Technical Guidance Series (TGS) for WHO Prequalification – Diagnostic Assessment

Quality control for in vitro diagnostic medical devices for WHO prequalification

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WHO Prequalification – Diagnostic Assessment: Technical Guidance Series

The WHO Prequalification Programme is coordinated through the Department of Essential Medicines and Health Products. The aim of WHO prequalification of in vitro diagnostic medical devices (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 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-test 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 from 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 documents are freely available on the WHO website.¹
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List of contributors

The draft technical specifications document was posted on the WHO website for public consultation on 29 March 2019. Various stakeholders – including manufacturers submitting to WHO prequalification of IVDs, IVD manufacturing industry associations, various national and international regulatory bodies, and IVD standards organizations – were informed of the consultation in order to solicit feedback. A 3-month response period was provided.

Comments were received from the following:
1 Abbreviations and definitions

1.1 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IFU</td>
<td>instructions for use</td>
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<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
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<td>IVD</td>
<td>in vitro diagnostic medical device</td>
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<td>QA</td>
<td>quality assurance</td>
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<td>QC</td>
<td>quality control</td>
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<td>QMS</td>
<td>quality management system</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>R&amp;D</td>
<td>research and development</td>
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1.2 Definitions

The definitions below related to risk management of in vitro diagnostic medical devices (IVDs), transcribed from *EN ISO 14971:2012 Medical devices – application of risk management to medical devices* (4), are generally used in this guidance. Where a source other than ISO 14971 is used, the source is indicated.

1 **The following definitions are used throughout this guide.**

2 **Accepted reference value**: A value that serves as an agreed-upon reference for comparison.

3 **Accuracy**: Closeness of agreement between a test result and the true, or the accepted reference value.

4 **Analytical Sensitivity**: Ratio between the variation of the information value of the analysis method and the variation of the analyte quantity. The variation of the analyte quantity is generally obtained by preparing various standard solutions, or by adding the analyte to a matrix.

5 **Analytical Specificity**: Property of an analysis method to respond exclusively to the determination of the quantity of the analyte considered, with the guarantee that the measured signal comes only from the analyte. Response in reagent blank and blank control samples.

6 **Batch /Lot**: Definite amount of material produced during a single manufacturing cycle, and intended to have uniform character and quality. The uniform conditions of manufacture or production of the batch or lot must be such as to ensure a homogeneous product.
Bias: Difference between the expected test results and an accepted reference value.

Blank: Test carried out on a matrix or a reagent which does not contain the analyte (matrix blank or reagent blank).

Calibrator: Reference material used for calibration of equipment or a measurement procedure.

Calibration: Series of operations establishing under specified conditions the relation between the values of the quantity indicated by a measuring instrument or system, or the values represented by a materialized measurement or a reference material, and the corresponding values of the quantity measured by standards or reference materials.

Certified reference material (CRM): Reference material, accompanied by a certificate, one or more whose property values are certified by a procedure which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence.

Commutability: Property of a reference material (RM), demonstrated by the equivalence of the mathematical relationships among the results of different measurement procedures for an RM and for representative samples of the type intended to be measured.

Evidence: Information that can be proved true based on facts obtained through observation, measurement, test or other means.

Source: Modified from (1), definition 3.8.1

Homogeneity: Uniformity of a specified property value throughout a defined portion of a reference material (RM). Tests for homogeneity are described in ISO Guide 35.

Intended use: Use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer.

Source: (4), definition 2.5

Note 1: The intended use is the clinical use for which the procedure was designed.

Note 2: The concept includes definition of the measurand, the target condition and the clinical use of the measurement procedure, which may include screening, diagnosis, prognosis or monitoring of patients.

Note 3: The concept includes the physical, economic and resource limitations in the environments of intended use.

IVD: Medical device intended by the manufacturer for the examination of specimens derived from the human body, 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.

They are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction and

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2 Notes 1 and 2 are from the website of the Clinical and Laboratory Standards Institute (CLSI); see http://htd.clsi.org
determination of physiological status.

Note 2: In some jurisdictions, certain IVDs may be covered by other regulations.

