WHO PREQUALIFICATION TEAM:
DIAGNOSTICS

World Health Organization

Technical Guidance Series for WHO prequalification of in vitro diagnostic medical devices

Standards applicable to the WHO Prequalification of in vitro diagnostic medical devices

TGS–1

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WHO Prequalification Programme: IVD Technical Guidance Series

WHO Prequalification of IVDs

The WHO Prequalification Programme is coordinated through the Department of Essential Medicines and Health Products. WHO prequalification of in vitro diagnostics (IVDs) is intended to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. The focus is on IVDs for priority diseases and their suitability for use in resource-limited settings. The WHO Prequalification Programme undertakes a comprehensive assessment of individual IVDs through a standardized procedure that is aligned with international best regulatory practice. It also undertakes post-qualification activities for IVDs to ensure their ongoing compliance with prequalification requirements.

Procurement of prequalified IVDs

Products that are prequalified by WHO are eligible for procurement by United Nations agencies. The products are then commonly purchased for use in low- and middle-income countries.

Prequalification requirements

IVDs prequalified by WHO are expected to be accurate, reliable and able to perform as intended for the lifetime of the IVD under conditions likely to be experienced by a typical user in resource-limited settings. The countries where WHO-prequalified IVDs are procured often have minimal regulatory requirements, and the use of IVDs in these countries presents specific challenges. For instance, IVDs are often used by health-care workers who do not have extensive training in laboratory techniques, in harsh environmental conditions, in the absence of extensive pre- and post-test quality assurance capacity, and for patients with a disease profile that differs from the profiles encountered in high-income countries. Therefore, the requirements of the WHO Prequalification Programme may differ from the requirements of high-income countries, or those of the regulatory authority in the country of manufacture.

About the Technical Guidance Series

The Technical Guidance Series (TGS) was developed following a consultation held on 10–13 March 2015 in Geneva, Switzerland. The consultation was attended by experts from national regulatory authorities, national reference laboratories and WHO prequalification dossier reviewers and inspectors. The guidance series is a result of the efforts of this and other international working groups.

Audience and scope

This guidance is intended for manufacturers interested in WHO prequalification of their IVD. It applies in principle to all IVDs that are eligible for WHO prequalification for use in WHO Member States. This guidance should be read in conjunction with relevant international and national standards and guidance.

The TGS guidance documents are freely available on the WHO website.

Contents

Acknowledgements

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1 Abbreviations

21 CFR	Title 21 of the US Code of Federal Regulations
AHWP	Asian Harmonization Working Party
ANSI/ASQ/CEN	American National Standards Institute /American Society for Quality/European Committee for Standardization
ANSI/AAMI/IEC	American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Electrotechnical Commission
ASTM	ASTM International
CEN	European Committee for Standardization
Cenelec	European Committee for Electrotechnical Standardization
CLSI	Clinical and Laboratory Standards Institute
FDA	US Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GHTF	Global Harmonization Task Force
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
IVD	In vitro diagnostic medical device
TDR	Special Programme for Research and Training in Tropical Diseases
TGA	Australian Government Department of Health Therapeutic Goods Administration
USP	United States Pharmacopeia
WHO / FIND / TDR / Roll Back Malaria	World Health Organization/ Foundation for Innovative New Diagnostics/ Special Programme for Research and Training in Tropical Diseases/Roll Back Malaria Partnership

2 Definitions

The definitions given below apply to the terms used in this document. They may have different meaning in other contexts.

Essential Principles of Safety and Performance ("Essential Principles"): The fundamental design and manufacturing principles relating to an in vitro diagnostic.
Source: (1)

In vitro diagnostic (IVD)medical device: A medical device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.
NOTE 1: IVDs include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.
Source: (2)

Standard: A document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context.
NOTE 1: Standards should be based on the consolidated results of science, technology and experience, and aimed at the promotion of optimum community benefits.
Source: (3)
NOTE 2: Standards include such guidance documents as standards, codes, specifications, handbooks and guidelines. This term is not to be mistaken as referring to a sample for calibration or control.
Recognized standard: Standard deemed to offer the presumption of conformity to specific Essential Principles of Safety and Performance.
Source: (3)

3 Introduction

3.1 Key concepts

This document identifies standards and guidance that contains valuable information on a range of issues that are encountered in the manufacture, verification, and validation of in vitro diagnostics medical devices (IVDs). This document should not be taken as a prescriptive checklist of all references, but those identified are most widely applicable to the IVDs that are assessed for WHO prequalification. The tables reference international standards, global[1], national, and regional and industry standards and regulatory authority guidelines. The tables will be updated as more standards and guidance are published, updated or superseded. In addition, there are links to useful websites from standards organizations and mature regulatory authorities that reference additional standards and guidance documents to consider.

3.2 Purpose of this document

The purpose of this document is to:

- provide IVD manufacturers and regulators of IVDs with references to standards and guidance that are applicable to IVDs ; and
- encourage manufacturers to use appropriate international standards when demonstrating the IVD conforms to relevant essential safety and performance principles.

[1] Standards that, while not being international standards, have gained acceptance in many parts of the world.

