experience with a given IVD to determine the scope and stringency of post-market actions in the future. For example, continued acceptable results in pre-distribution lot verification testing may lead to a change from systematic sampling of each lot towards random sampling of lots.

Figure 2 describes the process of risk management specifically for medical devices, and therefore, IVDs.

Figure 2 – Risk management process for medical devices (including IVDs)



*Adapted from ISO 14971 Medical devices -- Application of risk management to medical devices

42. Quoted from ISO 14971 Medical devices -- Application of risk management to medical devices, p.V

5. STAKEHOLDERS' ROLES IN POST-MARKET SURVEILLANCE FOR IVDs

The decision to implement post-market surveillance should involve all relevant stakeholders. End users (as well as procurers and implementers), manufacturers, national authorities (regulators and reference laboratories) and WHO should be involved in the decision to expand national regulatory function to post-market surveillance of IVDs. **Table 1** gives an summary of the roles of different stakeholders in post-market surveillance of IVDs, as described in Parts I-IV of this document.

Each country should be responsible for establishing and strengthening systems for post-market surveillance, with the necessary procedures in place to guide processes, and to define roles and responsibilities as these may differ from country to country depending on the existing regulatory arrangements.

Table 1 –Stakeholders’ roles in post-market surveillance for IVDs

Stakeholder	Activity	Details
I End users, procurers/ implementers (see <i>Part I</i> of this document)	<ol style="list-style-type: none"> 1. Identify problems 2. Document problems 3. Report complaints 4. Cooperate in lot verification testing 	<ul style="list-style-type: none"> • End users should document any problems, and report complaints (including adverse events) to the manufacturer, the relevant NRA and to WHO. • Trained and qualified personnel from testing sites (or laboratories) are responsible for sampling of test kits for post-distribution lot verification testing conducted under the oversight of NRAs. • Procurers (specialized procurement agencies or implementing agencies) should contribute to these activities on behalf of end users and in accordance with quality assurance policies that govern their procurement and distribution of IVDs.
II Manufacturers (see <i>Part II</i> of this document)	<ol style="list-style-type: none"> 1. Classify complaints 2. Undertake root cause analysis 3. Take corrective action 	<ul style="list-style-type: none"> • Manufacturers should implement an effective post-market surveillance system with both active and passive collection of post-market information, including complaints. • Manufacturers must establish a documented procedure for a feedback system to provide early warning of quality problems and for input into corrective action/preventive action processes (as required by the ISO 13485:2003 standard).
III National regulatory authorities (NRAs) (see <i>Part III</i> of this document)	<ol style="list-style-type: none"> 1. Collect reports of complaints 2. Oversee lot verification testing 3. Collect other post-market information 4. Take regulatory action 	<ul style="list-style-type: none"> • NRAs should conduct pre-market assessment and active rather than passive post-market surveillance for products on sale within their market. • Regulatory controls should be phased in depending on available regulatory capacity and resources, and using a risk-based approach.
IV National reference laboratories (NRLs) or other designated testing laboratories (see <i>Part IV</i> of this document)	<ol style="list-style-type: none"> 1. Receive and store samples of test kits from central medical stores and from end users 2. Prepare and maintain lot verification testing panels 3. Conduct testing and record data 4. Analyze data and report results to NRAs 	<ul style="list-style-type: none"> • Reference testing laboratories should conduct lot verification testing on behalf of NRAs. • An example of a lot verification testing protocol for HIV RDTs is included in <i>Part IV</i> this document.
V WHO Prequalification of IVDs Programme	Provide support for post-market surveillance of IVDs	<ul style="list-style-type: none"> • WHO assures that WHO-prequalified IVDs continue to uphold their safety, quality and performance, and ensures traceability of WHO-prequalified IVDs. It provides support to manufacturers, NRAs/NRLs, and end users facing problems with WHO-prequalified IVDs. • The WHO Prequalification of In Vitro Diagnostics Programme reserves the right to conduct follow-up inspections to ensure that corrective action have been implemented where necessary following a complaint, and to inform stakeholders.

THE ROLE OF WHO

Support for prequalified IVDs

The WHO Prequalification of In Vitro Diagnostics Programme in the department of Essential Medicines and Health Products provides technical support to national authorities (regulators and reference laboratories) manufacturers and end users (including procurers and implementing partners) facing problems with WHO-prequalified IVDs and other related IVDs in the post-market phase.

Centralized PMS data

A centralized collection of post-market data on WHO-prequalified IVDs, including results from lot verification testing, and complaint collection/evaluation ensures traceability of information on WHO prequalified IVDs and enables coordinated action in WHO Member States. These post-market data are submitted to WHO in the form of lot testing reports and IVD complaint forms as defined in **Annexes 2 and 3**. Certain adverse event reports are notified through vigilance information exchange to other NRAs and procurers/implementing partners such as non-governmental organizations.

WHO action for prequalified IVDs

Its network of post-market data sourcing and management enables WHO to take action with regard to WHO-prequalified IVDs as appropriate. These might include:

- Post market surveillance information exchange with NRAs;
- Post market surveillance information exchange with manufacturers;
- Publishing certain post market surveillance information on WHO's website;
- Removal of the product from the list of WHO-prequalified IVDs, if needed;
- Inspection of manufacturing site to ensure that corrective and preventive actions (CAPA) as a result of any complaint have been implemented.

PART I: END USERS

► OVERVIEW OF RESPONSIBILITIES

End User The end user may be “*the operator (meaning the individual performing the IVD; this individual can be a laboratory worker, a healthcare provider or a lay person with minimal training;)* or the healthcare provider (meaning the individual ordering, receiving or acting upon the examination results on behalf of a patient; this individual can be a physician, nurse, ambulance attendant or any other person) making a medical decision based upon IVD examination results”⁴³

Crucial role End user feedback on the IVD’s performance in the field is of crucial importance for post-market surveillance. It is through end users reporting on problems experienced with the use of IVDs that manufacturers capture an essential part of the product’s post-market data.

This section describes the responsibilities of end users, and the post-market surveillance activities that they should undertake – in cooperation with international procurers or programme implementers –for post-market surveillance of IVDs.

APPROPRIATE USE OF IVDs

End users should handle and use IVDs according to manufacturer’s instructions for use to maintain their quality, safety and performance.

Quality management system The principles for quality systems in medical laboratories are laid down in ISO 15189 *Medical laboratories — Particular requirements for quality and competence* and include: organization, personnel, equipment, purchasing and inventory, process control (quality control), information management, documents and records (standard operating procedures, standardized worksheets, reports), occurrence management, assessment (external quality assessment schemes and supervision), process improvement, customer service, and facilities and safety.

Storage Users must ensure proper storage of the test kits according to the manufacturers’ instructions for use (either at climate-controlled room temperature or in a refrigerator), and should monitor the temperature of the storage facility.

COMPLAINT REPORTING

The end users should notify the manufacturer of all complaints related to the use of their product. Furthermore, the relevant NRA and WHO should be notified of any serious, moderate or change in the trend of mild adverse event related to an IVD. These classifications will be described later in this guidance. In any case where the manufacturer is not aware of a complaint, WHO or the relevant NRA should ensure they are informed. Complaint reporting is a reactive post-market surveillance measure. It covers activities undertaken **after** any party becomes aware of adverse events, malfunctions, results of testing or other relevant information about an IVD placed on the market. It is based on a cooperative and effective exchange of information between all the parties.

Verify complaints In case of perceived complaints, the end user (in conjunction with appropriate technical expertise) should document the complaint fully by determining all aspects (lot number, expiry date, storage temperatures, etc.) and possible causes such as product quality, safety or performance, use error and abnormal use.

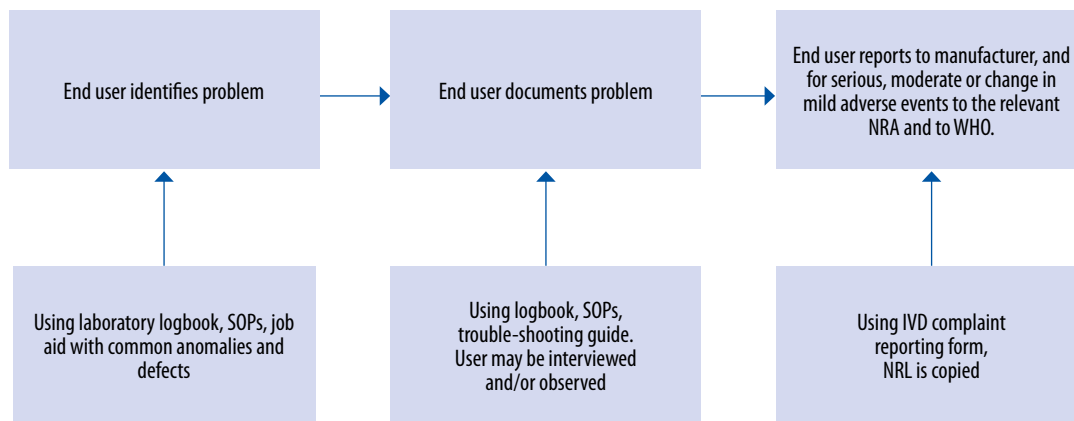
LOT VERIFICATION TESTING

The NRA (sometimes procurers and implementing partners), in conjunction with end users, should make arrangements for lot verification testing to ascertain proactively that IVDs continue to conform to their specifications, and have not been adversely affected by inappropriate storage and transport conditions.

⁴³ Taken from ISO14971 Medical devices — Application of risk management to medical devices

Figure 3 gives an overview of the steps involved in identifying and addressing user-reported problems

Figure 3—Flow chart for end users to report complaints related to IVDs



1. IDENTIFY COMPLAINTS

Types of complaints

Complaints may include:

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

See later in this part (section 4) for reporting timelines.

Adverse events (incidents)

Some technical complaints may lead to an **adverse event**. Adverse events (also called **incidents**) are consequences of problems with IVDs that may lead to death or serious deterioration in health of a patient, user or other person. As an IVD is not directly used on an individual, the harm is indirect *“a result of an action taken or not taken on the basis of an incorrect result obtained with an IVD”*.⁴⁴ Notification and evaluation of adverse events is also known as **vigilance**.

What should be reported?

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

1. When an incident **leads to death of a patient, user or other person**.
2. When an incident **leads to serious deterioration in health of a patient, user or other person** (also known as serious injury).
3. No death or serious deterioration in health occurs but the **event might lead to death or serious deterioration in health**.
4. When an incident might happen as a consequence of **a medical decision or action taken or not taken on the basis of results** given by the IVD, typically:
 - Misdiagnosis;
 - Delayed diagnosis;
 - Delayed treatment;

⁴⁴ Quoted from Guidelines on a medical devices vigilance system, MEDDEV 2.12-1 rev. 8 Vigilance Accessed 18 March 2015 http://ec.europa.eu/growth/sectors/medical-devices/documents/guidelines/files/meddev/2_12_1_1_en.pdf

- Inappropriate treatment;
 - Transfusion of inappropriate (contaminated) materials including blood products, tissues or organs.
5. **Use errors**⁴⁵ that did result in death or serious deterioration in health or that have a negative trend with the potential for death or serious deterioration in state of health or public threat.

Adverse events may come as a result of the below:

- A malfunction or deterioration in the characteristics or performance;
- An incorrect or out-of-specification test result (e.g. a false positive or a false negative test result that results in incorrect status given to individual);
- An inaccuracy in the labelling, instructions for use and/or promotional materials;
- Discovery of a serious public health threat;
- Use error;
- Any other information that becomes available.

Identifying incorrect test results

For IVDs used in a one-assay testing strategy (e.g. malaria IVDs), it may be easier to determine false positive and false negative rates.

For IVDs used in a multi-assay testing strategies (i.e. HIV IVDs), it may be difficult to attribute misdiagnosis of the HIV status to one assay over another. False results might be caused by cross-reactivity between test kits, which is not a product defect. Information on the testing algorithm must be captured to understand the specificity and/or sensitivity attributes of a given test kit. This is particularly important for a test kit that may be used interchangeably as a first line assay in one country but as a second or third line assay in another country.

Impact of incorrect test results

False positive HIV results may be less likely have an impact on people's health and survival than false negative HIV results. However, the psychological impact of a false positive HIV test result can be enormous. Commencing an individual on treatment when they are not indeed positive for an infection may increase the risk of drug toxicity, resistance, and in any case administering medication and perhaps ordering additional testing is a waste of resources (both financial and otherwise).