Source: (4), definition 2.6

Life cycle: All phases in the life of a medical device, from its initial conception to final decommissioning and disposal.

Source: (4), definition 2.7

Linearity: The ability of a method of analysis, within a certain range, to provide an instrumental response or results proportional to the quality of analyte to be determined in the laboratory sample. This proportionality is expressed by an a priori defined mathematical expression.

Lower Limit of Quantification (LLOQ): the lowest standard curve point that can still be used for quantification. It is the value above which quantitative results may be obtained with a specified degree of confidence, or the lowest concentration of an analyte that can be accurately measured.

Manufacturer: Natural or legal person with responsibility for the design, manufacture, packaging or labelling of a medical device, assembling a system, or adapting a medical device before it is placed on the market or put into service, regardless of whether these operations are carried out by that person or on that person’s behalf by a third party.

Note 1: The provisions of natural or regulations can apply to the definition of manufacturer.

Note 2: For the definition of labelling, see (6), definition 3.8.

Source: (4), definition 2.8

Medical device: Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article that is intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific purposes:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- investigation, replacement, modification, or support of the anatomy or of a physiological process;
- supporting or sustaining life;
- control of conception;
- disinfection of medical devices; and
- providing information for medical purposes by means of in vitro examination of specimens derived from the human body;

and that does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means.

Note 1: This definition has been developed by the Global Harmonization Task Force (GHTF).

Note 2: Products that could be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach are:

- aids for people with a physical disability;
— devices for the treatment or diagnosis of diseases and injuries in animals;
— accessories for medical devices (see Note 3);
— disinfection substances; and
— devices incorporating animal and human tissues that can meet the requirements
  of the above definition but are subject to different controls.

Note 3: Accessories intended specifically by manufacturers to be used together with a
“parent” medical device to enable that medical device to achieve its intended purpose
should be subject to this international standard.

Source: (4), definition 2.9

Precision: Closeness of agreement between independent test results obtained under
prescribed conditions. Precision depends on the distribution of random errors and
does not have any relationship with the true or specified value. The
measurement of precision is expressed on the basis of the standard deviation of
the test results. The expression “independent test results” refers to results
obtained such that they are not influenced by a previous result on the same or a
similar test.

Process: Set of interrelated or interacting activities that transforms inputs into outputs.

Note 1: Inputs to a process are generally outputs of other processes.

Note 2: Processes in an organization are generally planned and carried out under
controlled conditions to add value.

Source: (4), definition 2.13

Quantification limit: Lowest amount of an analyte to be examined in a test material that can be
quantitatively determined under the experimental conditions described in the
method with a defined variability (given coefficient of variation).

Reference material: Material or substance one or more of whose property values are sufficiently
homogeneous and well established to be used for the calibration of an apparatus,
the assessment of a measurement method, or for assigning values to materials.

Reference method: measurement method, that has been shown to have the appropriate trueness
and precision for its intended use and has been officially defined as reference
method by a competent body.

Repeatability: Conditions where independent test results are obtained with the same method on
identical test items in the same laboratory by the same operator using the same
equipment within short intervals of time.

Reproducibility: Conditions where independent test results are obtained with the same method on
identical samples by the same or different operator(s) using different IVD on
different days.

Risk: Effect of uncertainty on objectives.

Note 1: An effect is a deviation from the expected, either positive or negative or both.
Note 2: Objectives can have different aspects (e.g. financial, health and safety, and
environmental goals) and can apply at different levels (e.g. strategic, organization-wide,
project, product and process).
Note 3: Risk is often characterized by reference to potential events and consequences, or
a combination of these.
Note 4: Risk is often expressed in terms of a combination of the consequences of an event (including changes in circumstances) and the associated likelihood of occurrence.

Note 5: Uncertainty is the state, even partial, of deficiency of information related to understanding or knowledge of an event, and its consequence or likelihood.

Source: (12), definition 1.1 and (1), definition 3.7.9

Risk management: The systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

Source: [4]

Risk management plan: For the particular medical device being considered, the manufacturer shall establish and document a risk management plan in accordance with the risk management process.

