WHO PREQUALIFICATION TEAM:
DIAGNOSTICS

World Health Organization

Technical Guidance Series (TGS)

Standards applicable to the WHO Prequalification of in vitro diagnostics

TGS–1

Contents

WHO Prequalification Programme: IVD Technical Guidance Series

WHO Prequalification of IVDs

The World Health Organization (WHO) Prequalification Programme is coordinated through the Department of Essential Medicines and Health Products. The aim of WHO prequalification of in vitro diagnostics (IVDs) is to promote and facilitate access to safe, appropriate and affordable 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. The WHO Prequalification Programme undertakes a comprehensive assessment of individual IVDs through a standardized procedure aligned with international best regulatory practice. In addition, the WHO Prequalification Programme undertakes post-qualification activities for IVDs to ensure the ongoing compliance with prequalification requirements.

Use of prequalified IVDs

Products that are prequalified by WHO are eligible for procurement by United Nations (UN) 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 be able to perform as intended for the lifetime of the IVD under conditions likely to be experienced by a typical user in a resource-limited Member State. The recipient countries of WHO-prequalified IVDs often have minimal regulatory requirements. In addition, the use of IVDs in these countries presents specific challenges. For instance, IVDs are often used by health care workers without extensive training in laboratory techniques, in harsh environmental conditions, without extensive pre- and post-test services, and for patients with a disease profile different to those encountered in high income countries. Therefore, the requirements of the WHO Prequalification Programme may be different to the requirements of high-income countries, and/or of the regulatory authority in the country of manufacture.

About the Technical Guidance Series

The Technical Guidance Series was developed following a consultation, held on 10-13 March 2015 in Geneva, Switzerland 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. It should be read in conjunction with relevant international and national standards and guidance.

The TGS guidance documents are freely available on the WHO web site at http://www.who.int/diagnostics_laboratory/guidance/en/.

1 Introduction

1.1 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 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.

1.2 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.

2 Definitions and abbreviations

2.1 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): 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] definition 3.2
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]

2.2 Abbreviations

21 CFR	Title 21 of the US Code of Federal Regulations
ANSI/ASQ	American National Standards Institute /American Society for Quality
ANSI/AAMI/IEC	American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Electrotechnical Commission
ASTM	American Society for Testing and Materials International
CEN	European Committee for Standardization
Cenelec	European Committee for Electrotechnical Standardization
CLSI	Clinical and Laboratory Standards Institute
EC	European Commission
EU	European Union
FDA	US Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GHTF	Global Harmonization Task Force
HC	Health Canada
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
TDR	Special Programme for Research and Training in Tropical Diseases

3 Use of standards

3.1 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.

The WHO Prequalification Programme 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.

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.

WHO prequalification recommends the use of consensus guidelines and standards for the verification and validation of IVDs, produced by the International Standards Organization (ISO) and the Clinical and Laboratory Standards Institute (CLSI) as means to demonstrate conformity.

3.2 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.

3.3 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.

4 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.

4.1 Vocabulary

Source	Document number	Document name	Date published
ISO	ISO/IEC Guide 99:2007	International vocabulary of metrology -- Basic and general concepts and associated terms (VIM)	15-Dec-2007
ISO	ISO 3534-1:2006	Statistics -- Vocabulary and symbols -- Part 1: General statistical terms and terms used in probability	15-Oct-2006
ISO	ISO 3534-2:2006	Statistics -- Vocabulary and symbols -- Part 2: Applied statistics	15-Sep-2006
ISO	ISO 3534-3:2013	Statistics -- Vocabulary and symbols -- Part 3: Design of experiments	15-Apr-2013
CLSI	EP36-Ed1	Harmonization of Symbology and Equations, 1st Edition	18-Jun-2015
GHTF	GHTF/SC/N4:2012 (Edition 2)	Glossary and Definitions of Terms Used in GHTF Documents	9-Nov-2012