False positive malaria results may cause the operator to assume malaria as the cause of clinical signs and symptoms and mask another cause of febrile illness that may be life-threatening. False negative malaria results will likely lead to withholding a prescription of anti-malarial drugs and hence may have a life-threatening consequence.

Inadequate manufacturer instructions

In the case of potential errors by users, labelling and instructions for use should be carefully reviewed for any possible inadequacy. Inadequacies in the information supplied by the manufacturer that led or could have led to harm to users, patients or third parties should be reported by the manufacturer to WHO and/or the NRA.

2. DOCUMENT COMPLAINTS

Users should document any problems with IVDs using information taken from the testing/laboratory logbook and inventory records including affected product code(s), affected lot number(s), and expiry date(s), affected consignments or test kits, affected users, and any measures taken.

Photographs of affected test devices and/or test kits should be taken to illustrate the problem.

Users should keep and appropriately store at least 1-2 affected test kits (up to 60 tests) as retention kits for later testing, if required.

⁴⁵ Act, or omission of an act, that has a different result to that intended by the manufacturer or expected by the operator. See page 21 for details.

3. VERIFY COMPLAINTS

Documenting and verifying possible complaints will be conducted by the end user, in association with their site supervisor. Users should conduct a preliminary investigation to identify complaints that are related purely to **user error or abnormal use**, not to the IVD itself. These errors may be corrected at testing site, without need for additional intervention from the manufacturer.

It may be difficult to determine if an adverse event was the consequence of a problem with the IVD itself, or of an error by the user or third party. There should be a predisposition to report events to the manufacturer and also to WHO and to the relevant NRA if suspected to be a serious or moderate adverse event.

A preliminary investigation and documentation step will also generate more detailed information on the circumstances related to the complaint and enable the manufacturer to conduct a more in depth investigation of their own.

Approaches to identify, document and verify complaints are summarized in **Table 2**.

Table 2 –Steps for users to document and verify complaints

What	How	How it will help in verification
User identifies problem	<p>Accurate record-keeping, preferably using standardized testing/laboratory logbooks, to identify errors.</p> <p>Create a site-specific trouble-shooting guide that includes commonly observed anomalies (see below) and defects for the specific types of IVDs used at the site.</p> <p>Analyze EQAS and QC data.</p>	<p>To understand if the error can be attributed to a particular operator, a particular lot number, a particular testing site, etc.</p> <p>To guide users on what should be raised as a complaint.</p> <p>To reveal quality or performance issues related to specific IVDs.</p>
User documents problem	<p>Using testing/laboratory logbook and inventory records, document the problem, e.g. affected product code(s), affected lot number(s), and expiry date(s), affected consignments or kits, affected users, any measures taken, etc.</p> <p>Keep and appropriately store at least 1-2 affected test kits (up to 60 tests) as retention kits for later testing.</p>	<p>To ascertain which lots and/or consignments are affected, and the scope of the event.</p> <p>To trace the history of the issue and subsequent actions.</p> <p>To confirm kit-related errors.</p>
User investigates problem	<p>Test other lots, other consignments or kits.</p> <p>Repeat testing using concise but exact standard operating procedure as per manufacturers' instructions for use.</p> <p>Interview or observe operators in the affected facilities (see below for details).</p>	<p>To ascertain which lots and/or consignments are affected, and the scope of the event.</p> <p>To identify operator error due to noncompliance with instructions.</p> <p>To identify any human factors e.g. reading time used (minimum and maximum), specimen transfer device (pipette), specimen type, invalid rate (instrument failures and unable to return results error reports), etc.</p>

How to identify anomalies

Each testing site should create a job aid of common anomalies and defects to watch for which will depend on the IVD format. For example, the following list might be used for anomalies related to RDTs:

- dry alcohol swabs;
- very soft or very stiff specimen transfer devices that let out too much or too little liquid;
- graduation marks on specimen transfer devices that are printed in a way that may be erased easily;
- insufficient buffer to complete all tests within a test kit;
- excessively high background or streaking that obscures the reading window;
- misplaced test strip that means test and control lines are not lined up with the reading legend;
- visually obvious problems with specimen migration, etc.

Photographs of commonly occurring anomalies could be created for each of the IVDs in use for easier visual identification of defective IVDs.

Observation and interview

In order to more fully document any perceived complaint, the user may be observed by another user or site supervisor conducting a test for the IVD under question. This may be performed using specimens of known status, firstly with seronegative specimens, and later with seropositive specimens. This should only be undertaken within the bounds of ethical methods, with blinded testing and no linkage to patient details and results.

Use errors and abnormal use errors

Use error

A use error is an act, or omission of an act, that has a different result to that intended by the manufacturer or expected by the operator. This might include lapses or mistakes and reasonably foreseeable misuse. Examples include:

- Operator presses the wrong button;
- Operator misinterprets the icon and selects the wrong function;
- Operator disregards incubation or reading time;
- Unintentional use of pipette out of calibration range; and
- Analyzer placed in direct sunlight causing higher reaction temperature than specified.⁴⁶

Abnormal use error

An abnormal use error is an act, or omission of an act, by the operator or user of a medical device as a result of conduct that is beyond any reasonable means of risk control by the manufacturer. Examples include:

- Use of an recently installed IVD prior to completing all initial performance checks as specified by the manufacturer;
- Failure to conduct IVD's quality control checks prior to each use as defined by the manufacturer;
- Continued use of an IVD beyond the manufacturer defined planned maintenance interval as a result of operator's or user's failure to arrange for maintenance; and
- Product analysis showed that the IVD was working in accordance to specifications; but further investigation revealed that the operator was inadequately trained due to failure to obtain proper training.⁴⁷

Abnormal use related to WHO prequalified IVDs **does not need to be reported to WHO** under complaint reporting procedures. However, it may be useful for users to report abnormal use to manufacturers, and particularly, if the issue relates to unclear instructions for use.

If manufacturers become aware of instances of abnormal use, they may bring this to the attention of other appropriate organizations and healthcare facility personnel.

4. REPORT VERIFIED COMPLAINTS

Immediate reporting

All verified complaints should be reported by the end user to the manufacturer **as soon as possible** using the format in **Annex 3**.

In addition, any complaints that are classified as serious, moderate or a change in trend of mild adverse events should be reported to the relevant NRA, and WHO **as soon as possible** using the format in **Annex 3**.

⁴⁶ This list does not purport to be definitive and each case should be handled individually.

⁴⁷ This list does not purport to be definitive and each case should be handled individually.

5. COOPERATE IN LOT VERIFICATION TESTING

5.1 BASIC PRINCIPLES

The objective of lot verification testing is to verify that each lot supplied continues to meet its safety, quality and performance requirements, and that transport and/or storage conditions have been well controlled so as not to affect the performance of the IVD.

Lot verification testing should be organized under the oversight of the NRA, or of the procurement agency in accordance with their quality assurance policies. The testing should be done by a suitably qualified reference laboratory.

More details are given in **Part III**.

5.2 ORGANIZATION OF LOT TESTING

Table 3 gives an overview of the processes of pre- and post-distribution lot verification testing.

Table 3 – Rationale and processes for lot verification testing

	Pre-distribution	Post-distribution
Why	To verify that: <ul style="list-style-type: none"> • Safety, quality and performance requirements are met when the IVD is in use • Transport and/or storage conditions have not affected performance of the IVD • Stability (shelf life) claims made by the manufacturer are met. 	To verify that: <ul style="list-style-type: none"> • Safety, quality and performance requirements are met when the IVD is in use • Transport and/or storage conditions have not affected performance of the IVD • Stability (shelf life) claims made by the manufacturer are met.
When	On receipt, before distribution to testing sites/laboratories	Twice per year, after distribution to the testing sites/laboratories
Where sampled from?	Sampled from central medical stores or similar centralized warehouse. For laboratories/testing sites with direct procurement (i.e. no centralized storage), samples should be taken at those sites.	A sample of test kits from the same lot should be taken in laboratories/testing sites at different levels of the health system as follows: <ul style="list-style-type: none"> • A sample from 1 testing site in the community • A sample from 1 testing site/laboratory at primary care level • A sample from 1 laboratory at district level • A sample from 1 laboratory at regional/provincial level Different geographical areas should be covered, i.e. if test kits from a primary care laboratory from a geographical area has been sampled, the next sampling should not involve a primary care laboratory from the same geographical area
Who does sampling?	Appropriately trained and qualified personnel of central medical stores (or laboratory in case of direct procurement), or an agency independent of the manufacturer, agent or distributor.	Appropriately trained and qualified personnel of the testing site, or an agency independent of the manufacturer, agent or distributor.
Sampling frame	Each lot should be sampled initially. The sampling frame may be changed to random sampling after a period of consistently acceptable results.	Random sampling according to a sampling plan
How many tests per lot to sample?	A representative sample of tests per lot should be taken. The number of tests will depend on the protocol chosen. The cost of sampling and testing should be borne by the programme.	A representative sample of tests per lot should be taken. The number of tests will depend on the protocol chosen. The cost of sampling should be borne by the programme.
Adjusting order quantities	Sufficient additional quantities of IVDs should be ordered to enable collection of post-market surveillance data.	Sufficient additional quantities of IVDs should be ordered to enable collection of post-market surveillance data. Test kits sampled at testing sites for post-distribution testing should be replaced by the programme.

Good sampling practices	Sampling should be done without bias and free from obstruction. Samples should be taken by appropriately trained and qualified personnel.
Physical inspection	<p>During sampling the test kits should be inspected for damage or deterioration. Test kits with torn, ripped, broken outer or inner packaging, test pouches not sealed properly, desiccant not included, etc., should be documented, and excluded from testing.</p> <p>Other quality issues such as poorly affixed or illegible labelling should be documented as well as lack of components (accessories, instructions for use).</p> <p>Photographs of all components and labelling should be taken for each lot tested as a record.</p>
Transport to testing laboratory	Samples of test kits should be transported to the reference laboratory without delay, through the usually utilized means of transport of test kits within the country. A temperature monitoring device may be used.
Receive results	The testing laboratory will report the results within five days to WHO and the relevant NRA or other national authority delegated to evaluate post-market information on IVDs. (See lot testing report in Annex 2).
Outcomes	If the lot testing report confirms that the acceptance criteria are met, the lot can be distributed or continue to be used. After a period of consistently acceptable results, the sampling frequency for further lot testing may be reduced. WHO and the NRA should monitor the results of lot testing for any trends or shifts.
Handling non-conforming results	<p>If the report states that the criteria fail to be met, WHO should be informed and a joint decision with national authorities about next steps should be made. The use of the lot in question should be ceased, and the lot put into quarantine until the matter is resolved.</p> <p>For any nonconforming lot, WHO and NRA will ensure that the manufacturer undertakes a root cause analysis and conducts field safety corrective action, if required (see Part II for details).</p>

NB: The replacement of the purchased test kits is **not recommended until the root cause analysis is complete and the proposed corrective action has been verified by WHO and relevant NRA**. The sampling frequency for further lot testing may be increased.

PART II: MANUFACTURERS

This part describes the manufacturer's post-market surveillance obligations, and gives details on root cause analysis of reported adverse events and field safety corrective action to address them.

► OVERVIEW OF RESPONSIBILITIES

Knowledge of relevant standards Manufacturers of IVDs should be familiar with standards including ISO 9001:2008 *Quality management systems - Requirements*, ISO 13485:2003 *Medical devices - Quality management systems - Requirements for regulatory purposes* and ISO 14971:2007 *Medical devices - Application of risk management*, which outline their requirements for compliance with post-market surveillance aspects of these standards.

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

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

Responsible person To ensure an efficient post-market surveillance system, **manufacturers of prequalified IVDs should appoint a responsible person for post-market surveillance**⁴⁸ who shall collect and evaluate post-market surveillance information and coordinate all measures related to adverse events. This person should be in charge of post-market surveillance information exchange with end users, NRAs and WHO.

Complaint handling and vigilance All types of reports related to complaints (including adverse events) should be maintained by the manufacturer including: initial/follow-up/final manufacturer investigation reports, root cause analysis reports, corrective action/prevention action plans, any Field Safety Corrective Action and Field Safety Notices, and annual post-market surveillance summary reports. Vigilance information exchange with NRAs should be managed according to national regulations.