Source: [4], para 3.4

Stability: characteristic of a reference material, when stored under specified conditions, to maintain a specified property value within specified limits for a specified period of time.

Target value: property value of an RM specified on the basis of its intended use. The target value of an RM property is usually specified in the design phase of RM production.

Top management: Person or group of people who direct(s) and control(s) a manufacturer at the highest level.

Source: (4), definition 2.26

Trueness: the measure of trueness is normally expressed as “bias”. The closeness of agreement between the average value obtained from a series of test results (i.e. the mean recovery) an accepted reference or true value.

Uncertainty: The list of uncertainty sources and their associated standard uncertainties, established in order to assess the compound standard uncertainty associated with a measurement.

Verification: Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled.

Note 1: The term “verified” is used to designate the corresponding status.

Note 2: Confirmation can comprise activities such as:

- performing alternative calculations;
- comparing a new design specification with a similar proven design specification;
- undertaking tests and demonstrations; and
- reviewing documents before issues occur.

Source: (4), definition 2.28
2 Introduction

2.1 Key concepts

Quality control is an activity or a set of activities intended to ensure that a manufactured product adheres to a defined set of quality criteria, including meeting customer and regulatory requirements. The activity(ies) focus on identifying whether or not quality requirements for the product are being met, and specifically to identify defects in the products that are produced. It is part of quality management which is focused on fulfilling the quality requirements of the product (ISO 9000:2015) (1).

2.2 Rationale for quality control

2.2.1 Quality control

The testing of product to determine whether or not specifications have been met is referred to as quality control (QC). Since the quality of each and every IVD cannot be tested after it has been manufactured, effective QC activities can be implemented at each step of the manufacturing process, from raw material inputs, throughout the manufacturing process and final products to provide confidence in the quality, safety and performance of the finished product. Testing at the various stages of manufacturing helps identify where a production problem is occurring and the corrective actions that need to be undertaken in the manufacturing process to meet product specifications and product quality objectives.

Various QC techniques and activities are available to fulfill requirements for quality. Options include observation, inspection or testing of products to uncover defects or to determine if products adhere to established quality requirements. Standards against which products will be assessed need to be established. Sampling plans, including the number of production units to be assessed, collecting data and reporting results to management, especially where corrective action is required, are all elements of QC focusing on fulfilling quality requirements. For IVDs, some QC activities can be addressed through performance evaluation which is the assessment and analysis of data to establish or verify the ability of an in vitro diagnostic device to achieve its intend use (ISO 13485:2016)(2).
2.2.2 Quality Assurance

Quality assurance (QA) is all the planned and systematic activities implemented within the quality system that can be demonstrated to provide confidence that a product or service will fulfill requirements for quality. QA aims to improve and stabilize production and processes to avoid or minimize issues that lead to product defects. QA is part of quality management focused on providing confidence that quality requirements will be fulfilled (ISO 9000:2015)(1).

2.2.3 Quality Management System

A Quality Management System (QMS) includes establishing quality policies, responsibilities and processes to achieve quality objectives through quality planning, quality assurance, quality control and quality improvement (ISO 9000:2015) (1). Quality objectives in the IVD sector include both customer and regulatory requirements.

Many National Regulatory Authorities (NRAs) require that manufacturers design, develop, implement and monitor a QMS, combined with the other conformity assessment elements, to provide a level of assurance that IVDs will be safe and perform as intended by the manufacturer. Compliance with the international QMS standard ISO 13485 has become the norme upon which NRAs and manufacturers rely to provide this assurance. Proper use of this standard provides evidence that IVDs will consistently meet both customer and regulatory requirements.

The scope and complexity of the quality management system that a manufacturer needs to establish is influenced by varying needs, objectives, the products provided, processes employed, the size and structure of the organisation, and the specific regulatory requirements that need to be met (GHTF/SG1/N071:2012)(3).
2.3 Purpose of this document

The purpose of this document is to provide IVD manufacturers with guidance on ISO 13485 requirements related to the implementation of QC activities, including processes and procedures, to ensure that the results obtained through the use of an IVD are consistent, comparable, accurate and within specified limits of precision.