4.2 Assay design

Source	Document number	Document name	Date published
CLSI	MM03-Ed3	Molecular Diagnostic Methods for Infectious Diseases, 3rd Edition	27-Feb-2015
CLSI	MM06-A2	Quantitative Molecular Methods for Infectious Diseases; Approved Guideline - Second Edition	30-Nov-2010
CLSI	MM09-A2	Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine; Approved Guideline—Second Edition	28-Feb-2014
CLSI	MM12-A	Diagnostic Nucleic Acid Microarrays; Approved Guideline	30-May-2006
CLSI	MM16-A	Use of External RNA Controls in Gene Expression Assays; Approved Guideline	29-Aug-2006
CLSI	MM17-A	Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline	21-Mar-2008
CLSI	MM22-A	Microarrays for Diagnosis and Monitoring of Infectious Diseases; Approved Guideline	27-Feb-2014
CLSI	M53-A	Criteria for Laboratory Testing and Diagnosis of Human Immunodeficiency Virus Infection; Approved Guideline	30-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	30-Apr-2010
EU	EN 13641:2002	Elimination or reduction of risk of infection related to in vitro diagnostic reagents	17-Dec-2002
FDA	1546	Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems - Guidance for Industry and FDA Staff	10-Mar-2005
FDA	1620	Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests	13-Mar-2007
FDA	2231	Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material	07-Jun-2007
FDA	1646	Class II Special Controls Guidance Document: Plasmodium Species Antigen Detection Assays	20-May-2008
FDA	1737	In Vitro Companion Diagnostic Devices	06-Aug-2014

4.3 Risk

Source	Document number	Document name	Date published
ISO	ISO 14971:2007	Medical Devices – Application of Risk Management to Medical Devices	01-Mar-2007
ISO	ISO 14001:2004	Environmental management systems -- Requirements with guidance for use	15-Nov-2004
ISO	Guide 73	Risk management — Vocabulary	2009
IEC/ISO	IEC/ISO 31010:2009	Risk management – Risk assessment techniques	NOV-2009
ISO	ISO 31000:2009	Risk management — Principles and guidelines	15-NOV-2009
GHTF	N045:2008	GHTF SG1 - Principles of In Vitro Diagnostic (IVD) Medical Devices Classification	19-Feb-2008
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)	29-Mar-2012

4.4 Manufacturing

Source	Document number	Document name	Date published
CEN	EN 13975:2003	Sampling procedures used for acceptance testing of in vitro diagnostic medical devices - Statistical aspects	21-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	17-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	27-Nov-2008
IEC	IEC 62366:2015	Medical devices—Part 1: Application of usability engineering to medical devices	01-Feb-2015
CLSI	EP18-A2	Risk Management Techniques To Identify And Control Laboratory Error Sources; Approved Guideline - Second Edition.	Nov-2009
ISO	ISO 15198:2004	Clinical Laboratory Medicine - In Vitro Diagnostic Medical Devices - Validation of User Quality Control Procedures by the Manufacturer	20-Mar-2004
ANSI/ ASQ	ANSI/ASQ Z1.4–2003 (R2013)	Sampling Procedures and Tables for Inspection by Attributes	2013
WHO	Working document QAS/15.624 Draft document for comment	DRAFT Guidance on Good Data and Record Management Practices (September 2015)	SEPT-2015

4.5 Quality systems

Source	Document number	Document name	Date published
ISO	ISO 13485:2003	Medical devices - Quality management systems -- Requirements for regulatory purposes	15-Jul-2003
ISO	ISO/TR 14969:2004	Medical devices - Quality management systems -- Guidance on the application of ISO 13485:2003	15-Oct-2004
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	GP40-A4-AMD	Preparation and Testing of Reagent Water in the Clinical Laboratory; Approved Guideline - Fourth Edition	16-Jun-2016
CLSI	POCT07-A	Quality Management: Approaches to Reducing Errors at the Point of Care; Approved Guideline	7-Oct-2010
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
FDA	21 CFR Part 820	Quality System Regulation	
EU	EN 13975:2003	Sampling Procedures Used for Acceptance Testing of In Vitro Diagnostic Medical Devices - Statistical Aspects	21-Nov-2003
CLSI	EP18-A2	Risk Management Techniques To Identify And Control Laboratory Error Sources; Approved Guideline - Second Edition.	Nov-2009
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	27-Aug-2010

Source	Document number	Document name	Date published
		Control of Suppliers	
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