Field safety corrective action (FSCA) Manufacturers should have in place procedures to facilitate FSCA, including designated personnel, and to maintain records to facilitate traceability for lots of IVDs distributed to users.

Reporting timelines for complaints

1. Any **serious adverse event** should be reported by the manufacturer to the relevant NRA within their respective timelines, and **to WHO within 10 days**.
2. Any **moderate adverse event or any change in the trend of mild adverse events** should be reported by the manufacturer to the relevant NRA within their respective timelines, and **to WHO within 30 days**.
3. All complaints (both administrative and technical including serious, moderate and mild adverse events) must be reported by the manufacturer annually to the relevant NRA, and to WHO as a periodic summary report.

Any relevant NRA (NRA in the country where the complaint takes place) may have their own reporting templates and specific deadlines. These should be adopted, where appropriate. If no guidance exists from the relevant NRA, annexes to this guidance should be utilized.

⁴⁸ Manufacturers of prequalified IVDs should notify WHO of their responsible person for PMS during the WHO prequalification process.

Disclaimer

It is important to outline the fact that **the act of reporting a complaint is not an admission of manufacturer, user or patient liability for the event or its consequences**. Submission of an adverse event manufacturer investigation report does not, in itself, represent a conclusion by the manufacturer that the content of this report is complete or confirmed, that the device(s) listed failed in any manner. It is also not a conclusion that the device caused or contributed to the adverse event. It is recommended that reports carry a disclaimer to this effect.

Reporting timelines for manufacturer investigation reports

Manufacturers should submit the initial manufacturer investigation report to WHO in a timely manner; for any WHO-prequalified product within 15 days of first becoming aware of the adverse event (See template for adverse event manufacturer investigation reporting form in annex 4). Subsequent follow-up and final manufacturer investigation reports should be submitted in a timely manner as the nature of the adverse event dictates.

1. CLASSIFY COMPLAINTS

A method of classification should be used identify the quality, safety and performance issues that pose a high risk to individual health and to public health, and therefore require the most immediate action to protect public health and safety. As previously described, complaints may include:

- administrative/contractual complaints; and
- technical complaints.

As soon as it is received, any complaint must be classified by the manufacturer as part of the risk management file for the product, see Introduction (section 4.3) on risk management for IVDs. The degree of risk will determine the timeline for action, and who should be informed. The requirement for root cause analysis will remain, irrespective of the classification. In general, most technical complaints will be considered as an adverse event, and should be classified, an example is shown in **Table 4**.

Note: not every complaint may need to be considered as an adverse event, and not every adverse event or potential adverse event may lead to a field safety corrective action.

Table 4 – Examples of adverse event classifications (this is not a list of exhaustive examples)

Classification	Definition	Examples
Serious adverse event (10 days)	<ul style="list-style-type: none">• Death of patient, user or other person• Serious injury of patient, user or other person• Death or serious injury of patient, user or other person did not occur but might have• Any false negative result	<ul style="list-style-type: none">• One or more individuals receive HIV-contaminated blood product that has been produced from one blood donation that was screened as HIV negative by an HIV-1/2 RDT.• An individual presenting for ART initiation has testing repeated to confirm their HIV diagnosis. The re-testing results are negative.
Moderate adverse event (30 days)	<ul style="list-style-type: none">• Any false positive result (that resulted in misdiagnosis)• Higher than expected rate of anomalies that lead to invalid, unreturnable or inconclusive results	<ul style="list-style-type: none">• Invalid rate exceeds 5%.• High background for rapid diagnostic tests.• Greater than expected discrepant rate between assay 1 and assay 2 within a testing algorithm.
Mild adverse event (30 days)	<ul style="list-style-type: none">• Deficiency found by the user prior to use• Adverse event caused by patient conditions• Adverse event caused by device exceeding its service life or shelf life• Malfunction protection operated correctly• Negligible likelihood of occurrence of death or serious injury• Unexpected and foreseeable side effects• Adverse events that might be described by the manufacturer in FSN	<ul style="list-style-type: none">• Control line does not appear.• Higher than usual background, may or may not obscure reading window and prevent reading.• Desiccant has changed colour.• A component labelled lyophilized is found to be fluid, this is discovered by the user prior to use.• The packaging of a device is labelled with the caution 'do not use if the packaging is opened or damaged'. Prior to use, obvious damage to the packaging was observed, and the device was not used.

2. UNDERTAKE ROOT CAUSE ANALYSIS

For each complaint received, the manufacturer should undertake a root cause analysis to determine if the complaint (including adverse events) can be verified and root cause can be established. Depending on the findings the risk management file should be updated.

Root cause analysis is a systematic approach to investigating why and how a problem took place, in order to prevent its reoccurrence. There are a number of tools that may be used such as a fishbone diagram.

Fishbone (Ishikawa) diagram which requires consideration to the following aspects:

- Machine
- Methods
- Materials
- Man
- Mother nature
- Measurement .

3. TAKE CORRECTIVE ACTION

In certain circumstances, corrective action may take place before the root cause can be definitively identified, in order to protect individual health and public health.

3.1 GENERAL PRINCIPLES

Following the investigation of the complaint, the manufacturer should consider the following possibilities:

- No action;
- Immediate correction;
- Additional surveillance of the IVD in use;
- Design modification, manufacturing process modification, etc.;
- Field safety corrective action, including recall or quarantine of existing stock, modification instructions for use or product labeling;
- Field safety advisory notice issuance, including urgent information to inform those responsible for the device, or affected by the problem;
- Retraining;
- Other possible action, such as retesting of individuals and/or special monitoring of individuals previously tested using the affected IVD.

Corrective and preventive action (CAPA)

Based on the results of root cause analysis, corrective and/or preventive action should be taken, where necessary. Corrective action/preventive action (CAPA) are improvements made to the manufacturing process as part of the overall quality management system to eliminate causes of nonconformities. Any process for CAPA should focus on the systematic investigation of discrepancies (failures and/or deviations) in an attempt to prevent their reoccurrence. To ensure that corrective and preventive actions are effective, the systematic investigation of the failure incidence is pivotal in identifying the corrective and preventive action undertaken. The degree of action taken should be dependent upon and related to the risk, size and nature of the problem and its effect(s) on product quality.

Corrective action should be handled according to ISO 13485:2003, Section 8.3. (control of nonconforming product) and 8.5.2. (corrective action), depending on whether a nonconforming IVD is involved or if action is taken to prevent recurrence of a nonconforming IVD.

Preventive action is a proactive process undertaken by the manufacturer to identify opportunities for improvement of the IVD in advance, before a problem is identified. Preventive action is taken when a potential nonconformity is identified as the result of lot testing, complaints from the

field, and other relevant sources of information. Examples of preventive action include (but are not limited to):

- Reviews of contracts (with key suppliers), purchasing, processes, design;
- Software validation and verification for analyzers;
- Supplier surveillance;
- Preventive maintenance and calibration controls for analyzers;
- Management review of quality management system;
- User training programmes, job aids;
- Trend analysis;
- Benchmarking.

Risk management

The risk management file should be updated including:

- Risk analysis
 - through identification of intended use and characteristics related to safety of IVD, identification of hazard and estimation of risk for the hazardous situation;
- Risk evaluation;
- Risk control
 - risk control option analysis, implementation of risk control measures, residual risk evaluation, risk/benefit analysis, risks arising from risk control measures, completeness of risk control;;
- Evaluation of overall residual risk acceptability;
- Risk management report; and
- Production and post-production information.

See section 4.3 on the basic principles of risk management.

3.2 FIELD SAFETY CORRECTIVE ACTION

Definition

A field safety corrective action (FSCA) is an action taken by the manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market.

What can trigger FSCA

A FSCA is triggered by information about any problem with an already distributed IVD that poses an unacceptable increased risk when that IVD is used. Such problems include malfunction or deterioration affecting the performance or operational characteristics of an IVD, as well as any inadequacy in the instructions for use which might lead or might have led to the death of a patient, user or other individual or to a serious deterioration in his/her state of health.

Such information may arise from any aspect of post-market surveillance: pre-distribution or post-distribution lot testing, report from the field, review of IVD design, changes in production or component specifications, etc.

Assessing the need for FSCA

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

Risk assessment is thus a key element of the manufacturer determining the need for a FSCA. Appropriate expertise must be used to determine the potential harm and the risk properly.

Undertaking FSCA

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

Possible actions	<p>FSCA may include:</p> <ul style="list-style-type: none"> • Return of an IVD to the manufacturer or its representative; • IVD modification; • IVD exchange; • IVD destruction⁴⁹; • Advice given by the manufacturer regarding the use of the IVD (e.g. where the IVD is no longer on the market or has been withdrawn but could still possibly be in use). <p>IVD modifications can include:</p> <ul style="list-style-type: none"> • Retrofitting in accordance with the manufacturer’s modification or design change; • Permanent or temporary changes to the labeling or instructions for use; • Software upgrades including those carried out by remote access; • Modification to the clinical management of patients to address the risk of death or serious injury or death specifically to the characteristics of the device. For example the manufacturer may advise to: <ul style="list-style-type: none"> - Retest affected patients or specimens, or review previous results. - Change the way the device is used e.g. use a revised quality control procedure, use third party quality controls, or do more frequent calibration.
Communicating FSCA	<p>A FSCA is communicated through a Field Safety Notice (FSN); see section 3.3 for details.</p>
Reporting FSCA	<p>The manufacturer is required to report any FSCA related to a WHO-prequalified IVD to WHO and to the relevant NRA where the IVD is supplied.</p>
	<p>The manufacturer should issue a notification to WHO and to NRAs of all the countries affected through a FSCA report. A format is proposed in Annex 5.</p>
	<p>The FSCA report should include the following information:</p> <ul style="list-style-type: none"> • Name of the manufacturer; • Product name, product code and lot number of the affected IVD: <ul style="list-style-type: none"> - in the case that the FSCA related to certain lots only, an explanation why the other lots are not affected; • List of all affected countries; • Background information and reason for the FSCA: <ul style="list-style-type: none"> - include a description of the IVD deficiency or malfunction, clarification of the potential hazard associated with the continued use of the IVD and the associated risk for the patient, user or other person and any possible risks to patients associated with previous use of affected IVD; • Relevant parts from the risk analysis; • Description and justification of the corrective and/or preventive action; • Advice on the actions to be taken by the distributor and the user (include as appropriate): <ul style="list-style-type: none"> - Identifying and quarantining the IVD; - Method of recovery, disposal or modification of the IVD; - Recommended patient follow up; - A request to pass any attached Field Safety Notice to all those who need to be aware of it.
Follow-up FSCA report	<p>A follow-up report should be submitted by the manufacturer to WHO within a maximum of 30 days from the initial notification of the FSCA.</p>
	<p>The follow-up report should provide:</p> <ul style="list-style-type: none"> • An update of the progress of reconciliation of the FSCA and estimated timescales for completion. • Confirmation, where practical, that users have received the FSN.

⁴⁹ The NRA should ensure a record of disposal of affected product, and inform the manufacturer so that they may reconcile product distributed and product destroyed.

Final FSCA report	<p>A final report should be submitted to WHO and other relevant NRAs after implementation of the FSCA. This should include information on the effectiveness of the action per country involved (e.g. percentage of IVDs that underwent the FSCA).</p> <p>If the FSCA includes return of affected stock to the manufacturer or an update of the instructions for use or a modification/update of existing IVDs on- or off-site, records of completed actions should be fully reconciled against distribution records in order to maintain control of the progress of the FSCA.</p> <p>The final report should contain the following information:</p> <ul style="list-style-type: none"> • The final outcome of the reconciliation of the FSCA; • Root cause of the problem, if known, and proposed action to reduce the chance of recurrence <i>e.g.</i> redesign, update in the field, improved instructions for use, etc.
-------------------	--

3.3 FIELD SAFETY NOTICE (FSN)

Purpose	Field Safety Notices are an important means of communicating FSCA and related safety information to users. They may also be used to provide updated information about how an IVD should be used.
Distribution of FSN	<p>Manufacturers should inform affected users of any FSCA via FSN, with copy to the relevant NRAs and to WHO. The manufacturer should ensure that the FSN is distributed to all affected users, and must keep track of confirmation of receipt of the FSN. A full, detailed distribution list with contact name and email address for each intended recipient must be kept and must be made available on request.</p> <p>Affected users are will usually receive the FSN via their procurement agents or through in-country distributors who are obligated to inform all users within their region of supply. Distributors may need to translate the FSN from English or other common language to local language but this needs to be managed to ensure that the translation is of good quality and interprets the message of the FSN correctly.</p> <p>Further purchasing information requirements are specified in the ISO/TR 149696:2004 <i>Medical devices - Quality management systems - Guidance on the application of ISO 13485:2003</i>.</p>
Content and format	<p>The manufacturer should use a standardized format for a FSN (see example in Annex 6).The FSN should be written on company letter head and in English. It may be translated into the official language(s) of the country by in-country distributors.</p> <p>The FSN should include the following items:</p> <ul style="list-style-type: none"> • A clear title like “Urgent Field Safety Notice” on the notice itself, the envelope if sent by mail and the subject line if sent by email or fax; • The intended audience: clear statement about the intended recipient of the notice; • Concise description of product, product code, lot number; • A factual statement explaining the reasons for the Field Safety Corrective Action, including description of the problem; • A clear description of the hazards associated with the specific failure of the device and, where appropriate, the likelihood of occurrence, being mindful of the intended audience; • The recommended action(s) to be taken by the recipient of the Field Safety Notice including any action(s) recommended for people that have previously used or been treated by affected diagnostics, including recalls; • Where appropriate, include timeframes by which the action(s) should be taken by the manufacturer and user; • Designated contact point for the recipient of the Field Safety Notice to obtain further information.