2.4 Limitations of this guidance

This guidance document should not be taken as a prescriptive checklist of what quality control activities should be performed on product. It is intended to guide manufacturers to consider and implement quality control measures that are applicable to their particular product(s), taking into consideration QC standards, procedures, sampling plans, testing, inspection and any other applicable activity in order to generate evidence that products meet quality requirements.

It is possible that, depending on the type or classification of the product and on the particular regulatory jurisdiction that additional quality control activities may be required. Manufacturers must be aware that regulatory and legal issues are specific for each regulatory authority and are beyond the scope of this document.

Given the diversity of IVDs, this guidance document is not intended to cover specific aspects of all manufactured IVDs and the various configurations of product, their design and manufacturing processes. QC plans should be risk-based, established on individual products.
and it is the manufacturer’s responsibility to describe and establish the appropriate plan for each product placed on the market. Incorporating risk management will require the manufacturer to identify the hazards associated with the IVD, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls (ISO 14971:2012) (4).

Certain generic standards provide the framework for quality management system. These generic standards belong to the ISO 9000 series and stand alone standards such as ISO 13485 (2) that is based on ISO 9001. The guidance from GHTF (3) is also primarily concerned with quality management systems.
3 Preamble

IVDs are intended for use in the collection, preparation and examination of samples taken from the human body. These devices include reagents, instruments, software, sample collection devices and receptacles, calibrators, control materials and related accessories. These devices can be used alone or in combination as a system (ISO 14971:2007 – H1 – General) (5). They are intended by the manufacturer for the examination of specimens derived from the human body to provide information for diagnostic, monitoring or compatibility purposes (ISO 14971:2007) (5). IVDs are used on biological specimens or on constituents obtained from biological specimens. They provide for qualitative or quantitative measurement methods for one biomarker or combinations of biomarkers.

In ISO 13485: 2016 (Clause 8.2.6) (2) it states that “The organization shall monitor and measure the characteristics of the product to verify that product requirements have been met. This shall be carried out at applicable stages of the product realization process in accordance with the planned arrangements and documented procedures.

Evidence of conformity with the acceptance criteria shall be maintained. The identity of the person authorizing release of product shall be recorded (see 4.2.5). As appropriate, records shall identify the test equipment used to perform measurement activities.

Product release and service delivery shall not proceed until the planned and documented arrangements have been satisfactorily completed.”

The organization shall apply suitable methods for the monitoring, and where applicable, the measurement of the product.

QC is intended to provide assurance that the IVD will perform within specifications for safety and performance. IVDs need to be suitable for user requirements and for their intended clinical use. As an output of risk analysis process, QC offers a means of risk mitigation by providing evidence of the performances of the devices, or the process under investigation (ISO 14971:2007 - A.2.4.2 Intended use and identification of characteristics related to the safety of the medical device) (5).
QC enables the monitoring and measurement of the product or the process by identifying nonconformities or bias that require corrective or preventive actions in the devices or in modification to the QMS. Validated statistical QC procedures are a key tool to maintain risk at an acceptable level.
Quality management system requirement

ISO 13485:2016 sets out requirements for a QMS that can be used by an organization involved in one or more stages of the life-cycle of a medical device, including design and development, production, storage and distribution, installation, servicing and final decommissioning and disposal of medical devices, and design and development, or provision of associated activities (e.g. technical support). (2) The scope of a manufacturer’s QMS can also extend to suppliers or to activities sub-contracted to an external organization.

A QMS is intended to assist organizations in improving quality and enhancing customer satisfaction. Customers require products with characteristics that satisfy their needs and expectations. An effective and well implemented QMS requires organizations to analyse customer requirements, define the processes that contribute to the achievement of a product which is of acceptable quality to the customer and to keep the processes for achieving quality under control. A QMS provides confidence to the organization and its customers that it is able to provide products that consistently fulfil requirements.