4 Use of standards

4.1 General principles

International guidance and standards specify in detail how regulatory compliance with the Essential Principles of Safety and Performance for in vitro diagnostics (IVDs) can be achieved. They are building blocks for harmonized regulatory processes to assure the safety, quality and performance of IVDs. They represent the opinion of experts from all interested parties, including industry, regulators, users and others. International standards should thus be used by the manufacturers to assure the safety, quality and performance of medical devices and should be recognized by regulatory authorities as a means to harmonize regulatory processes.

WHO Prequalification – Diagnostic Assessment team follows internationally recognized practices in its assessment of a product, and has a focus on identifying if a product for prequalification will meet the Essential Principles of Safety and Performance (hereafter referred to as Essential Principles) when used in WHO Member States. WHO assessment therefore recognizes the use of international standards as a means for a manufacturer to demonstrate compliance with the Essential Principles and for the verification and validation of their IVD.

Standards should represent the generally acknowledged state of technology and practice. However, the preference for the use of recognized standards should not discourage the introduction of new technologies. Not all IVDs, or elements of safety and/or performance, may be addressed by recognized standards, especially for new types of IVDs and emerging technologies.

4.2 Alternatives to international standards

In the absence of international standards or guidance, national, regional or industry standards are another means of demonstrating conformity. For certain issues, relevant international standards may not be available, are impractical or lacking in detail. In these situations, recognized national guidance developed by stringent regulatory authorities should be used as a reference. Guidance documents developed by such regulatory bodies have been included in the list below for this purpose.

Manufacturers may use alternative solutions or standards not listed in this guidance document to demonstrate their IVD meets the relevant Essential Principles (e.g. national standards, industry agreed methods, internal manufacturer standard operating procedures). The acceptability of such other solutions should be justified and may be subject to review by WHO as part of the product assessment, as appropriate.

4.3 Use of standards by manufacturers

When using standards to demonstrate conformity to the Essential Principles and other requirements, the manufacturer should:

- Identify the version and date of the relevant recognized standard(s) in its technical documentation.
- Retain documentation to demonstrate that the device conforms to the standard or the Essential Principles or alternatively include a declaration of conformity to a recognized standard in the technical documentation to substitute for the source document itself.

If the standard used by the manufacturer is a superseded version of the recognized standard, the manufacturer is not required to take any action unless there are safety implications, in which case the manufacturer should implement a risk mitigation strategy and take appropriate action to address these safety concerns.

If a manufacturer chooses not to apply a recognized standard in part or in full, this may be acceptable if conformity with the Essential Principles can be demonstrated by another means and/or the manufacturer can demonstrate that the standard or its parts are not applicable to the IVD under assessment.

5 Tables of standards

The tables below contain a list of applicable standard and guidance documents and have been divided into the various stages in IVD design, manufacture and post market activities. The tables list the source of the guidance document, the document number if applicable, the document name and the date published. The following international standards and guidance documents are given preference and listed in the order below in the tables

1. WHO,
2. Global Harmonization Task Force (GHTF)
3. International Medical Device Regulators Forum (IMDRF)
4. Asian Harmonization Working Party (AHWP)
5. International Organization for Standardization (ISO),
6. International Electrotechnical Commission (IEC), and
7. Clinical and Laboratory Standards Institute (CLSI).

National, regional or industry standards and guidance documents are an alternative when international standards are not suitable or available and are listed in the latter part of the following tables in italics.

5.1 Vocabulary

Source	Document number	Document name	Date published
GHTF	GHTF/SC/N4:2012 (Edition 2)	Glossary and Definitions of Terms Used in GHTF Documents	Nov-2012
ISO/IEC	ISO/IEC Guide 99:2007	International vocabulary of metrology -- Basic and general concepts and associated terms (VIM)	Dec-2007
ISO	ISO 9000:2015	Quality management systems – Fundamentals and vocabulary	Sep-2015
ISO	ISO 3534-1:2006	Statistics -- Vocabulary and symbols -- Part 1: General statistical terms and terms used in probability	Oct-2006
ISO	ISO 3534-2:2006	Statistics -- Vocabulary and symbols -- Part 2: Applied statistics	Sep-2006
ISO	ISO 3534-3:2013	Statistics -- Vocabulary and symbols -- Part 3: Design of experiments	Apr-2013