No misuse of FSN	<p>The FSN should not include any:</p> <ul style="list-style-type: none"> • Comments and descriptions that downplay the level of risk; • Information that is intended to promote a manufacturer or their product’s market visibility for the purposes of sales and marketing.
Prior consultation with WHO and NRA	<p>It is recommended that manufacturers should provide a draft of the FSN to WHO and the relevant NRA, allowing a minimum of 48 hours for comment unless the nature of the FSCA dictates shorter timescale e.g. for serious public health threat.</p> <p>In a very few cases, where an urgent FSCA is needed because of serious safety risks, WHO accepts that prior consultation may not be possible.</p> <p>Where WHO believes that the FSN does not fully meet the requirements as described in this document, and in particular explain the risk and how it will be removed/reduced, WHO may issue its own information notice and send it to the relevant NRAs for further dissemination to users.</p>
WHO information notices	<div style="background-color: #e6f2ff; padding: 10px; border: 1px solid #cfe2f3;"> <p>WHO reserves the right to issue information notices for users in certain circumstances: if the manufacturer has not undertaken an appropriate FSCA within an appropriate time frame, if the manufacturer has not disseminated an appropriate FSN, and to give information to users about how to interpret the contents of FSN.</p> </div> <p>WHO information notices may include any recommendations to programmes and implementing partners for alternative testing arrangements and to procurers for past, on-going or future purchase orders of affected or potentially affected products.</p>

SUMMARY OF OBLIGATIONS FOR WHO PREQUALIFIED PRODUCTS

Obligations for WHO prequalified IVDs	<p>Manufacturers of WHO-prequalified products agree, as a condition of WHO prequalification, to undertake the following post-market surveillance obligations:</p> <ul style="list-style-type: none"> • Notify WHO of any post-market events relating to the WHO prequalified product that have affected (or could have affected) the performance of the assay, safety of the individual being tested, safety of users of the assay or safety of any person associated with the assay. <ul style="list-style-type: none"> - All complaints (both administrative and technical including serious, moderate and mild adverse events) must be reported to WHO annually, as a periodic summary report. - Any serious adverse event should be reported to WHO within 10 days. - Any moderate adverse event or any change in the trend of mild adverse events should be reported to WHO, within 30 days. • WHO may request that the manufacturer provide further information relating to the incident, including details regarding the preventive and corrective action taken. • Manufacturers of WHO-prequalified IVDs are responsible for activating their complaint reporting and vigilance system and must inform WHO of reportable adverse events. The manufacturer should encourage end users to report on problems experienced with the use of an IVD. • Notify WHO of all events which require FSCAs such as withdrawal of IVDs from sale or distribution, physical return of the IVD to the manufacturer, IVD exchange, destruction of the IVD, IVD modification/s or additional advice provision to customers to ensure that the IVD continues to function as intended; and • Submit information on all complaints, including any FSCA, carried out in the previous calendar year as part of the mandatory annual summary reporting.
---------------------------------------	--

PART III: NATIONAL REGULATORY AUTHORITIES

► OVERVIEW OF RESPONSIBILITIES

Organizational setup	<p>The Ministry of Health should designate a National Regulatory Authority (NRA) responsible for IVDs.</p> <p>The NRA should appoint a person/unit within the organization responsible for post-market activities related to IVDs including post-market information exchange within the country (manufacturers, end users/laboratories/testing sites, NRL) and with WHO.</p> <p>A national IVD focal point should be assigned. The IVD focal point may already exist, if a functional unit for IVDs exists within the NRA, but if this is not the case the focal point may come from the NRL, or the Ministry of Health. Preferably one national IVD focal point should be assigned for all IVDs (with particular emphasis on WHO-prequalified products), irrespective of the analyte or test kit format.</p>
Reference testing laboratory	<p>The NRA should designate a NRL or other recognized laboratory that is assigned the overall responsibility for coordinating and conducting pre-distribution and post-distribution lot verification testing.</p>
Information-sharing	<p>The NRA should establish an information circuit between end users (and procurers/implementers) and IVD manufacturers, and the NRA's responsible person for post-market surveillance (or national IVD focal point), allowing post-market information exchange.</p>
Lot verification testing	<p>To ensure that IVDs continue to meet their specifications, national regulatory authorities have the mandate to arrange proactive lot verification testing by a reference laboratory including:</p> <ul style="list-style-type: none">• Pre-distribution to testing sites (when a consignment of test kits arrives in country);and• Post-distribution to testing sites (after the lot has already been in use).
Complaints	<p>The NRA should ensure that any FSCA recommended by the manufacturer are implemented.</p>
Regulatory action	<p>The NRA should take regulatory actions as appropriate to address any issues identified through post-market surveillance activities.</p>
Interaction with WHO	<p>Post-market data on WHO-prequalified IVDs gathered through pre-distribution and post-distribution lot testing and vigilance procedures or collected through other means are encouraged to be shared with WHO as a part of post-market information exchange process for prequalified IVDs, ensuring product traceability and contributing to public health protection. See Annex 7 for a post-market information exchange reporting form template for NRAs to use.</p>
Risk-based approach	<p>Full and complete post-market surveillance for all products is not feasible with available regulatory capacity and resources. Therefore, NRAs are encouraged to adopt a risk-based approach to both pre-market assessment and post-market surveillance of IVDs placed on their market according to a set of risk classification rules. The rules set down by the Global Harmonization Task Force (GHTF) are useful in this regard, given their adoption by the successor of GHTF; the International Medical Device Regulators Forum (IMDRF). Risk classes A through D were developed taking into account risk to the individual and risk to the public.⁵⁰ The level of regulatory scrutiny will depend on the risk the IVD presents and the setting of its intended use.</p> <p>Other prioritization criteria may be the risk class of an IVD, its scope of use and other factors. The information given in Table 4 (Part II) may be useful in this regard.</p>

⁵⁰ Taken from "A risk based approach for the assessment of in vitro diagnostics (IVDs) accessed 12 December 2014 http://www.who.int/diagnostics_laboratory/evaluations/140513_risk_based_assessment_approach_buffer.pdf?ua=1

Phased implementation The implementation of post-market surveillance measures will depend on the maturation and capacity of the NRA to handle complaints. In the absence of fully fledged post-market regulatory controls, WHO will serve to handle complaints from end users, including procurers and implementers, and ensure that manufacturers are informed and follow-up appropriately.

1. COLLECT COMPLAINT REPORTS, INCLUDING FOR WHO-PREQUALIFIED IVDs

1.1 COLLECT COMPLAINT REPORTS

End users The NRA should receive reports for certain categories of complaints submitted by end users as described in *Part I* of this document and take appropriate regulatory action.

Sentinel sites An alternative arrangement may be to establish sentinel surveillance sites with primary responsibility to look for issues related to safety, quality and performance of IVDs; these should be under the supervision of the NRL (or designated competent laboratory) and NRA. A sentinel site would be responsible for active collection of information on safety, quality and performance of IVDs, through external quality assessment (on-site supervision, etc.). Sentinel sites may also provide testing sites within their geographical area with specimen panels for lot verification testing.

1.2 FOLLOW-UP ON COMPLAINTS

The procedure for receiving, reviewing and acting on complaints (including adverse events) comprises of the following mechanisms:

- Manufacturer** (see also *Part II*)
- Reports from end users (including implementing partners) are forwarded **all complaints to manufacturer** and **all serious and moderate adverse events to the relevant NRA and WHO**;
 - WHO and the relevant NRA ensures manufacturer is aware of complaints, equally manufacturers must inform WHO and the relevant NRA of all serious and moderate adverse events;
 - Manufacturer evaluates the reported complaint, including serious, moderate, and mild adverse events, and conducts root cause analysis;
 - Manufacturer submits initial adverse event manufacturer investigation report to the relevant NRA and WHO;
 - Where appropriate, manufacturer recommends Field Safety Corrective Action and submits a FSCA report to WHO and/or NRA;
 - Where appropriate, manufacturer disseminates information related to the FSCA to affected users through a Field Safety Notice;
 - Where appropriate, manufacturer in collaboration with the relevant NRA and WHO recommend modifications of the IVD or its removal from the market and therefore the list of WHO-prequalified products;
 - WHO ensure implementing partners are informed;
 - Manufacturer submits adverse event manufacturer investigation report to WHO and/or the NRA.

NRA follow-up The NRA follows up on the results of the manufacturer's report by appropriate regulatory action.

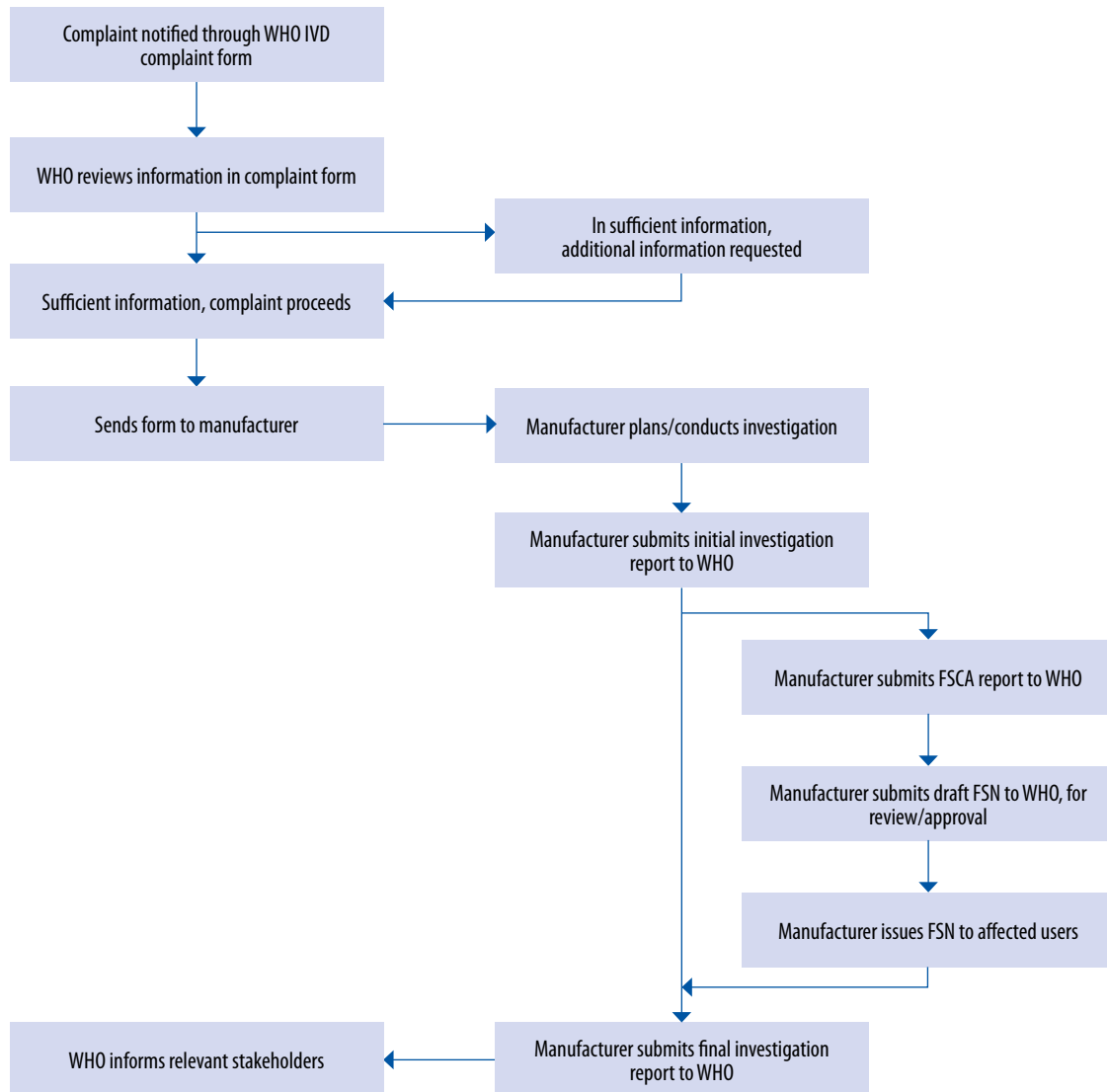
1.3 COMPLAINTS REPORTING FOR WHO-PREQUALIFIED IVDs

The WHO Prequalification of In Vitro Diagnostics Programme has its own complaints handling procedure (**Figure 4**). WHO will handle any complaints received about WHO prequalified IVDs. WHO will notify the manufacturer of the complaint, and will notify the relevant NRA in the country/region where the product is manufactured and where the product is being supplied.