An effective QMS requires top management commitment to the development and implementation of the QMS and maintenance of its effectiveness. Evidence of this commitment is in the form of communication to the organization of the importance of meeting customer and applicable regulatory requirements; a documented quality policy and objectives; undertaking management reviews; and the availability of resources (ISO 13485:2016 5.1) (2).

QC activities reside within an effective QMS and should be carried out by qualified and independent staff, under controlled and established delegations (ISO 13485:2016 5.5.1) (2). Quality control authorities, processes, activities and approvals should be independent from manufacturing activities. The outputs of design and development shall be in a form suitable for verification against the design and development inputs and shall be approved prior to release of product. (ISO 13485:2016 7.3.4) (2).

QC also applies to all purchased product used in the manufacture of an IVD (e.g.: components) to determine if specified purchasing requirements have been met. An organization will determine the extent of its verification activities based on evaluations.
undertaken and provided by the supplier. Consideration shall also be given to the risks associated to product that is being purchased. If incoming product deviates from requirements a determination is required as to whether the changes will affect the product realization process or the IVD (ISO 13485:2016 7.4.3) (2).
5 Quality control process design

5.1 Risk management and assessment

IVDs are designed to have performance characteristics that determine the accuracy of diagnostic results. Failure to meet the performance characteristics required for the intended use of an IVD could result in a hazardous situation that should be evaluated as a risk to patients. These hazards or hazardous situations can occur prior, during or after use. The importance and likelihood of these failures can vary depending upon the IVD, the sample, the user, the environment, and the skill and knowledge level among end users.

For this reason, it is imperative for a manufacturer to establish, document and maintain an ongoing process for identifying hazards and managing risks associated with an IVD, estimating and evaluating the associated risks, controlling the risks and monitoring the effectiveness of the controls. (6) An effective process shall include risk analysis; risk evaluation; risk control; and collecting production and post-production information. Risk management activities need to be planned. The plan shall include what risk activities will be undertaken and when during the IVDs life cycle; who will be responsible for administering the plan and their authorities; the review of risk management activities; establishing criteria for risk acceptability; verification activities; and activities to collect and review production and post production information (ISO 14971:2007) (4).

Quality control is a means to verify that risks occurring during the design or manufacturing processes are identified, eliminated or reduced to an acceptable level. (EP18-A2 Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline – Second Edition) (7).

Further information on how to apply a risk management plan for IVDs can be found in Annex H – Guidance on risk management for in vitro diagnostic medical devices in ISO 14971:2007. (5) Annex H sets out considerations for undertaking risk analysis, risk evaluation, production and post-monitoring in the risk management of IVDs.
5.2 QC – Monitoring and Measurement of Product

ISO 13485:2016 sets out requirements for an organization to monitor and measure the characteristics of product or processes to verify that requirements have been met. It is the responsibility of the manufacturer to determine at which stages of the product realization process that planned QC activities, in accordance with documented arrangements and procedures, need to occur.

Documenting QC responsibilities, such as delegation of authorities, decision making charts and product status charts shall be developed during the product design and development phase in order to clarify the process. Those responsible for authorizing release of product at various stages of product realization need to be identified and documented (ISO 13485:2016 – 4.2.5) (2). As appropriate, records shall identify the test equipment used to perform measurement activities. No product can be released or service delivered until the planned and documented QC arrangements have been satisfactorily completed.

The means of verifying that the product realization processes achieve specified level of quality requirements (homogeneity, reproducibility, repeatability, etc.) must be developed. The analytical performance characteristics of products, such as analytical sensitivity, analytical specificity, accuracy, repeatability, reproducibility, range and limitations need to be verified through QC steps with appropriate sampling processes and procedures.

The design and documentation of the QC processes should describe the nature of the controls, the description and specification of the reference materials, the origin of the materials, the metrological traceability, calibrators and trueness-controllers.