5.2 IVD design

Source	Document number	Document name	Date published
IEC	IEC 62366:2015	Medical devices—Part 1: Application of usability engineering to medical devices	Feb-2015
IEC/TR	IEC/TR 62366-2:2016	Medical devices -- Part 2: Guidance on the application of usability engineering to medical devices	Apr-2016
CLSI	MM03-Ed3	Molecular Diagnostic Methods for Infectious Diseases, 3rd Edition	Feb-2015
CLSI	MM06-A2	Quantitative Molecular Methods for Infectious Diseases; Approved Guideline - Second Edition	Nov-2010
CLSI	MM09-A2	Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine; Approved Guideline—Second Edition	Feb-2014
CLSI	MM12-A	Diagnostic Nucleic Acid Microarrays; Approved Guideline	May-2006
CLSI	MM16-A	Use of External RNA Controls in Gene Expression Assays; Approved Guideline	Aug-2006
CLSI	MM17-A	Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline	Mar-2008
CLSI	MM22-A	Microarrays for Diagnosis and Monitoring of Infectious Diseases; Approved Guideline	Feb-2014
CLSI	M53-A	Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline	Jun-2011
CLSI	I/LA18-A2	Specifications for Immunological Testing for Infectious Diseases; Approved Guideline	Sept-2001
CLSI	POCT04-A2	Point-of-Care In Vitro Diagnostic (IVD) Testing; Approved Guideline—Second Edition	Aug-2006
CLSI	POCT09-A	Selection Criteria for Point-of-Care Testing Devices; Approved Guideline	Apr-2010
CEN	*EN 13641:2002*	*Elimination or reduction of risk of infection related to in vitro diagnostic reagents*	*Dec-2002*
FDA	*1546*	*Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems - Guidance for Industry and FDA Staff*	*Mar-2005*
FDA	*1620*	*Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests*	*Mar-2007*
FDA	*2231*	*Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material*	*Jun-2007*
FDA	*1646*	*Class II Special Controls Guidance Document: Plasmodium Species Antigen Detection Assays*	*May-2008*
FDA	*1737*	*In Vitro Companion Diagnostic Devices*	*Aug-2014*

5.3 Risk

Source	Document number	Document name	Date published
GHTF	N045:2008	GHTF SG1 - Principles of In Vitro Diagnostic (IVD) Medical Devices Classification	Feb-2008
ISO	ISO 14971:2007	Medical Devices – Application of Risk Management to Medical Devices	Mar-2007
ISO	ISO/TR 24971:2013	Medical devices -- Guidance on the application of ISO 14971	Jun-2013
ISO	ISO 14001:2004	Environmental management systems -- Requirements with guidance for use	Nov-2004
ISO	Guide 73:2009	Risk management — Vocabulary	Nov-2009
IEC	IEC31010:2009	Risk management – Risk assessment techniques	Nov-2009
ISO	ISO 31000:2009	Risk management — Principles and guidelines	Nov-2009
FDA	*1772*	*Guidance for Industry and FDA Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications (PDF - 827KB)*	*Mar-2012*

5.4 Manufacturing

Source	Document number	Document name	Date published
WHO	TGS 4	DRAFT Guidance on Test Method Validation of in vitro diagnostic medical devices	Dec-2016
WHO	WHO TRS 996 Annex 5	Fiftieth report of the WHO Expert Committee on specifications for pharmaceutical preparations. (WHO technical report series ; no. 996) Guidance on good data and record management practices	May 2016
ISO	ISO 15198:2004	Clinical Laboratory Medicine - In Vitro Diagnostic Medical Devices - Validation of User Quality Control Procedures by the Manufacturer	Mar-2004
CLSI	EP18-A2	Risk Management Techniques To Identify And Control Laboratory Error Sources; Approved Guideline - Second Edition.	Nov-2009
ANSI/ ASQ	*ANSI/ASQ Z1.4–2003 (R2013)*	*Sampling Procedures and Tables for Inspection by Attributes*	*2013*
CEN	*EN 13975:2003*	*Sampling procedures used for acceptance testing of in vitro diagnostic medical devices - Statistical aspects*	*Nov-2003*
Cenelec	*EN 61010-2-101:2002*	*Safety requirements for electrical equipment for measurement, control, and laboratory use - Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment*	*Dec-2002*
Cenelec	*EN 61326-2-6:2006*	*Electrical equipment for measurement, control and laboratory use - EMC requirements - Part 2-6: Particular requirements - In vitro diagnostic (IVD) medical equipment*	*Nov-2008*

5.5 Quality systems

Source	Document number	Document name	Date published
GHTF	GHTF/SG3/N19:2012	Quality Management System - Medical Devices - Nonconformity Grading System for Regulatory Purposes and Information Exchange	2-Nov-2012
GHTF	GHTF/SG3/N18:2010	Quality Management System - Medical Devices - Guidance on Corrective Action and Preventive Action and Related QMS Processes	4-Nov-2010
GHTF	GHTF/SG3/N17:2008	Quality Management System - Medical Devices - Guidance on the Control of Products and Services Obtained from Suppliers	11-Dec-2008
GHTF	SG3 N15R8	Implementation of Risk Management Principles and Activities within a Quality Management System	20-May-2005
GHTF	GHTF/SG3/N99-10:2004	Quality Management Systems - Process Validation Guidance	02-Jan-2004
GHTF	GHTF/SG4/N30:2010	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 2: Regulatory Auditing Strategy	27-Aug-2010
GHTF	GHTF/SG4/N83:2010	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 4: Multiple Site Auditing	27-Aug-2010
GHTF	GHTF/SG4/N84:2010	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 5: Audits of Manufacturer Control of Suppliers	27-Aug-2010
GHTF	GHTF/SG4/N28R4:2008	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 1: General Requirements	27-Aug-2008
GHTF	GHTF-SG4-N33 R16	Guidelines for Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers - Part 3: Regulatory Audit Reports	02-Oct-2007
GHTF	GHTF-SG4-(00)3	Training Requirements for Auditors	24-Feb-2000
ISO	ISO 13485:2016	Medical devices - Quality management systems - Requirements for regulatory purposes	1Mar-2016
ISO	ISO 9000:2015	Quality management systems – Fundamentals and vocabulary	15-Sep-2015
ISO	ISO 9001:2015	Quality management systems - Requirements	15-Sept-2015
CLSI	QMS02-A6	Quality Management System: Development and Management of Laboratory Documents; Approved Guideline - Sixth Edition	28-Feb-2003
CLSI	POCT07-A	Quality Management: Approaches to Reducing Errors at the Point of Care; Approved Guideline	7-Oct-2010
CLSI	EP18-A2	Risk Management Techniques To Identify And Control Laboratory Error Sources; Approved Guideline - Second Edition.	Nov-2009