WHO will also inform affected procurement agencies and other UN organizations of any relevant FSCA, if it is felt that this information would be of interest. Subject to the protection of commercially sensitive information WHO is entitled to make public any relevant Field Safety Notices and information notices for users. In addition, WHO reserves the right to share the post-market surveillance reports with the relevant authorities of interested Member States and UN agencies. The responsibilities of manufacturers of WHO-prequalified IVDs in this regard are described in **Part II**.

NRAs may choose to establish similar procedures for non-WHO-prequalified IVDs placed on their markets.

Figure 4 – Flow chart of reporting complaints for WHO-prequalified IVDs



2. OVERSEE LOT VERIFICATION TESTING

2.1 RATIONALE

NRAs have the mandate to order lot testing to verify the quality, safety and performance of IVDs. Where the relevant NRA does not exist or insufficient capacity to conduct post-market surveillance activities, the end user (including procurers and implementing partners) may request lot verification testing.

In the context of WHO-prequalified IVDs, lot verification testing ensures that manufactured lots continue to meet the WHO prequalification requirements for safety, quality, and performance⁵¹. Secondly, lot testing can assess variation between lots and captures deviation in performance in comparison with the preceding lot(s).

Lot verification testing is not intended to duplicate the manufacturer's quality control (QC) lot testing undertaken throughout the manufacturing process, and at final release of the product. Rather it aims to ascertain that IVDs continue to meet their standards at all stages of their distribution and use.

Manufactured lots can differ greatly	Despite the manufacturers' obligation to test each lot during production and at release, variations in the performance characteristics of each lot may occur due to differences in the lots of key components (starting materials) used, different personnel involved in production processes, variations in manufacturing processes, and a range of other variables.
What is meant by "lot"?	Lot sizes may vary from 5,000 tests per lot to 1,000,000 tests per lot, depending on how the manufacturing site configures their operations. The EU standard EN 13975: 2003 <i>Sampling procedures used for acceptance testing of in vitro diagnostic medical devices – Statistical aspect</i> defines the term lot/batch as follows: "A defined amount of material that is uniform in its properties and has been produced in one process or series of processes. The material can be either starting material, intermediate material or finished product". In the context of these guidelines, lot testing is focused on a commercially available test kit which is provided with a unique lot number and where the single components are matched to this kit, e.g. micro-plate or nitrocellulose membrane, antigen, conjugate, specimen diluent, etc.
Transport and storage affect IVDs	Inappropriate transport and storage conditions such as high or low temperature, high humidity and the presence of direct sunlight can have a considerable effect on the performance and quality of an IVD.
Pre-distribution testing	<p>The approach described here supposes that adequate pre-market assessment has been conducted and that the clinical and analytical sensitivity and specificity of the IVDs are well known. The objective of pre-distribution lot verification testing is to ensure lot-to-lot consistency when performance of a baseline lot is known (through WHO prequalification or otherwise).</p> <p>The purpose of pre-distribution testing is to ensure that the diagnostics delivered to country meet requirements for safety, quality and performance and that the manufacturer's claims of product's performance can be verified in the state as it is procured. Lot testing ensures that only lots with acceptable test results are distributed to laboratories and testing sites all over the country.</p>
Post-distribution testing	Post-distribution lot testing assumes that pre-distribution lot testing has been undertaken on the same lot and brings additional information on the safety, quality and performance of the IVD after it has been distributed to end users. Testing of samples from the field, in combination with pre-distribution lot verification testing, guarantees monitoring of IVD quality throughout the distribution chain thus ensuring that only quality lots of IVDs that fully meet manufacturers' claims for stability are used by end users.

⁵¹ For non-WHO prequalified IVDs, lot verification testing will ensure that pre-market assessment performance criteria remain adhered to.

2.2 LIMITATIONS

This approach to lot verification testing will not necessarily be able to detect quality issues if the lot has not been homogeneously produced. Pre-distribution lot testing cannot detect stability issues that might lead to degradation of the shelf-life of the product, including all components and accessories. However, post-distribution lot testing may detect stability issues.

2.3 METHOD

Testing known specimens Lot verification testing verifies whether or not the IVD correctly classifies a set of clinically-derived reference specimens in a panel. Where possible the panel will be locally or regionally derived, so that the same specimen panel can be used by a number of countries with similar epidemiology and genetic diversity, and data can be compared. Detail on preparation of specimen panels and lot verification testing by the reference laboratory is given in **Part IV** of this document.

Sampling Samples should be taken by appropriately trained and qualified personnel from the **NRA** (or central medical stores) for pre-distribution testing, and from the **testing sites** for post-distribution testing (see also **Part I**). Samples should be transported to the reference testing laboratory in such a way that the integrity of the test kits is not adversely affected and that the appropriate storage conditions, as specified by the manufacturer, are maintained. Temperature log monitors should be included within the transportation packing for the samples.

Sampling frame For **pre-distribution** lot verification testing, each lot should be sampled initially. After a certain period of acceptable results (12 months or 10 lots, whichever comes first), the sampling frame may change from systematic sampling and testing of each lot, to random sampling of lots delivered to countries. The random sampling frame should be selected (every 5th lot). If any issue is observed with random pre-distribution lot verification testing, the national authorities may elect to recommence systematic testing of each lot. The decision about the sampling frame is therefore made using a risk-based approach.

Post-distribution lot testing carries a different risk as the product has already been in use, and depending on the through-put of the testing site, it may or may not be close to its expiry date. Therefore, the sampling frame does not need to include every lot delivered to country, but should rather be conducted twice per year.

See **Part I (Table 3)** for details on sampling at central medical stores and in laboratories/testing sites.

Reference laboratory A reference laboratory should be identified to perform lot verification testing as described in **Part IV**. The same laboratory should perform both pre-distribution and post-distribution lot verification testing for the same lot of product. A suggested protocol for HIV RDT lot verification testing, with provisions for reporting of results and confidentiality, is included in **Part IV**.

2.4 USE OF EXISTING SYSTEMS

For malaria rapid diagnostic test (RDTs), a system for lot testing through the WHO/FIND Lot Testing Programme already exists.

3. COLLECT OTHER POST-MARKET INFORMATION

In addition to lot verification testing and complaints, sources of data on the quality and performance of IVDs on the market include external quality assessment schemes (EQAS), also known as proficiency testing, and from quality control (QC) programmes.

EQAS Where it exists, the data generated by an EQAS can be assessed. Although the primary purpose of EQAS is inter-laboratory comparison, these data can provide very useful information about the performance of IVDs.

EQAS data analysis may indicate not only operator-related errors (for example transcription errors), but also errors related to the test itself, especially if large numbers of laboratories/testing sites are using the same test kit.

QC A QC specimen is a specimen that has reactivity that is just above the cut-off for positivity of a test kit. It is usually a manufactured specimen that is optimized for the test kit and may be provided by a national authorities to all laboratories/testing sites using the test kit as part of a QC programme. All attempts should be made to procure and distribute QC material to any site undertaking testing QC specimens should be tested in each test run (for an immunochromatographic RDT, no more than 10 tests per run). The results of QC specimens can be graphically represented and results outside a pre-determined acceptance range identified and investigated. This approach is typically not all that useful for RDTs that generally are used in settings outside of the laboratories without test kit controls and external QC specimens.

Sentinel sites If sentinel surveillance sites are established, these sites could collect information on safety, quality and performance of IVDs.

4. TAKE REGULATORY ACTION

Depending on the seriousness of the IVD's deficiency discovered in the post-market phase and/or potential for future harm, NRAs should consider the following possibilities⁵²:

- No action;
- Perform additional in use surveillance of the IVD concerned;
- Issue an alert giving advice to end users;
- Require the manufacturer to make appropriate changes in the design, manufacturing process or information supplied with the product;
- Mandate a field safety corrective action (for example a recall/withdrawal);
- Send the data acquired to the manufacturer and store it in a database to help identify trends that require action.

The classification of complaints given in **Table 4 (Part II)** may be useful in prioritizing regulatory action.

At country level, the NRA may not have a function that relates specifically to IVDs. WHO can bridge this lack of capacity and support/conduct post-market surveillance activities. However, WHO encourages each WHO Member State to building pre-market assessment and post-market surveillance capabilities, specifically for IVDs.

⁵² This list does not purport to be definitive and each case should be handled individually.

PART IV: NATIONAL REFERENCE LABORATORIES

► OVERVIEW OF RESPONSIBILITIES

Authority and capacity

The reference laboratory should have the authority and capacity for assessing the quality, safety and performance of IVDs as they are received into the country under the direction of the NRA. Test kits will most likely be stored at central medical stores prior to distribution to users in the field. For countries where centralized procurement of IVDs is not performed, alternate methodologies will need to be implemented for sampling of test kits for pre-distribution lot verification testing.

The reference laboratory should:

- Be mandated by national authorities to perform laboratory testing for post-market surveillance of IVDs (both pre-distribution and post-distribution), and therefore have sufficient resources to conduct lot verification testing;
- Strive to adhere to internationally recognized quality standards, e.g., ISO 15189: *Medical laboratories — Particular requirements for quality and competence* or ISO 17025: *General requirements for the competence of testing and calibration laboratories*;
- Participate in external quality assessment schemes (EQAS), and act on results, if required.

Pre-distribution lot verification testing

The reference laboratory should receive samples for pre-distribution lot verification testing which have been sampled from newly arriving consignments at the central medical stores. For laboratories with direct procurement (i.e. no centralized storage as central medical stores), samples should be taken by their staff and sent to the reference laboratory for testing. The samples should be transported to the reference laboratory in such a way that the integrity of the IVDs is not adversely affected and that the storage conditions specified by the manufacturer are maintained. **The testing should be conducted on a standardized lot verification panel.** Further details on sampling procedures at central medical stores and laboratories/testing sites are found in **Part I (Table 3)**. The reference laboratory should present testing results in the form of a lot testing report as defined in **Annex 2** which would be sent to the relevant NRA and to WHO.

Post-distribution lot verification testing

The reference laboratory should receive samples taken from test kits in the field by staff at the testing sites themselves (or NRA or central medical stores) and transported to the reference laboratory through the specimen referral network or other network for distributing IVDs within the country. The testing should be carried out using the same standardized lot verification panel as the pre-distribution lot testing, and testing results presented in the form of a lot testing report as defined in **Annex 2**.

Competencies of testing staff

The staff performing the lot testing should be qualified and competent to undertake the task and to demonstrate that they can perform the test procedure correctly.

The **technical supervisor** should:

- Ensure that technicians are blinded to the reference test results for the lot testing panel by assigning the specimen vials with codes;
- Supervise the performance of the testing;
- Ensure that the testing results of subjectively read test kits are read independently by two technicians;
- Collate the readings from each technician and sign off the data collection sheets at the end of each testing day;
- Transcribe or verify that correct transcription of final results of lot testing into the lot testing report to be provided to the NRA and WHO.