All materials required for the manufacturing of an IVD, including reference materials and reference measurement procedures, as well as equipment to be used, must be defined. The accepted reference values assigned for reference materials should be determined and maintained. Acceptability limits are to be determined during the design and development phase of the product. The manufacturer shall have documented procedures and records that define appropriate statistical techniques appropriate for the function that are used to monitor or detect trends in the process.
The preparation, calibration and maintenance of a metrologically-traceable calibrator should be designed and documented for each QC procedure. Analysis methods shall be described in documented procedures specifying all the means and actions required to carry out the analysis of the analyte, notably the scope, principle, definitions, reagents, apparatus, procedures, expression of results, precision and test report.
The calculations and interpretation of results shall be detailed for each QC procedure. Where relevant, clinical QC performance, such as diagnostic sensitivity and diagnostic specificity, quantification limits, linearity, etc. on specified and characterized clinical samples and acceptance intervals, must be documented in the design outputs.
Calculation of means for the determination and control of the values, such as cut-off values, calibrator values or standard materials values shall be considered.
Specifications should detail acceptance and rejection criteria, that should be extensively assessed during QC validation processes.

5.3 Design change and risk analysis reviews
The QC process should be reviewed periodically and also during design change of the products or the processes. The design of the QC process shall also be updated in accordance with periodical risk analysis reviews. If the outputs of the risk analysis is determine that a change to the detection activity (i.e. QC processes) is required then further analysis of the process is required. (6)
6 Standards and reference materials for QC activities utilising performance panels

QC activities associated with monitoring the performance of an IVD are used to validate that product quality requirements (as defined by both the customer and the NRA, as applicable) have been met.

6.1 Reference material characterization

Reference materials shall be characterized and tested to ensure that they are fit for use in a measurement process. To become a characterized reference material, materials need to be investigated to determine if they are sufficiently homogeneous and stable with respect to one or more specified properties, and they are fit for their intended use in the development of measurement and test methods that target those properties.

The trueness of reference materials and QC methods used in routine procedures must be established through higher order reference material or by using a reference method. Metrological traceability must be assessed and documented in order to establish the pertinent characteristics of the analyte into the reference materials.

The trueness of measurement of a value assigned to a defined quantity of a calibrator or trueness control material, depends on the metrological traceability of the value established through a chain of comparison of measurement procedures and measurement standards (calibrators), usually having successively decreasing uncertainties of measurement. The uncertainty of the value assigned to a given calibrator or trueness control material depends on the chain of stated metrological traceability and the combined uncertainties. (8)

A metrological traceability chain or calibrators used in routine testing should be defined with the relevant International System of Units if there is an existing international primary standard or a high order level standard.

Nevertheless, even when there is existing reference material, different procedures may lead to different measured results, particularly when using proteins with several epitopes and immunological methods or for catalytic concentration measures of some conjugated enzymes.
due to biomolecules interactions. The metrological traceability of the assigned value for a product calibrator would require other measured procedures and new calibrations in order to assign specific internal values.

Some reference materials with no assigned value can be used for precision, repeatability or reproducibility control procedures (precision control materials).

For the internal calibrated reference materials the preparation is sometimes carried out using concentrated analytes spiked in a biological matrix. The origin of the analyte used to prepare spiked samples and the nature of the matrix will affect the measured value and stability of the resulting calibrated reference materials. The metrological traceability of the internal calibrated reference materials and their relations to a medical discrimination limit shall be established.

For spiked matrix-based calibration standards, samples should be prepared based on the theoretical concentration of analytes, for specific criteria set up in advance, to achieved accuracy and precision over the range of the standards.

It is often usefull to have a reference defined as non specific or interfering material with determined values which could be used to control the calibration and accuracy of the test. Dilution above and below the lower limit of detection of relevent non-specific analytes or samples are generally essential to verify the specificity of the test.

The values assignment and the intervals of acceptable values, for each calibrated reference material, should be established through validated statistical methods in accordance with a specified measurement procedure.

The number of reference panel members validated for routine controls should be maintained. Procedures for the preparation, validation and release of new panel members should be documented.

The procedure to determine the value of each reference material should specify the required testing material for the calculation of the coefficient variation, standard deviations and confidence intervals that are statistically based to determine the values or range and acceptance criteria.
The assessment of the stability of the samples should be based on a real time basis and if no data is available, accelerated studies can provide an initial base that will be complemented with real time data.