4.6 Labelling

Source	Document number	Document name	Date published
ISO	ISO 18113-1:2011	In Vitro Diagnostic Medical Devices - Information Supplied by the Manufacturer (Labelling) - Part 1: Terms, Definitions and General Requirements	31-Oct-2011
WHO / FIND / TDR / Roll Back Malaria		Purchasing and Using RDTs – RDT instructions and training	2009
ISO	ISO 18113-2:2011	In Vitro Diagnostic Medical Devices. Information Supplied by the Manufacturer (Labelling) - Part 2: In Vitro Diagnostic Reagents for Professional Use	30-Nov-2011
ISO	ISO 18113-3:2011	In Vitro Diagnostic Medical Devices - Information Supplied by the Manufacturer (Labelling) – Part 3: In Vitro Diagnostic Instruments for Professional Use	30-Nov-2011
ISO	ISO 18113-4:2011	In Vitro Diagnostic Medical Devices – Information Supplied by the Manufacturer (Labelling) – Part 4: In Vitro Diagnostic Reagents for Self-Testing	30-Nov-2011
ISO	ISO 18113-5:2011	In Vitro Diagnostic Medical Devices – Information Supplied by the Manufacturer (Labelling) – Part 5: In Vitro Diagnostic Instruments for Self-Testing	30-Nov-2011
ISO	ISO 15223-1:2012	Medical Devices – Symbols to be Used with Medical Device Labels, Labelling and Information to be Supplied	01-Jul-2012
CLSI/NCCLS	GP14-A	Labelling of Home-Use In Vitro Testing Products; Approved Guideline	01-JAN-1996
GHTF	SG1 N70:2011	Label and Instruction for Use for Medical Devices	16-Sept-2011
IMDRF	IMDRF/UDIWG/N7 FINAL:2013	UDI Guidance: Unique Device Identification (UDI) of Medical Devices	18-Dec-2013
EC	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
FDA	1128	Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers	19-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	30-Nov-2004
Health Canada		Draft Guidance for the labelling of in vitro diagnostic devices	24-JUN-1998
MHRA		Guidance for notified bodies on the regulation of	JULY-2012

		IVDs for self-testing	
CEN	EN 13532:2002	General requirements for in vitro diagnostic medical devices for self-testing	17-DEC-2002
CEN	EN 980:2008	Symbols for use in the labelling of medical device	23.-Jul-2008

4.7 Analytical performance

Source	Document number	Document name	Date published
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	1-May-2009
ISO	ISO 16269-4:2010	Statistical interpretation of data - Part 4: Detection and treatment of outliers	15-Oct-2010
ISO	ISO 16269-6:2014	Statistical interpretation of data - Part 6: Determination of statistical tolerance intervals	15-Jan-2014
ISO	ISO 16269-7:2001	Statistical interpretation of data - Part 7: Median - Estimation and confidence intervals	1-Mar-2001
ISO	ISO 16269-8:2004	Statistical interpretation of data -- Part 8: Determination of prediction intervals	15-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	15-Aug-2003
ISO	ISO 5725-1:1994	Accuracy (trueness and precision) of measurement methods and results - Part 1: General principles and definitions	22-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	22-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	22-Dec-1994
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	22-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	23-Jul-1998
ISO	ISO 5725-6:1994	Accuracy (trueness and precision) of measurement methods and results - Part 6: Use in practice of accuracy values	22-Dec-1994
CLSI	C24-A3	Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition	16-Jun-2006
CLSI	EP05-A3	Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline—Third Edition	29-Oct-2014

Source	Document number	Document name	Date published
CLSI	EP06-A	Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline	01-Apr-2003
CLSI	EP07-A2	Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition	23-Nov-2005
CLSI	EP09-A3	Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition	30-Aug-2013
CLSI	EP12-A2	User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline— Second Edition	25-Jan-2008
CLSI	EP15-A3	User Verification of Precision and Estimation of Bias; Approved Guideline - Third Edition	11-Sep-2014
CLSI	EP17-A2	Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition	18-Jun-2012
CLSI	EP18-A2	Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition	30-Nov-2009
CLSI	EP21-A	Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline	20-Apr-2003
CLSI	EP26-A	User Evaluation of Between-Reagent Lot Variation; Approved Guideline	30-Sep-2013
CLSI	EP27-A	How to Construct and Interpret an Error Grid for Quantitative Diagnostic Assays; Approved Guideline	27-Sep-2012
CLSI	EP28-AC3	Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition	19-Oct-2010
CLSI	EP29-A	Expression of Measurement Uncertainty in Laboratory Medicine; Approved Guideline	31-Jan-2012
CLSI	EP30-A	Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline	28-May-2010
CLSI	EP32-R	Metrological Traceability and Its Implementation; A Report	17-Feb-2006
CLSI	I/LA21-A2	Clinical evaluation of immunoassays; Approved guideline	29-Aug-2008
CLSI	I/LA30-A	Immunoassay Interference By Endogenous Antibodies; Approved Guideline	18-Mar-2009
CLSI	MM17-A:2008	Verification and Validation of Multiplex Nucleic Acid Assays; Approved Guideline	21-Mar-2008