The **technicians** should:

- Perform the test procedure according to the manufacturers' instructions for use;
- Record readings on the data collection sheet; and
- Store all data collection sheets in a folder.

The supervisor and technicians should not proceed with testing until they are confident regarding every aspect of the testing procedure.

Quality assurance measures must be in place and be adhered to at all times.

The reference laboratory (in conjunction with the end user) should be able to undertake an investigation of perceived problems to eliminate all other possible causes that are not test kit-related (i.e. use errors, abnormal use, poor implementation of the quality management system at the testing site).

EXAMPLE: PROTOCOL FOR HIV RDT LOT VERIFICATION TESTING (PRE- OR POST-DISTRIBUTION)⁵³

Objective of lot verification testing To verify the performance of an IVD (i.e. sensitivity and specificity) in the state that the test kit is delivered to the buyer by testing of the lot verification panel of well-characterized biological specimens.

Each lot is evaluated by testing the same set of specimens so that variation in assay performance over time can be monitored and any catastrophic product failure identified.

1. RECEIVE AND STORE SAMPLES OF TEST KITS

Registration As test kit samples are received at the reference laboratory for testing, details of each should be documented. The product name, product code (catalogue number), lot number (including for all components if these are different to outer test kit box), expiry date(s) should be recorded. The version number of the instructions for use should be recorded, and the instructions for use reviewed for any changes since the last lot testing event took place.

Storage Test kits must be stored at the temperatures indicated by the manufacturer up to the expiry dates printed on the labels. Since many RDTs allow for storage at a wider temperature range (e.g. 2-30°C), RDTs may be stored permanently in a consistent temperature range, e.g. in a refrigerator at 2-8°C or at climate-controlled room temperature. If a test kit package is opened and kit components are reconstituted, the reagents should be labelled with the appropriate date of opening of the component and the remaining residual amount of tests. Any separate shorter storage periods in compliance with the instructions for use should be taken into account.

2. PREPARE AND MAINTAIN LOT VERIFICATION TESTING PANELS

2.1 COLLECT AND PROCESS BIOLOGICAL SPECIMENS

Safety The testing of all biological specimens should be performed in such a manner as to minimize occupational risk. For further details see the *Laboratory Biosafety Manual, third edition*, World Health Organization, Geneva, 2004 (ISBN 92 4 154650 6).

Best practice Biological specimens should be collected under usual best practice for phlebotomy for use in the lot verification panel. In order for specimens to be of good quality (free of clotting, lipids, hemolysis, microbial contamination), all specimens should be processed to serum or plasma within 6 hours of collection and any clots and particulate matter removed. The specimens should then be aliquotted into appropriate volumes (e.g. 50 – 200 µl) and stored until required.

It is best to collect sufficient specimen volume to last up to 5 years. Therefore an estimation of the lot testing needs should be undertaken.

⁵³ Through the WHO-FIND Malaria RDT Lot Testing Programme, separate protocols are in place for lot verification of malaria RDTs. See the FIND website for further details http://www.finddiagnostics.org/programs/malaria-afs/malaria/rdt_quality_control/lot_testing/

Storage Specimens should be stored at -20 °C, or -80 °C if containing antigen. The number of freeze-thaw cycles should be limited to three, with thawing at 37 °C to ensure dissolution of proteins that are insoluble at cold temperature. Once thawed, the aliquots may be stored at 2 to 8 °C for up to 7 days.

The specimens should be stored in freezers and refrigerators that are monitored through an alarm system. Panels may be split among a number of freezers so that the risk of damage to stored panels due to power outage to a freezer is mitigated.

2.2 COMPOSITION OF THE HIV RDT LOT VERIFICATION PANEL

The HIV RDT lot verification panel will consist of well-characterized HIV seropositive and seronegative clinical specimens, including some dilution series. This panel should be specifically constructed for the RDTs to be lot-tested. The claims for performance made by the manufacturer in the instructions for use should be reflected in the lot testing panel, e.g. detection of HIV type (HIV-1 and HIV-2), HIV-1 group O, and for HIV-1 p24 antigen should be reflected.

RDTs vs EIAs Different panels will need to be constructed for RDTs and for EIAs, as the analytical sensitivity of EIAs is expected to be greater than that of RDTs and thus EIAs may not be sufficiently challenged by RDT lot verification testing panels.

Specimen types To meet the general objective of the lot verification testing, it will be sufficient to test characterized specimens only, especially if adequate pre-market assessment has been undertaken for all specimen matrices. For IVDs that utilize specimen types other than serum/plasma and that require fresh collection and use, i.e. oral fluid or capillary whole blood, consideration should be given to whether these alternate specimen types should form part of the lot verification testing panel.

National/regional panels Lot testing panels should be created from locally derived specimens, meaning specimens collected nationally or regionally. A regional lot verification testing panel would be ideal for initial implementation of lot verification testing as a range of lots of the same IVD from within the same geographical area could be tested on the same panel, for increased ability to compare lot verification testing data between countries.

Composition The lot verification specimen panels shown in **Tables 5 and 6** are intended for IVDs that have undergone stringent pre-market assessment such as WHO prequalification assessment. Pre-market assessment would generate sufficient evidence of clinical sensitivity and specificity, thus the lot verification can be kept to a minimum and will only be used to verify that performance is comparable to the performance at the time of approval. **Table 5** shows the composition of a panel for RDTs that detect antibodies to HIV-1/2. For RDTs that detect HIV-1 p24 antigen, in addition to HIV-1/2 antibodies, analytical sensitivity to p24 antigen will need to be added to the lot verification panel (**Table 6**).

Table 5 – Lot verification specimen panel for RDTs that detect antibodies to HIV-1/2

Testing objective	Specimen details	Testing replicates	Total
Anti-HIV-1 analytical sensitivity	4 HIV-1 specimens each presented in a 3 member, 2-fold dilution series that includes the last two reactive and the first non-reactive dilutions, determined as described below (See "Determine cutoff")	Tested in triplicate ^(a)	12 x 3
Anti-HIV-2 analytical sensitivity	1 HIV-2 specimen each presented in a 3 member, 2-fold dilution series that includes the last two reactive and the first non-reactive dilutions, determined as described below (See "Determine cutoff")	Tested in triplicate ^(a)	3 x 3
Sensitivity	2 low HIV seropositive specimens	Tested singly	2
Specificity	3 seronegative specimens (including dilution matrix) ^(b)	Tested singly	3
Grand total			50

Table 6—Lot verification specimen panel for RDTs that detect antibodies to HIV-1/2 and HIV-1 p24 antigen

Testing objective	Specimen details	Testing replicates	Total
Anti-HIV-1 analytical sensitivity	As above	Tested in triplicate ^(a)	12 x 3
HIV-1 p24 analytical sensitivity	WHO International Standard HIV-1 P24 Antigen NIBSC code: 90/636	Tested in duplicate	8 x 2
Anti-HIV-2 analytical sensitivity	As above	Tested in triplicate ^(a)	3 x 3
Sensitivity	2 low HIV seropositive specimens	Tested singly	2
Specificity	3 seronegative specimens (including dilution matrix) ^(b)	Tested singly	3
Grand total			66

Notes:

- (a) By testing the dilution series in triplicate, the precision of the assay can be evaluated, and expressed as the coefficient of variation (% CV).
- (b) The negative dilution matrix used as diluent for the various specimens and dilution series should be included as a negative reference specimen, (i) to monitor the background reactivity of the IVD, and (ii) to control matrix effects which may impact the analytical sensitivity.

2.3 PREPARE DILUTION SERIES

Differences in analytical sensitivity between RDTs

RDTs for detection of HIV-1/2 antibodies may vary considerably in their ability to detect diluted specimens. Indeed there is no correlation between detection of the absolute number of HIV-1/2 antibodies present in a specimen and lowest antibody concentration that can be detected by a given HIV-1/2 RDT. Nevertheless proportional quantification of antibody reactivity between different specimens in the same HIV-1/2 RDT. Moreover, the analytical sensitivity also differs between anti-HIV-1 and anti-HIV-2 by several magnitudes in most HIV-1/2 RDTs.

To select a 3-member dilution series, five HIV positive specimens (four dilution series for HIV-1 and one dilution series for HIV-2). The dilution series must contain three members that span the assay's cut-off. To establish which three dilutions should form the series, each of the five specimens are diluted 2-fold in normal human serum or plasma (1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512, etc.) down to the endpoint (test kit cut-off). Each set of these dilutions should be tested on the given RDT and three dilutions that cross the cutoff are selected for inclusion in the lot verification panel i.e. (1) the reactive dilution two dilutions above the assay's cut-off, (2) the reactive dilution just above cut-off, and (3) the first non-reactive dilution (See **Figure 5**). Each of the three reference dilutions should be tested in triplicate on the same lot to verify their reactivity.

Figure 5—Dilution sensitivity of two specimens on one HIV-1/2 RDT

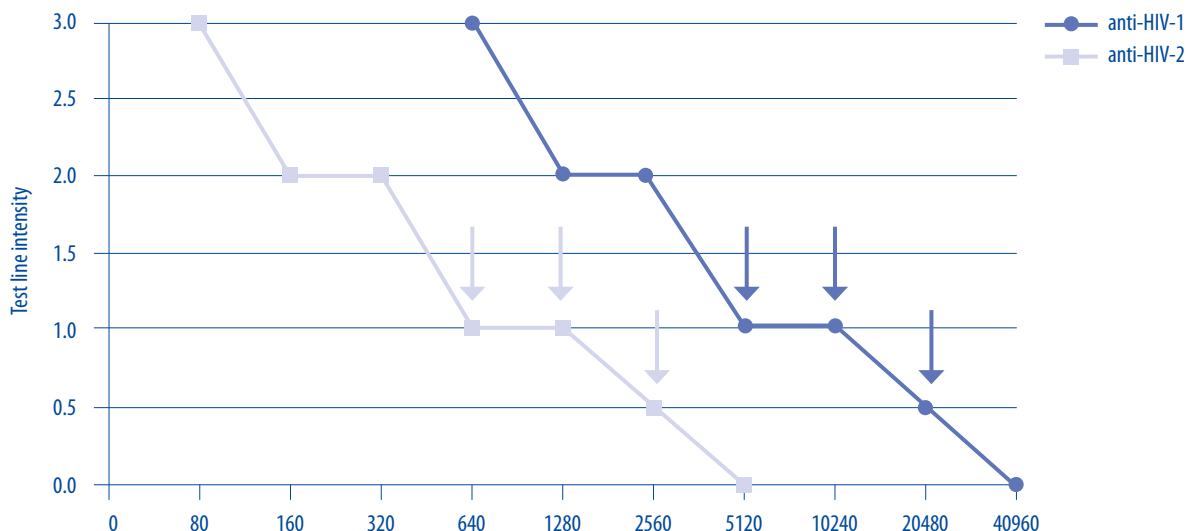
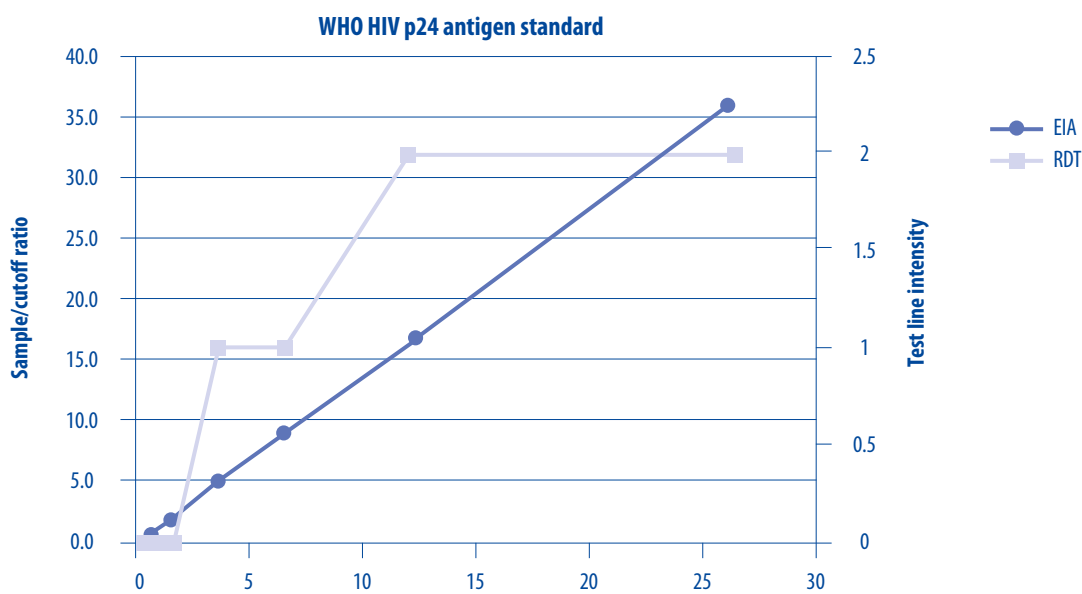


Figure 5 includes determination of the three members around the cutoff to be tested. The arrows indicate the point where individual members of the dilution series approach the assay cutoff.