### 6.2 Reference methods

If calibrators with traceable values to an international standard are not available, then international conventional reference measurement procedures or reference methods could be referred to as known gold standard tests. Calibration materials with no international values assigned (e.g., some antibodies, tumour markers or commercially available seroconversion characterized panels) can also be used.

However, for many biomarkers, there is neither high level standards nor reference measurement procedures. The manufacturer will have to design documented measurement procedures to support internal value assignment to its calibrators. The trueness of the calibrators should then be assigned through a hierarchy of comparisons with internal high level, and lower level, calibrators in agreement with available objective data (clinical data, comparators, bibliography, prevalence data, etc.).

### 6.3 Reference material preparation and storage

Documented procedures shall describe all necessary activities and tasks leading to the release and maintenance of a reference material (certified or non-certified, primary or secondary reference material, stock or working solutions of reference material).

Reference standards shall be well characterized, during and after their preparation, and their specifications and qualification shall be documented.

Each standard shall be uniquely identified and the dates of reception, preparation, dispensing, and labeling recorded. Traceability of each aliquot shall be established. Their storage conditions shall be specified (temperature, light, humidity, etc.), expiry dates based on the suppliers’ information or allocated dates, according to internal studies shall be specified.
Criterion to develop a sufficient amount of reference material (stock and working samples) for each QC step, the need of positive and negative controls and their nature, the need for blank controls and interference controls shall be documented.

The method to prepare, validate and qualify new reference material shall be established and documented. Stock reference material and working reference material preparation and handling procedures shall be developed and recorded.

Their preparation shall specify the size of the aliquots in order to be suitable for single use if applicable, and freeze / thawing cycles.

The source and lot number, expiration date, certificates of internal or external analyses, characteristics and specifications shall be documented for each reference material.

The recovery of an analyte can vary depending on the matrix. To compensate for such effects, calibration standards and reference materials shall be prepared in the same biological matrix as the samples defined in the intended use of the product with sufficient range to ensure upper and lower detection levels are covered. Selectivity, accuracy and precision of the reference materials have to be determined and documented.

The commutability of the prepared reference materials shall be assessed. The design of the internal reference material shall be documented and its preparation recorded to ensure the traceability of the matrix and spiked material characterization, origins, clinical data, labelling and treatment.

Procedures to avoid discrepancies between old and new reference material, or stock solution and routine samples shall be implemented. All reference substances prepared in the laboratory or externally supplied shall be retested at regular intervals to ensure that deterioration has not occurred. It is recommended that the WHO guidance document, *WHO Manual for the establishment of Secondary Standards* (9) is consulted for detailed guidance on establishment and maintenance of reference materials.

The interval for retesting depends on a number of factors including stability of the substance, storage conditions employed, type of container and extent of use (how often the container is opened and closed).
Detailed information on the handling, storage and retesting of reference substances is given in the WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances (9).

The results of these tests shall be recorded and signed by the authorized person.

In the event of noncompliant reference substance retesting results, a retrospective check of tests performed using this reference substance since its previous examination shall be carried out. Risk analysis shall be applied in evaluating outcomes, retrospective checks and consideration of possible corrective actions.

In addition to reference materials, preparation of original patient specimens, compliant with the test intended use, should be introduced in the control panel. Their characteristics shall complement panels and permit control of the tests behaviour done under real conditions.

For further information on the development of performance panels, refer to WHO guidance TGS 3– Principles of Performance Studies. (10)

7 Quality Control Plan

Manufacturers of IVDs are required to plan, develop and document the processes needed for product realization. Processes for risk management must also be included as part of the product realization process and shall be maintained. One of the elements that a manufacturer needs to consider for incorporation into its product realization process are requirements for verification, validation, monitoring, measurement, inspection and test, handling, storage, distribution and traceability activities specific to the product together with the criteria for product acceptance (2).

As a result, QC processes and plans need to be developed and documented. These should include:

- Quality control process flowchart
- Responsibilities and delegations
- Quality controls steps
- Quality control methods, equipment and reference materials
- Decision points which have an impact on product status

Product realization plans, and specifically QC plans, should specify the acceptance and rejection criteria for each control. The procedures planned shall ensure objectivity of inspections and of test results.