Source	Document number	Document name	Date published
FDA	*21 CFR Part 820*	*Quality System Regulation*	
CEN	*EN 13975:2003*	*Sampling Procedures Used for Acceptance Testing of In Vitro Diagnostic Medical Devices - Statistical Aspects*	*21-Nov-2003*

5.6 Pre-market evaluation

Source	Document number	Document name	Date published
GHTF	GHTF/SG1/N68:2012	Essential Principles of Safety and Performance of Medical Devices	Nov-2012
GHTF	SG1 N071:2012	Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic Medical Device'	May-2012
GHTF	GHTF/SG1/N063:2011	Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices	Mar-2011
GHTF	GHTF/SG1/N065:2010	Registration of Manufacturers and Other Parties and Listing of Medical Devices	Aug-2010
GHTF	GHTF/SG1/N055:2009	Definition of the Terms Manufacturer, Authorised Representative, Distributor and Importer	Mar-2009
GHTF	N046:2008	Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices	Jul-2008
GHTF	N044:2008	GHTF SG1 - Standards in the Assessment of Medical Devices	Mar-2008
IMDRF	IMDRF/RPSWG/N13 FINAL:2014	In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)	Aug-2014
ISO	16142-2	Medical devices - Recognized essential principles of safety and performance of medical devices - Part 2: General essential principles and additional specific essential principles for all IVD medical devices and guidance on the selection of standards	Sept-2016
FDA	*1584*	*Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision*	*Dec-2008*
FDA	*21 CFR Part 809*	*In Vitro Diagnostic Products for Human Use*	

5.7 Analytical performance

Source	Document number	Document name	Date published
WHO	TGS-3 Draft for public comment	Principles of performance studies of an in vitro diagnostic for WHO Prequalification	May-2016
WHO	TSS-1 ISBN 978-92-4-151174-2	Technical Specifications Series for submission to WHO Prequalification – Diagnostic Assessment: Human Immunodeficiency Virus (HIV) rapid diagnostic tests for professional use and/or self-testing	Dec-2016
WHO	TSS-2 ISBN 978-92-4-151186-5	Technical Specifications Series for submission to WHO prequalification – diagnostic assessment: in vitro diagnostics medical devices to identify Glucose-6-phosphate dehydrogenase (G6PD) activity	Dec-2016
WHO	TSS-3 ISBN 978-92-4-151227-5	Technical Specifications Series for submission to WHO prequalification – diagnostic assessment: Malaria rapid diagnostics tests	Dec-2016
ISO	ISO 15193:2009	In Vitro Diagnostic Medical Devices – Measurement of Quantities in Samples of Biological Origin – Requirements for Content and Presentation of Reference Measurement Procedures	May-2009
ISO	ISO 16269-4:2010	Statistical interpretation of data - Part 4: Detection and treatment of outliers	Oct-2010
ISO	ISO 16269-6:2014	Statistical interpretation of data - Part 6: Determination of statistical tolerance intervals	Jan-2014
ISO	ISO 16269-7:2001	Statistical interpretation of data - Part 7: Median - Estimation and confidence intervals	Mar-2001
ISO	ISO 16269-8:2004	Statistical interpretation of data -- Part 8: Determination of prediction intervals	Sep-2004
ISO	ISO 17511:2003	In Vitro Diagnostic Medical Devices – Measurement of Quantities In Biological Samples – Metrological Traceability of Values Assigned to Calibrators and Control Materials	Aug-2003
ISO	ISO 5725-1:1994	Accuracy (trueness and precision) of measurement methods and results - Part 1: General principles and definitions	Dec-1994
ISO	ISO 5725-2:1994	Accuracy (trueness and precision) of measurement methods and results - Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method	Dec-1994
ISO	ISO 5725-3:1994	Accuracy (trueness and precision) of measurement methods and results - Part 3: Intermediate measures of the precision of a standard measurement method	Dec-1994