HIV-1 p24 antigen The WHO international biological reference standard for HIV-1 p24 Ag (NIBSC 90/636) may be used in the lot verification panel. A dilution series with two-fold dilutions from 20 IU/ml to 0.125 IU/ml has been found to cover the analytical sensitivity of most HIV 4th generation RDTs (see **Figure 6**– Standard curve for HIV-1 p24 antigen. Each member of the dilution series was tested in duplicate to verify their reactivity).

Figure 6– Standard curve for HIV-1 p24 antigen in 4th generation serology assays



3. CONDUCT TESTING AND RECORD DATA

3.1 GENERAL GUIDELINES

1. Each assay should be performed under identical conditions to minimize the chance that differences in lot testing results were not caused by differences in the environmental and/or testing conditions (including equipment such as instruments, pipettes, etc.);
2. Testing should be performed by one technician where possible, to avoid technician-dependent differences;
3. All testing on the one lot should be performed on the same day;
4. All specimens should be tested in a randomized and blinded fashion, i.e., the testing personnel should not know the status of the specimen before testing;
5. Test kits (devices and components) should be bought to room temperature before testing, and should be used immediately after opening the pouch;
6. Test kits should always be stored at recommended temperatures and must be in good condition. If a desiccant is included in the package and it has changed color, the kit should not be used;

7. Damaged kits should be discarded;
8. Reagents from one lot should not be used with those of another lot; and

It is essential to inspect test kits for signs of damage caused by heat or humidity before initiating the assessment. Temperature or time-temperature indicators are a good means of monitoring of the products' thermal history.

The assay is to be performed exactly according to manufacturer's instructions for use. If these contain several different methods for the test procedure, a consensus on the exact test procedure must be made and then onwards always followed when testing the lot verification panel on subsequent lots.

3.2 RECORDING RESULTS FOR SUBJECTIVELY READ ASSAYS

Each test should be read at both the minimum and maximum reading times stated in the instructions for use. A maximum of 10 immunochromatographic (lateral flow) and 5 immunofiltration (flow through) RDTs can be tested in one batch at one time to maximize logistics of testing.

For subjectively read assays, all test results should be entered as band intensities, e.g. 1+ to 3+ as shown below.

- +/- barely visible test line (inconclusive)
- 1+ faint but clear test line
- 2+ medium intensity test line
- 3+ strong intensity test line

Faint lines should be interpreted according to the manufacturer's instructions for use as their interpretation may vary from product to product. Weaker test lines, weaker control lines, and high membrane background that disturbs reading of test and/or control lines must be recorded.

Invalid results should be recorded when they occur as defined within the instructions for use e.g. control line does not appear, high background that obscures strip and prevents accurate reading, displaced strip prevents accurate reading, etc.

If a digital camera or smartphone is available, it would be useful to take photographs of test devices side-by-side for electronic storage of results. This is particularly important for invalid test results and results that do not meet the acceptance criteria.

3.3 DETERMINATION OF INTER-READER VARIABILITY FOR SUBJECTIVELY READ ASSAYS

Visual interpretation of results of subjectively read assays is made independently by two readers (without the knowledge of the other set of results and blinded to the reference result for the specimen). These results are compared by the operator carrying out the assay so that any mistakes may be identified and rectified immediately. Should recording errors be identified, both the original and corrected result are recorded and initialed by the reader. When the two readers interpret the results differently from each other, the technical supervisor is called to make a third reading. When the three readers interpret the results differently from each other, the consensus is recorded as that interpretation which occurs two out of three times. In cases where all three interpretations are different, the result is recorded as inconclusive.

The inter-reader variability is expressed as the percentage of specimens for which the test results were differently interpreted (i.e. between +/- and 1+, between 1+ and 3+ between +/- and 2+) by the independent readers.

A colour intensity chart should be created for each RDT with photos of the test devices with varying intensity test bands.

3.4 LOT TESTING DATA ENTRY

Data entry

Each assay should be performed and read by the technician according to the site-specific SOP based on the manufacturer's instructions for use, and results recorded on the data collection form, see **Annex 1**.

A second person should read the test results independently and record the test results on a same data collection form but with a piece of paper/cardboard that hides the results from the first reader.

At the end, any discrepancies in reading should be reviewed by the technical supervisor and resolved. The test results should be entered into the lot testing report by the technical supervisor and double-checked against the data collection sheets, see **Annex 2**.

The following information should be recorded:

- Product name;
- Product code/catalogue number;
- Lot number;
- Expiry date;
- Manufacturer name;
- Distributor/importer name;
- Test date;
- Site name;
- Operator name;
- Materials and equipment used, if any;
- Specimens used, including number of freeze/thaw cycles;
- Reference to SOP used;
- Raw data, RDT test results in reading format prescribed above;
- Final status assigned for each specimen.

The data collection sheets should be kept in a folder and signed off by the technical supervisor at the end of each day.

If the results are invalid or inconclusive, they should be recorded as such. The test may be repeated if there are sufficient test kits available.

If the test is repeated for any reason, all results should be entered into the data collection sheets as well as the reasons for repeating testing.

All data collection sheets and lot testing reports should be kept for a period of 5 years following the conclusion of the testing.

4. ANALYSE DATA AND REPORT RESULTS

4.1 ACCEPTANCE CRITERIA

For national HIV programmes that use one (or more) validated national testing algorithm(s), the exact assay used will be well known and so it will be easier to ensure that the lot verification testing panel is suitable, particularly for analytical sensitivity.

The lot testing verification panel should have been tested on each product used within the country to establish the reference result for each specimen of the lot verification specimen panel. This information will guide the criteria for acceptance.

The recommended acceptance criteria for HIV-1/2 RDTs are shown in **Table 7**.

Table 7– Acceptance criteria for HIV-1/2 RDTs

Specimen type	Acceptance criteria for RDTs
4x HIV-1 dilutions	All triplicates to be concordant for each specimen. Non-reactive specimen to be non-reactive; most concentrated reactive specimen to be reactive.
1x HIV-2 dilution	All triplicates to be concordant for each specimen. Non-reactive specimen to be non-reactive; most concentrated reactive specimen to be reactive.
2x HIV low seropositive specimens	Both specimens to be reactive.
3x HIV seronegative specimens	All three specimens to be non-reactive.

4.2 DATA ANALYSIS

The testing results should be compared to the acceptance criteria.

Discrepant testing results

If a result falls outside of the acceptance criteria, the following algorithm should be followed.

- Rule out aliquot failure (repeat testing on same aliquot);
- Rule out specimen failure (repeat testing on same specimen from a different aliquot);
- Rule out operator failure (repeat with another operator).
- Rule out quality management system failing of the testing laboratory, e.g. verify refrigerators and freezers that store lot verification testing specimen panels, verify run worksheets for transcription errors.
- Rule out other robustness issues may be related to precise volumes of specimen and running buffer and volume variations with drop vials and disposable pipettes leading to e.g. increased membrane background.

4.3 LOT TESTING REPORT

The technical supervisor shall generate a lot testing report following the format in **Annex 2**. The lot testing report will be sent to the requestor, usually the relevant NRA and WHO, and will be retained by the testing site. In some cases, the requestor may be a procurer or implementing partner, in this case any lot testing report should be copied to the relevant NRA and to WHO when sent to the requestor. For WHO prequalified IVDS, all lot testing reports will be filed with their prequalification files.

Any observations or unexpected outcomes, e. g. instability of specimen or reagent, defects, etc. as well as any deviation from the defined procedures shall be recorded in the lot testing report.

4.4 CONFIDENTIALITY

The protection of all confidential data must be ensured during the lot testing process. The testing reports will remain the property of the NRA (and WHO) which has the mandate to order lot testing. If the NRA wishes, they may release lot verification testing reports to the manufacturer. This will be a requirement when the lot fails to meet the lot testing acceptance criteria.

ANNEX 1 – LOT TESTING DATA COLLECTION FORM

Date tests received	dd/mm/yyyy
Test date	dd/mm/yyyy
Product name	[add product name]
Distributor/imp order name and address	[add name and complete street address, email, phone]
Product code	[add product code]
Expiry date	dd/mm/yyyy
Lot number	[add]
Pre-distribution [tick one]	Post-distribution lot testing [tick one]
Name and signature of operator	
Signature of technical supervisor	

If subjectively read assay – ensure that specimens are run in a randomized manner. This template is for illustrative purposes.

Panel Specimen ID	Test results		Lot testing result	Reference result
	Reading 1	Reading 2		
Expand as required				

ANNEX 2 – TESTING REPORT FORMAT FOR LOT VERIFICATION TESTING

1. General information about the lot testing event

Date tests received	dd/mm/yyyy
Test date	dd/mm/yyyy
Product name	[add]
Distributor/imp order name and address	[add]
Product code	[add product code]
Expiry date	dd/mm/yyyy
Lot number	[add]
Pre-distribution lot testing [tick one]	Post-distribution lot testing [tick one]
Laboratory performing the testing	[name of testing laboratory]
Site test kits were sampled from	[add site name]
Report number	[add report number assigned by testing laboratory]
Report date	dd/mm/yyyy
Responsible person	[add name]

2. Introduction

The objective of lot testing is to verify the performance of the IVD and to ensure that it continues to meet WHO requirements for prequalification⁵⁴ by identifying any form of product failure.

3. Materials and method

The lot testing verification panel of well-characterized specimens constituted of the following specimens. The specimens were characterized with [state test kit name and manufacturer name].

Testing objective	Specimen details	Total
Anti-HIV-1 analytical sensitivity	4 HIV-1 specimens 2-fold dilutions (first non-reactive and last two reactive specimens)	12x3
Anti-HIV-2 analytical sensitivity	1 HIV-2 specimen 2-fold dilutions (first non-reactive and last two reactive specimens)	3x 3
Sensitivity	2 (undiluted) HIV low seropositive specimens	2
Specificity	3 seronegative specimens	3
Grand total		50

The IVD was performed exactly according to manufacturer's instructions for use. For rapid diagnostic tests and other subjectively read assays, the band intensity was scored.

⁵⁴ Or continues to meet the initial performance criteria for pre-market assessment for non-WHO-prequalified IVDs.

POST-MARKET SURVEILLANCE OF IN VITRO DIAGNOSTICS

4. Results and analysis

The evaluation results were interpreted by two technicians, recorded in a standardized data collection worksheet. These data were then transcribed into this lot testing report.

Panel Specimen ID	Test results		Lot testing result	Reference result
	Reading 1	Reading 2		
Series 1, Dilution 1				
Series 1, Dilution 1				
Series 1, Dilution 1				
Series 1, Dilution 2				
Series 1, Dilution 2				
Series 1, Dilution 2				
Series 1, Dilution 3				
Series 1, Dilution 3				
Series 1, Dilution 3				
Series 2, Dilution 1				
Series 2, Dilution 1				
Series 2, Dilution 1				
Series 2, Dilution 2				
Series 2, Dilution 2				
Series 2, Dilution 2				
Series 2, Dilution 3				
Series 2, Dilution 3				
Series 2, Dilution 3				
Series 3, Dilution 1				
Series 3, Dilution 1				
Series 3, Dilution 1				
Series 3, Dilution 2				
Series 3, Dilution 2				

POST-MARKET SURVEILLANCE OF IN VITRO DIAGNOSTICS

Panel Specimen ID	Test results		Lot testing result	Reference result
	Reading 1	Reading 2		
Series 3, Dilution 2				
Series 3, Dilution 3				
Series 3, Dilution 3				
Series 3, Dilution 3				
Series 4, Dilution 1				
Series 4, Dilution 1				
Series 4, Dilution 1				
Series 4, Dilution 2				
Series 4, Dilution 2				
Series 4, Dilution 2				
Series 4, Dilution 3				
Series 4, Dilution 3				
Series 4, Dilution 3				
Series 5, Dilution 1				
Series 5, Dilution 1				
Series 5, Dilution 1				
Series 5, Dilution 2				
Series 5, Dilution 2				
Series 5, Dilution 2				
Series 5, Dilution 3				
Series 5, Dilution 3				
Series 5, Dilution 3				
HIV +				
HIV +				
HIV -				
HIV -				
HIV -				

POST-MARKET SURVEILLANCE OF IN VITRO DIAGNOSTICS

5. Acceptance criteria

Specimen type	Acceptance criteria for RDTs
4x HIV-1 dilution series	All triplicates to be concordant for each specimen. First non-reactive specimen to be non-reactive, last reactive specimen to be reactive.
1x HIV-2 dilution series	All triplicates to be concordant for each specimen. First non-reactive specimen to be non-reactive, last reactive specimen to be reactive.
2x HIV seropositive specimens	Both specimens to be reactive.
3x HIV seronegative specimens	All three specimens to be non-reactive.