Source	Document number	Document name	Date published
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	10-Mar-1999
ICH	Q6A	ICH Harmonised Tripartite Guideline. Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances	6-Oct-1999
HC		Health Products and Food Branch: Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory	7-Dec-2011

4.8 Clinical safety/performance

Source	Document number	Document name	Date published
ISO	ISO 14155:2011	Clinical investigation of medical devices for human subjects -- Good clinical practice	01-Feb-2011
ISO	ISO 22870:2006	Point-of-care testing (POCT) -- Requirements for quality and competence	01-Feb-2006
ISO	ISO 15189:2012	Medical laboratories -- Requirements for quality and competence	01-Nov-2011
CLSI	EP09-A3	Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition	30-Aug-2013
CLSI	EP10-A3-AMD	Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline - Third Edition	14-May-2014
CLSI	EP12-A2	User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline - Second Edition	25-Jan-2008
CLSI	EP14-A3	Evaluation of Commutability of Processed Samples; Approved Guideline - Third Edition	15-Aug-2014
CLSI	EP24-A2	Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves; Approved Guideline - Second Edition	30-Nov-2011
GHTF	GHTF/SG5/N5:2012	Reportable Events During Pre-Market Clinical Investigations	10-Aug-2012
GHTF	GHTF/SG5/N6:2012	Clinical Evidence for IVD Medical Devices - Key Definitions and Concepts	02-Nov-2012
GHTF	GHTF/SG5/N7:2012	Clinical Evidence for IVD Medical Devices - Scientific Validity Determination and Performance Evaluation	02-Nov-2012
GHTF	GHTF/SG5/N8:2012	Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices	02-Nov-2012
GHTF	SG5-N1R8	Clinical Evidence - Key Definitions and Concepts	01-May-2007
FDA	1587	Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions	25-Jun-2010
World Medical Association	Not applicable	DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects	Oct-2013
MHRA		Guidance for notified bodies on the regulation of IVDs for self-testing	July 2012
HC		Health Products and Food Branch: Guidance for Manufacturers of Human Immunodeficiency Virus (HIV) Test Kits intended to be used in the Laboratory	7-Dec-2011
CEN	EN 13612:2002/AC:200	Performance Evaluation of In Vitro Diagnostic Medical Devices	02-Dec-2009

	2		
CEN	EN 13532:2002	General requirements for in vitro diagnostic medical devices for self-testing	17/12/2002

4.9 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	3-Feb-2016

4.10 Pre-market evaluation

Source	Document number	Document name	Date published
IMDRF	IMDRF/RPSWG/N13 FINAL:2014	In Vitro Diagnostic Medical Device Market Authorization Table of Contents (IVD MA ToC)	14-Aug-2014
GHTF	GHTF/SG1/N68:2012	Essential Principles of Safety and Performance of Medical Devices	2-Nov-2012
GHTF	SG1 N071:2012	Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic Medical Device'	16-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	17-Mar-2011
GHTF	GHTF/SG1/N065:2010	Registration of Manufacturers and Other Parties and Listing of Medical Devices	27-Aug-2010
GHTF	GHTF/SG1/N055:2009	Definition of the Terms Manufacturer, Authorised Representative, Distributor and Importer	26-Mar-2009
GHTF	N046:2008	Principles of Conformity Assessment for In Vitro Diagnostic (IVD) Medical Devices	31-Jul-2008
GHTF	N044:2008	GHTF SG1 - Standards in the Assessment of Medical Devices	5-Mar-2008
FDA	1584	Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision	11-Dec-2008
FDA	21 CFR Part 809	In Vitro Diagnostic Products for Human Use	

4.11 Software

Source	Document number	Document name	Date published
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	
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
IEC	IEC 62304:2006-Ed.1.0	Medical Device Software - Software Life Cycle Processes	May-2006
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
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
EU	MEDDV 2.1/6	Qualification and Classification of Stand Alone Software	Jan-2012