Source	Document number	Document name	Date published
ISO	ISO 5725-4:1994	Accuracy (trueness and precision) of measurement methods and results - Part 4: Basic methods for the determination of the trueness of a standard measurement method	Dec-1994
ISO	ISO 5725-5:1998	Accuracy (trueness and precision) of measurement methods and results - Part 5: Alternative methods for the determination of the precision of a standard measurement method	Jul-1998
ISO	ISO 5725-6:1994	Accuracy (trueness and precision) of measurement methods and results - Part 6: Use in practice of accuracy values	Dec-1994
CLSI	C24-A3	Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition	Jun-2006
CLSI	EP05-A3	Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition	Oct-2014
CLSI	EP06-A	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline	Apr-2003
CLSI	EP07-A2	Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition	Nov-2005
CLSI	EP09-A3	Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition	Aug-2013
CLSI	EP12-A2	User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline— Second Edition	Jan-2008
CLSI	EP15-A3	User Verification of Precision and Estimation of Bias; Approved Guideline - Third Edition	Sep-2014
CLSI	EP17-A2	Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition	Jun-2012
CLSI	EP18-A2	Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition	Nov-2009
CLSI	EP21-A	Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline	Apr-2003
CLSI	EP26-A	User Evaluation of Between-Reagent Lot Variation; Approved Guideline	Sep-2013
CLSI	EP27-A	How to Construct and Interpret an Error Grid for Quantitative Diagnostic Assays; Approved Guideline	Sep-2012
CLSI	EP28-AC3	Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition	Oct-2010

Source	Document number	Document name	Date published
CLSI	EP29-A	Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline	Jan-2012
CLSI	EP30-A	Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline	May-2010
CLSI	EP32-R	Metrological Traceability and Its Implementation; A Report	Feb-2006
CLSI	I/LA30-A	Immunoassay Interference By Endogenous Antibodies; Approved Guideline	Mar-2009
CLSI	MM17-A:2008	Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline	Mar-2008
ICH	*Q6B Current Step 4 version.*	*ICH Harmonised Tripartite Guideline Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Current Step 4 version*	*Mar-1999*
ICH	*Q6A*	*ICH Harmonised Tripartite Guideline. Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*	*Oct-1999*
European Commiss-ion	*2009/108/EC*	*Commission Decision of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for in vitro-diagnostic medical devices. Official Journal of the European Union; L39/34-L39/49*	*Feb-2009*
Health Canada		*Health Products and Food Branch: Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory*	*Dec-2011*

5.8 Specimen collection and transport

Source	Document number	Document name	Date published
CLSI	MM13-A	Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline	Jan-2005
CLSI	M29-A4	Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Fourth Edition	May-2014
CLSI	GP34-A	Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guideline	Dec-2010
CLSI	GP39-A6	Tubes and Additives for Venous and Capillary Blood Specimen Collection; Approved Standard - Sixth Edition	Dec-2010
CLSI	GP41-A6	Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard - Sixth Edition	Oct-2007
CLSI	GP42-A6	Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard - Sixth Edition	Sept-2008
CLSI	GP44-A4	Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline - Fourth Edition	May-2010
CLSI	NBS01-A6	Blood Collection On Filter Paper For Newborn Screening Programs: Approved Standard - Sixth Edition	Jul-2013
CEN	*EN 14254:2004*	*In Vitro Diagnostic Medical Devices - Single-Use Receptacles for the Collection of Specimens, Other Than Blood, from Humans*	*Apr-2005*
CEN	*EN 14820:2004*	*Single-Use Containers for Human Venous Blood Specimen Collection*	*Apr-2005*
FDA	*1563*	*Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: RNA Preanalytical Systems (RNA Collection, Stabilization and Purification Systems for RT-PCR used in Molecular Diagnostic Testing)*	*Aug-2005*

5.9 Stability

Source	Document number	Document name	Date published
WHO	TGS2 Draft for Comment	Establishing stability of an in vitro diagnostic for WHO Prequalification	Dec-2015
ISO	ISO 23640:2011	In Vitro Diagnostic Medical Devices – Evaluation of Stability of In Vitro Diagnostic Reagents	Jan-2011
CLSI	EP25-A	Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline	Sep-2009
CLSI	M07-A10	Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Tenth Edition	Jan-2015
CLSI	M11-A8	Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard—Eighth Edition	Feb-2012
ASTM	*D4169 – 14*	*Standard Practice for Performance Testing of Shipping Containers and Systems*	*2014*
CEN	*EN 13640:2002*	*Stability testing of in vitro diagnostic reagents*	*Dec-2002*
European Union	*Ph. Eur.*	*European Pharmacopoeia 8th Edition*	*2015*
Peoples Republic of China	*2000*	*Pharmacopoeia of the People's Republic of China. English edition.*	*2000*
USP	*USP 31-NF 26*	*United States Pharmacopeia and National Formulary*	*2008*

5.10 Self-testing considerations

Source	Document number	Document name	Date published
WHO	TSS-1 ISBN 978-92-4-151174-2	Technical Specifications Series for submission to WHO Prequalification – Diagnostic Assessment: Human Immunodeficiency Virus (HIV) rapid diagnostic tests for professional use and/or self-testing	Dec-2016
ISO	ISO 15197:2013	In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus	May-2013
EN	*EN 13532:2002*	*General requirements for in vitro diagnostic medical devices for self-testing*	*May-2002*
FDA	*1756*	*Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use*	*Jan-2014*

5.11 Flex studies (Robustness)

Source	Document number	Document name	Date published
FDA	*1757*	*Guidance for Industry and Food and Drug Administration Staff : Applying Human Factors and Usability Engineering to Medical Devices*	*Feb-2016*
ANSI/AAMI	*HE75:2009/(R)2013*	*2013 Human factors engineering – Design of medical devices*	*Nov-2013*