Lot testing specimens	Lot number [add lot number]
HIV-1 dilution series #1	[Pass/Fail]
HIV-1 dilution series #2	[Pass/Fail]
HIV-1 dilution series #3	[Pass/Fail]
HIV-1 dilution series #4	[Pass/Fail]
HIV-2 dilution series	[Pass/Fail]
Undiluted HIV seropositives	[Pass/Fail]
HIV seronegatives	[Pass/Fail]

6. Conclusion

Lot number [add] of [add assay name] with expiry date [add] was tested on [dd/mm/yyyy]. The results showed that this lot produced acceptable results for the lot verification testing panel. *Any unexpected outcomes, e. g. instability of reagent, defects, software errors etc. as well as any deviation from the defined procedures shall be properly recorded and be part of the evaluation report.*

ANNEX 3 – IVD COMPLAINT REPORTING FORM

USER COMPLAINT FORM FOR REPORTING COMPLAINTS AND/OR ADVERSE EVENTS RELATED TO IN VITRO DIAGNOSTICS

Send to: Manufacturer

If serious or moderate adverse event, report to the relevant National Regulatory Authority and WHO Prequalification of In Vitro Diagnostics Programme

Email: diagnostics@who.int

Report Number:	Date received :
----------------	-----------------

1. Contact details of the reporting person/organization

Name of person/organization:	Street Name and No.:
City and postcode:	Country:
Telephone:	Fax:
Name and position of contact person:	Email of contact person:
Report date:	Site report number:

2. Product details

Product name/commercial name/brand name:	Product code (catalogue number)(s):
Lot number/batch number/serial number:	Expiry date:
Associated devices/accessories (lot numbers/expiry dates):	Instructions for use version number:
Distributor name and address:	Manufacturer name and address:

Please attach a copy of the instructions for use.

3. Event/problem details

Event/problem description narrative (explain what went wrong with the product and the observed or likely/probable consequences):	
Date of the event/problem:	Number of tests involved:
Event classification: <input type="checkbox"/> Serious <input type="checkbox"/> Moderate <input type="checkbox"/> Mild <input type="checkbox"/> Other (specify):	% of tests involved :
	Number of patients involved:
Operator/user at the time of the event/problem (please choose): <input type="checkbox"/> Laboratory technician/technologist <input type="checkbox"/> (Non-laboratory) health worker <input type="checkbox"/> Other (specify):	Has more than one user experienced the problem with the product? <input type="checkbox"/> Yes <input type="checkbox"/> No
Type of specimen used (please specify):	State reading time used:
Have you informed the distributor? <input type="checkbox"/> Yes <input type="checkbox"/> No	Date:
	What measures have been recommended?
Have you informed the manufacturer? <input type="checkbox"/> Yes <input type="checkbox"/> No	Date:
	What measures have been recommended?
Measures taken by the operator/user:	
Comments:	
Date of report:	Signature:

Annex 3 – Disclaimer: The act of reporting an event is not an admission of manufacturer, user or patient liability for the event or its consequences. Submission of an adverse event report does not, in itself, represent a conclusion by the manufacturer that the content of this report is complete or confirmed, that the device(s) listed failed in any manner. It is also not a conclusion that the device caused or contributed to the adverse event.

ANNEX 4 – ADVERSE EVENT MANUFACTURER INVESTIGATION REPORTING FORM

ADVERSE EVENT INVESTIGATION REPORTING FORM FOR IN VITRO DIAGNOSTICS

Send to:

The relevant National Regulatory Authority and WHO Prequalification of In Vitro Diagnostics Programme
World Health Organization, 20 Avenue Appia CH-1211, Geneva 27 Switzerland

Email: diagnostics@who.int

1. Recipient details

Name of recipient organization:	
Street Name and No.:	City and postcode:
Country:	Telephone:
Name and position of recipient contact person:	Email of contact person:
Event reference number assigned by the manufacturer:	Report reference number assigned by NRA:
Date of this report:	
Type of report: <input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up report <input type="checkbox"/> Combined initial and final report <input type="checkbox"/> Final report	Classification of event: <input type="checkbox"/> Serious <input type="checkbox"/> Moderate <input type="checkbox"/> Mild <input type="checkbox"/> Other (specify)
State any other NRAs who were also sent this report:	

2. Submitter details

Name of submitter (manufacturer; distributor, other):	
Street Name and No.:	City and postcode:
Country:	Telephone:
Contact person for submitter:	Email of contact person:

3. Product details

Product name:
Product code (catalogue number):
Lot number/batch number/serial number:
Expiry date:
Associated devices/accessories (lot numbers/expiry dates):
Instructions for use version number:

Please attach a copy of the instructions for use.

4. Event/problem details

Where did the event happen:	
Date(s) event happened:	
Date complaint reported to manufacturer (and/or distributor):	
Event/problem description narrative (explain what went wrong with the product and the observed or likely/probable consequences):	
Number of tests involved:	% of tests involved :
Operator/user at the time of the event/problem (please choose): <input type="checkbox"/> Laboratory technician/technologist <input type="checkbox"/> (Non-laboratory) health worker <input type="checkbox"/> Other (specify):	Has more than one user experienced the problem with the product? <input type="checkbox"/> Yes <input type="checkbox"/> No

5. Manufacturer's preliminary comments (initial/follow-up reports)

Manufacturer's preliminary analysis of event:
Initial corrective action/ preventive action implemented by manufacturer:
Expected date of next report:

6. Results of the final investigation (final report)

Manufacturer's analysis of event:
Remedial action, corrective action, preventive action/Field Safety Corrective Action:
Time schedule for implementation of the identified actions:
Final comments from the manufacturer:
Further investigations:
Is the manufacturer aware of similar events with this IVD with a similar root cause? <input type="checkbox"/> Yes <input type="checkbox"/> No
If yes, state in which countries: If yes, number of similar incidents:
State which countries this report has been disseminated to:

7. Signature

Name:
Signature:
Date:

ANNEX 5 – FIELD SAFETY CORRECTIVE ACTION REPORT FORM

FIELD SAFETY CORRECTIVE ACTION REPORTING FORM FOR IN VITRO DIAGNOSTICS

Send to:

The relevant National Regulatory Authority and
WHO Prequalification of In Vitro Diagnostics Programme
World Health Organization, 20 Avenue Appia CH-1211, Geneva 27, Switzerland
Email: diagnostics@who.int

1. Recipient details

Date of this report:	
Type of report: <input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up report <input type="checkbox"/> Final report	
FSCA reference number assigned by NRA:	
Name of recipient organization:	
Name of contact person:	Email of contact person:
Street and No.:	City and postcode:
Country:	Telephone:

2. Manufacturer details

Name of manufacturer:	
Street and No.:	City and postcode:
Country:	Telephone:
Name of contact person:	Email of contact person:
Reference number assigned by the manufacturer:	

3. Product details

Product name:
Product code (catalogue number):
Lot number/batch number/serial number:
Expiry date:
Associated devices/accessories (lot numbers/expiry dates):
Instructions for use version number:

Please attach a copy of the instructions for use.

4. FSCA description

Background information and reason for the FSCA:	
Description and justification of action (corrective/preventive):	
Date complaint reported to manufacturer (and/or distributor):	
Advice on actions to be taken by distributor and the user:	
Field Safety Notice attached: <input type="checkbox"/> Yes <input type="checkbox"/> No	Status of FSN: <input type="checkbox"/> Draft <input type="checkbox"/> Final
Time schedule for implementation of different actions:	
List of countries this FSCA has been distributed to:	

5. Comments

--

6. Signature

Name:
Signature:
Date:

ANNEX 6 – EXAMPLE FIELD SAFETY NOTICE

URGENT FIELD SAFETY NOTICE

Product name: [insert name of the affected product]

FSCA-identifier: [insert]

Type of action: [e.g. return of IVD to supplier, IVD modification (including instructions for use), IVD exchange, IVD destruction, retrofit of IVD by purchaser or manufacturers modification or design change, advice given by manufacturer regarding use of the IVD and/or follow-up of patients, users, or others].

Date: dd/mm/yyyy

Attention: [insert intended audience]

Details on affected IVD:

[Specific details to easily identify the affected IVD e.g. product name, product code, lot number]

Description of the problem:

[A factual statement explaining the reasons for the FSCA, including description of the problem and a clear description of the potential hazard associated with the continued use of the IVD and the associated risk to the patient, user or other person.]

Advice on action to be taken by the user: [include, as appropriate]

- Identifying and quarantining the device;
- Method of recovery, disposal or modification of device, including instructions for use and labelling;
- Recommended patient follow up;
- Timelines;
- Confirmation form to be sent back to the manufacturer.

The above recommended action(s) are to be taken by all recipients of this FSN, including action(s) recommended for people that have previously used or been treated by affected IVDs.

Transmission of this Field Safety Notice: [as appropriate]

This notice needs to be passed on all those who need to be aware within your organization or to any organization where the potentially affected product has been transferred. Please be aware of this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action.

Contact person for further information:

[Insert name, organization, address, contact details]

The undersigned confirms that this notice has been notified to the appropriate National Regulatory Authorities.

Signature:

ANNEX 7 – POST-MARKET INFORMATION EXCHANGE REPORTING FORM FOR NRAS

The following information exchange reporting form should be used by NRAs for sharing post-market surveillance data on IVDs gathered through pre-distribution lot testing or post-distribution lot testing, vigilance procedures or analysis of EQA and QC programme data. This reporting form should be completed and the relevant lot testing report and initial/final investigation report or FSCA report attached to it.

This form is adapted from the document “Medical Devices: Post Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form” (IMDRF/NCAR WG (PD1)/N14R4 proposed by the International Medical Device Regulatory Forum (IMDRF). The document describes a system for NRAs to exchange confidential information about safety, quality and performance of IVDs where there is an anticipated or unanticipated serious public health threat, defined as:

Death of a patient, user or other person;

Serious injury of a patient, user or other person;

No death or serious injury occurred but the event might lead to death or serious injury of a patient, user or other person if the event recurs.

This programme is used to exchange early information on significant concerns or potential trends that individual NRAs have observed, but that have not yet resulted in FSCA or recall. Participation currently includes the regulators from Australia, Brazil, Canada, China, Europe, Japan, Russia and the United States of America.

POST-MARKET INFORMATION EXCHANGE REPORTING FORM FOR NRAS

1. Report details

NRA report number:
Purpose of exchange: <input type="checkbox"/> Share information <input type="checkbox"/> Events leading or highly likely to lead to unanticipated public health threat <input type="checkbox"/> Observations from national trend analysis <input type="checkbox"/> Request information <input type="checkbox"/> Summary of query findings
Confidentiality: <input type="checkbox"/> Yes <input type="checkbox"/> No

2. Details of initiating NRA

Name of NRA:	
Name of contact person:	Email of contact person:
Street and No.:	City and postcode:
Country:	Telephone:

6. Details of responding NRA

Name of NRA:	
Name of contact person:	Email of contact person:
Street and No.:	City and postcode:
Country:	Telephone:

7. Signature

Name:
Signature:
Date:



CONTACT

Department of Essential Medicines and Health Products

World Health Organization

20 Avenue Appia

CH-1211 Geneva 27

Switzerland

E-mail: diagnostics@who.int

www.who.int/diagnostics_laboratory

978 92 4 1509213



Prequalification Team-Diagnostics