4.12 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	12-Jan-2005
CLSI	M29-A4	Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Fourth Edition	29-May-2014
CLSI	GP34-A	Validation and Verification of Tubes for Venous and Capillary Blood Specimen Collection; Approved Guideline	31-Dec-2010
CLSI	GP39-A6	Tubes and Additives for Venous and Capillary Blood Specimen Collection; Approved Standard - Sixth Edition	29-Dec-2010
CLSI	GP41-A6	Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard - Sixth Edition	31-Oct-2007
CLSI	GP42-A6	Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard - Sixth Edition	23-Sept-2008
CLSI	GP44-A4	Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline - Fourth Edition	25-May-2010
CLSI	NBS01-A6	Blood Collection On Filter Paper For Newborn Screening Programs: Approved Standard - Sixth Edition	31-Jul-2013
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)	25-Aug-2005
EU	EN 14254:2004	In Vitro Diagnostic Medical Devices - Single-Use Receptacles for the Collection of Specimens, Other Than Blood, from Humans	28-Apr-2005
EU	EN 14820:2004	Single-Use Containers for Human Venous Blood Specimen Collection	28-Apr-2005

4.13 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	01-Jan-2011
CLSI	EP25-A	Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline	23-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	29-Feb-2012
ASTM	D4169 – 14	Standard Practice for Performance Testing of Shipping Containers and Systems	2014
USP	USP 31-NF 26	United States Pharmacopeia and National Formulary	2008
European Union	Ph. Eur.	European Pharmacopoeia 8th Edition	2015
N/A	2000	Pharmacopoeia of the People's Republic of China. English edition.	2000
CEN	EN 13640:2002	Stability testing of in vitro diagnostic reagents	17-Dec-2002

4.14 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
EC	MEDDEV 2.12-1 rev 8 Vigilance	Guidelines on a Medical Devices Vigilance System	Jan-2013
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
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

Source	Document number	Document name	Date published
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
GHTF	GHTF-SG2-N008R4	Guidance on How to Handle Information Concerning Vigilance Reporting Related to Medical Devices	29-Jun-1999
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

4.15 Changes

Source	Document number	Document name	Date published
WHO	PQDx 121	Reportable Changes to a WHO Prequalified In Vitro Diagnostic	01-Feb-2016
NPOG	NPOG BPG 2014-3	Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System	Mar-2014
FDA	K97-1	Deciding When to Submit a 510(k) for a Change to an Existing Device. Center for Biologics Evaluation and Research, MD, USA; 1997	10-Jan-1997
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

4.16 Self-testing considerations

Source	Document number	Document name	Date published
FDA	1756	Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use	07-JANUARY-2014
ISO	ISO 15197:2013	In vitro diagnostic test systems - Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus	15-MAY-2013
EN	EN 13532:2002	General requirements for in vitro diagnostic medical devices for self-testing	MAY-2002

5 Websites with additional information

Source	Website address
CLSI	Documents available for purchase: http://shopping.netsuite.com/clsi
EU	Harmonized standards http://ec.europa.eu/enterprise/policies/european-standards/harmonised-standards/iv-diagnostic-medical-devices/index_en.htm Medical device guidelines http://ec.europa.eu/health/medical-devices/documents/guidelines/
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
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
IMDRF	GHTF documents http://www.imdrf.org/ghtf/ghtf-archived-docs.asp IMDRF documents http://www.imdrf.org/documents/documents.asp#imdrf
ISO	Documents available for purchase: http://shopping.netsuite.com/s.nl/c.1253739/sc.7/category.2406/.f

6 Authors and acknowledgements

The document **TGS-1 Standards applicable to the WHO prequalification of in vitro diagnostics** was prepared by Elliot Cowan (consultant, USA), Deirdre Healy (WHO/HIS/EMP) and Robyn Meurant (WHO/HIS/EMP). WHO also wishes to thank Jinjie Hu (consultant, USA), Julian Duncan (consultant, London, United Kingdom), and Monika Zweygarth (consultant, editor) for their contributions. This document was developed as part of the Bill and Melinda Gates Foundation Umbrella Grant. This document was produced under the coordination and supervision of Deirdre Healy, Robyn Meurant and Irena Prat (WHO/HIS/EMP), Geneva, Switzerland.

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, Switzerland: International Organization for Standardization; 2004.