5.12 Clinical performance

Source	Document number	Document name	Date published
WHO	TGS-3 Draft for public comment	Principles of performance studies of an in vitro diagnostic for WHO Prequalification	May-2016
WHO	TSS-1 ISBN 978-92-4-151174-2	Technical Specifications Series for submission to WHO Prequalification – Diagnostic Assessment: Human Immunodeficiency Virus (HIV) rapid diagnostic tests for professional use and/or self-testing	Dec-2016
WHO	TSS-2 ISBN 978-92-4-151186-5	Technical Specifications Series for submission to WHO prequalification – diagnostic assessment: in vitro diagnostics medical devices to identify Glucose-6-phosphate dehydrogenase (G6PD) activity	Dec-2016
WHO	TSS-3 ISBN 978-92-4-151227-5	DRAFT Technical Specifications Series for submission to WHO prequalification – diagnostic assessment: Malaria rapid diagnostics tests	Dec-2016
GHTF	GHTF/SG5/N5:2012	Reportable Events During Pre-Market Clinical	Aug-2012

		Investigations	
GHTF	GHTF/SG5/N6:2012	Clinical Evidence for IVD Medical Devices - Key Definitions and Concepts	Nov-2012
GHTF	GHTF/SG5/N7:2012	Clinical Evidence for IVD Medical Devices - Scientific Validity Determination and Performance Evaluation	Nov-2012
GHTF	GHTF/SG5/N8:2012	Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices	Nov-2012
ISO	ISO 14155:2011	Clinical investigation of medical devices for human subjects -- Good clinical practice	Feb-2011
ISO	ISO 22870:2006	Point-of-care testing (POCT) -- Requirements for quality and competence	Feb-2006
ISO	ISO 15189:2012	Medical laboratories -- Requirements for quality and competence	Nov-2011
CLSI	EP09-A3	Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition	Aug-2013
CLSI	EP10-A3-AMD	Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline - Third Edition	May-2014
CLSI	EP12-A2	User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline - Second Edition	-Jan-2008
CLSI	EP14-A3	Evaluation of Commutability of Processed Samples; Approved Guideline - Third Edition	Aug-2014
CLSI	EP24-A2	Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline - Second Edition	Nov-2011
CLSI	I/LA21-A2	Clinical evaluation of immunoassays; Approved guideline	Aug-2008
CEN	*EN 13612:2002/AC:2002*	*Performance Evaluation of In Vitro Diagnostic Medical Devices*	*Dec-2009*
CEN	*EN 13532:2002*	*General requirements for in vitro diagnostic medical devices for self-testing*	*Dec-2002*
European Commiss-ion	*2009/108/EC*	*Commission Decision of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for in vitro-diagnostic medical devices. Official Journal of the European Union; L39/34-L39/49*	*Feb-2009*
FDA	*1587*	*Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions*	*Jun-2010*
World Medical Associati	*Not applicable*	*DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects*	*Oct-2013*

on		
MHRA	*Guidance for notified bodies on the regulation of IVDs for self-testing*	*July 2012*
Health Canada	*Health Products and Food Branch: Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory*	*Dec-2011*
TGA	*Clinical performance requirements and risk mitigation strategies for HIV tests version 1.0*	*Mar-2015*

5.13 Labelling

Source	Document number	Document name	Date published
WHO	TRS No. 970 Annex 4	Forty-sixth report of the WHO Expert Committee on specifications for pharmaceutical preparations. (WHO technical report series ; no. 970) Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part	Jun-2012
WHO / FIND / TDR / Roll Back Malaria		Purchasing and Using RDTs – RDT instructions and training	2009
GHTF	GHTF/SG1/N70:2011	Label and Instruction for Use for Medical Devices	Sept-2011
IMDRF	IMDRF/UDIWG/N7 FINAL:2013	UDI Guidance: Unique Device Identification (UDI) of Medical Devices	Dec-2013
ISO	ISO 18113-1:2009	In Vitro Diagnostic Medical Devices - Information Supplied by the Manufacturer (Labelling) - Part 1: Terms, Definitions and General Requirements	Dec-2009
ISO	ISO 18113-2:2009	In Vitro Diagnostic Medical Devices. Information Supplied by the Manufacturer (Labelling) - Part 2: In Vitro Diagnostic Reagents for Professional Use	Dec-2009
ISO	ISO 18113-3:2009	In Vitro Diagnostic Medical Devices - Information Supplied by the Manufacturer (Labelling) – Part 3: In Vitro Diagnostic Instruments for Professional Use	Dec-2009
ISO	ISO 18113-4:2009	In Vitro Diagnostic Medical Devices – Information Supplied by the Manufacturer (Labelling) – Part 4: In Vitro Diagnostic Reagents for Self-Testing	Dec-2009
ISO	ISO 18113-5:2009	In Vitro Diagnostic Medical Devices – Information Supplied by the Manufacturer (Labelling) – Part	Dec-2009

		5: In Vitro Diagnostic Instruments for Self-Testing	
ISO	ISO 15223-1:2016	Medical Devices – Symbols to be Used with Medical Device Labels, Labelling and Information to be supplied - Part 1: General requirements	02-Nov-2016
FDA	*1128*	*Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers*	*Apr-2001*
FDA		*Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care*	*Aug-1993*
FDA	*2003D-0383*	*Use of Symbols on Labels and in Labelling of In Vitro Diagnostic Devices Intended for Professional Use*	*Nov-2004*
FDA	*1750*	*Guidance for Industry and Food and Drug Administration Staff. Design Considerations for Devices Intended for Home Use*	*Nov-2014*
European Commission	*MEDDEV. 2.14/3 rev.1*	*Guidelines on medical devices. IVD guidances: Supply of Instructions For Use (IFU) and other information for In-vitro Diagnostic (IVD) Medical Devices. A guide for manufacturers and notified bodies*	*Jan-2007*
CEN	*EN 13532:2002*	*General requirements for in vitro diagnostic medical devices for self-testing*	*Dec-2002*
CEN	*EN 980:2008*	*Symbols for use in the labelling of medical devices*	*Jul-2008*
Health Canada		*Guidance Document - Labelling of In Vitro Diagnostic Devices*	*Apr-2016*
MHRA		*Guidance for notified bodies on the regulation of IVDs for self-testing*	*Jul-2012*

5.14 Software

Source	Document number	Document name	Date published
IMDRF	IMDRF/SaMDWG/ N12 FINAL:2014	Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations	18-Sep-2014
IMDRF	IMDRF/SaMDWG/ N10 FINAL:2013	Software as a Medical Device (SaMD): Key Definitions	18-Dec-2013
IEC	IEC 62304:2006-Ed.1.0	Medical Device Software - Software Life Cycle Processes	May-2006
ANSI/ AAMI/ IEC	TIR80002-1:2009	Medical device software – Part 1: Guidance on the application of ISO 14971 to medical device software	24-Dec-2009
CLSI	AUTO11-A2	Information Technology Security of In Vitro Diagnostic Instruments and Software Systems; Approved Standard - Second Edition	31-Oct-2014
CLSI	AUTO13-A2	Laboratory Instruments and Data Management Systems: Design of Software User Interfaces and End-User Software Systems Validation, Operation, and Monitoring; Approved Guideline—Second Edition	
FDA	*337*	*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*	*11-May-2005*
FDA	*585*	*Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices*	*09-Sep-1999*
FDA	*1553*	*Guidance for Industry - Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software*	*14-Jan-2015*
FDA	*1500067*	*Dissemination of Patient-Specific Information from Devices by Device Manufacturers (Draft guidance)*	*10-Jun-2016*
FDA	*1400044*	*Guidance for Industry and Food and Drug Administration Staff: Postmarket Management of Cybersecurity in Medical Devices*	*28-Dec-2016*
European Commission	*MEDDEV 2.1/6*	*Qualification and Classification of Stand Alone Software*	*Jan-2012*

5.15 Post Market Surveillance

Source	Document number	Document name	Date published
WHO	ISBN 978 92 4 150921 3	Post-Market Surveillance of In Vitro Diagnostics	2015
GHTF	SG2 N87:2012	An XML Schema for the Electronic Transfer of Adverse Event Data between Manufacturers, Authorised Representatives and National Competent Authorities (Based on GHTF/SG2/N54: 2006)	27-Jul-2012
GHTF	SG2 N87:2012	XML Schema for Electronic Transfer of Adverse Event Data - XLS	27-Jul-2012
GHTF	GHTF/SG2/N38R19:2009	Application Requirements for Participation in the GHTF National Competent Authority Report Exchange Program	01-Jul-2009
GHTF	GHTF/SG2/N79R11:2009	Medical Devices: Post Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form	17-Feb-2009
GHTF	GHTF/SG2/N54R8:2006	Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices	30-Nov-2006
GHTF	GHTF/SG2/N57R8:2006	Medical Devices Post Market Surveillance: Content of Field Safety Notices	27-Jun-2006
GHTF	GHTF/SG2/N47R4:2005	Review of Current Requirements on Postmarket Surveillance	01-May-2005
GHTF	GHTF/SG2/N68R3:2005	Summary of Current Requirements for Where to Send Adverse Event Reports	01-May-2005
GHTF	GHTF/SG2/N61R4:2004	PMS Harmonization Chart	01-Nov-2004
GHTF	GHTF/SG2/N31R8:2003	Medical Device Postmarket Vigilance and Surveillance: Proposal for Reporting of Use Errors with Medical Devices by their Manufacturer or Authorized Representative	01-Feb-2003
GHTF	GHTF/SG2/N32R5:2002	Medical Device Postmarket Vigilance and Surveillance: Universal Data Set for Manufacturer Adverse Event Reports	01-Feb-2003
GHTF	GHTF/SG2/N9R11:2003	Global Medical Devices Competent Authority Report	01-Jan-2003
GHTF	GHTF/SG2/N36R7:2003	Manufacturer's Trend Reporting of Adverse Events	01-Jan-2003
GHTF	GHTF/SG2/N33R11:2002	Medical Device Postmarket Vigilance and Surveillance: Timing of Adverse Event Reports	27-Sep-2007
GHTF	GHTF/SG2/N6R3:2002	GHTF SG2 - Comparison of the Device Adverse Reporting Systems in USA, Europe, Canada, Australia & Japan	21-May-2002
GHTF	GHTF/SG2/N20R10:2002	GHTF SG2 - Medical Devices: Post Market Surveillance: National Competent Authority Report Exchange Criteria	21-May-2002

Source	Document number	Document name	Date published
GHTF	GHTF-SG2-N008R4	Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices	29-Jun-1999
IMDRF	AE WG(PD1)/N43R1	PROPOSED DOCUMENT IMDRF terminologies for categorized Adverse Event Reporting (AER): terms, terminology structure and codes	22-Jul-2016
IMDRF	IMDRF/NCAR WG/N14 FINAL:2015	Medical Devices: Post-Market Surveillance: National Competent Authority Report Exchange Criteria and Report Form.	26-Mar-2016
ISO	2859-10:2006	Sampling procedures for inspection by attributes - Part 10: Introduction to the ISO 2859 series of standards for inspection by attributes	01-Jul-2006
CEN	*EN 14136:2004*	*Use of external quality assessment schemes in the assessment of the performance of in vitro diagnostic examination procedures*	*15-Nov-2006*
European Commis-ion	*MEDDEV 2.12-1 rev 8 Vigilance*	*Guidelines on a Medical Devices Vigilance System*	*Jan-2013*

5.16 Changes

Source	Document number	Document name	Date published
WHO	WHO/EMP/RHT/PQT/2016.01	Reportable Changes to a WHO Prequalified In Vitro Diagnostic Medical Device	Dec-2016
AHWP	AHWP/WG1/PF002:2016	Guidance for Minor Change Reporting	Nov-2016
NBOG	*NBOG BPG 2014-3*	*Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System*	*Mar-2014*
FDA	*1500054*	*Draft Guidance for Industry and Food and Drug Administration Staff. Deciding When to Submit a 510(k) for a Change to an Existing Device. Center for Biologics Evaluation and Research, MD, USA; 1997*	*08-Aug-2016*
FDA	*1584*	*Guidance for Industry and FDA Staff. Modifications to Devices Subject to Premarket Approval (PMA) – The PMA supplement decision-making process.*	*11-Dec-2008*
FDA	*950*	*Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy*	*11-Dec-2003*
FDA	*FDA-2008-N-0642*	*Assay Migration Studies for In Vitro Diagnostic Devices*	*25-Apr-2013*
FDA	*1584*	*Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision*	*11-Dec-2008*
Health Canada		*Guidance for the Interpretation of Significant Change of a Medical Device*	*20-Jan-2011*

6 Websites with additional information

Source	Website address
AHWP	Reference and guidance documents: http://www.ahwp.info/index.php?q=node/287$ http://www.ahwp.info/index.php?q=taxonomy/term/20
ANSI	Documents available for purchase: http://webstore.ansi.org/
ASTM	Documents available for purchase: https://www.astm.org/Standard/standards-and-publications.html
CLSI	Documents available for purchase: http://shopping.netsuite.com/clsi
European Union and European Commission	IVD directives and the list of harmonized standards (CEN or Cenelec) published in the Official Journal of the European Union http://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/iv-diagnostic-medical-devices/ Medical device guidelines http://ec.europa.eu/growth/sectors/medical-devices/guidance_en
FDA	Complete list of IVD-related guidance documents: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm Device Advice (regulatory information resource for medical device manufacturers) http://www.fda.gov/medicaldevices/deviceregulationandguidance/default.htm
FIND	Training material for Malaria rapid diagnostics tests https://www.finddx.org/implementation-resources/
GHTF and IMDRF	GHTF documents http://www.imdrf.org/ghtf/ghtf-archived-docs.asp IMDRF documents http://www.imdrf.org/documents/documents.asp#imdrf
Health Canada	Therapeutic Products Directorate's List of Recognized Standards for Medical Devices: http://www.hc-sc.gc.ca/dhp-mps/md-im/standards-normes/md_rec_stand_im_norm_lst-eng.php
ICH	Full list of ICH guidelines: http://www.ich.org/products/guidelines.html
IEC	Documents available for purchase: https://webstore.iec.ch/?ref=menu
ISO	Documents available for purchase: http://shopping.netsuite.com/s.nl/c.1253739/sc.7/category.2406/.f
TGA	List of guidance documents https://www.tga.gov.au/standards-guidelines-publications-medical-devices-ivds
USP	Documents available for purchase: http://www.usp.org/products

WHO	WHO Prequalification- Diagnostic assessment documents: http://www.who.int/diagnostics_laboratory/guidance/en/ http://www.who.int/diagnostics_laboratory/evaluations/en/ http://www.who.int/diagnostics_laboratory/postmarket/en/ WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series http://www.who.int/medicines/publications/pharmprep/en/

7 References

1 GHTF/SG1/N68:2012.Essential Principles of Safety and Performance of Medical Devices. Global Harmonization Task Force (GHTF) Steering Committee; 2012.

2 GHTF/SC/N4:2012 (Edition 2). Glossary and Definitions of Terms Used in GHTF Documents. Global Harmonization Task Force (GHTF) Steering Committee; 2012.

3 ISO/IEC Guide 2:2004. Standardization and related activities - General vocabulary. Geneva, International Organization for Standardization/International Electrotechnical Commission; 2004.