The QC plan must be developed in accordance with the intended use of the product (nature and type of sample, population, range of measurement, limits) and shall be established and defined for each type of control and assay. The standard reference material values used for QC shall be established during the design phase using documented processes.

All data relating to QC checkpoints and sampling processes, inspection and test methods, reference material, test panels and specifications, statistical methods and interpretation, acceptance criteria and decisions shall be documented and detailed in the product realization plans. All outsourced QC shall go through the same level of control.

The QC plan and checkpoints should take into consideration all the steps of the manufacturing process. This includes raw materials, (including water quality, chemicals, biologicals, components, consumables, labels, printed goods), sub-assembly controls, in process controls, semi-finished goods controls, references materials controls, finished goods controls, subcontracted QC and certificate of analysis controls including the Instructions for Use (IFU). QC of retention samples of the products, or when applicable, returned goods and control and qualification of reference materials is also required.

The analytical procedures and tests methods for each control point shall specify the required equipment, materials, instructions, records and decision matrices of the QC.

QC inspection, testing and / or measurement must be performed using qualified and calibrated equipment, or based on instruments linked to international standards or referenced panels. Methods to qualify internal reference material and international reference standards shall be determined during the design phase.

The sampling process developed for each step of the QC should provide evidence of statistical analysis and supporting data.
The specifications for reference material used for QC procedure shall be documented in the QC plan in order to ensure the availability of reference material calibrated or compared to international standards.

### 7.1 QC activities associated with monitoring performance

The methods used for QC shall be planned to identify the specification of conformity of the assay’s or subcomponent performance.

- For IVDs that produce a result expressed quantitatively, where there are two specified limits for the results, QC activities to verify trueness, precision, limits of detection and cut off verification shall be planned.
- For semi-quantitative IVDs, where the results can have any value between two specified limits, QC activities to verify the accuracy, trueness, precision, limits of detection and cut off of the test should be considered.
- For qualitative IVDs, where the true quantitative signal can only have a specified value between the lower and upper confidence bounds, QC activities to verify the sensitivity, specificity, accuracy, trueness, precision and cut off of the test should be considered.

<table>
<thead>
<tr>
<th>Nature of the assay / testing</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Trueness</th>
<th>Precision</th>
<th>Cut off value</th>
<th>Limits of detection</th>
<th>Stability</th>
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</table>
Table 1 – Nature of the Controls

The QC plan must also integrate the need for planning QC procedure validation. Method validation should be performed to provide evidence that the QC methods are fit for purpose and achieve specified accuracy, precision, selectivity, sensitivity and reproducibility. Refer to WHO guidance TGS 4 Guidance on test method validation for in vitro diagnostic medical devices. (11)

QC method validation is a requirement to establish testing validity and shall be supported and extended by planned method performance verification during routine analysis (analytical QC and on-going method validation).

A decision matrix for results obtained and QC flowchart for approved, rejected or reprocessed product should be considered in the product realization planning including responsibilities for out-of-specification results, re-testing (criteria and limitations), rejection, rework or release under concession.

8 Sampling Process

8.1 Sampling procedures

Procurement of samples for QC activities should be done and recorded in accordance with approved written procedures and the sampling plan used should be appropriately justified. Samples should be representative, in terms of characteristics and performance, of the batch of materials or products from which they are taken. The analytical sample shall consist in parts, units or subparts, or subunits of the batch from which it has been taken and should include sampling from throughout the production batch or run (e.g. beginning, middle and end).

The lot defines a quantity of material or product processed in one process or series of processes, expected to be homogeneous.
8.2 Risk analysis / performance evaluation

The sampling procedures, for each specific product, shall be established according to statistical principles. The minimum analytical sample size of the product to obtain significant results will be established according to determined criteria for acceptable risk and confidence level.

The type and nature of all materials used in the manufacturing process should be considered. All of the components, subcomponents and materials involved in the process should go through an approval procedure with specified QC processes to ensure they meet the specified requirements.

For the calculation of the acceptable confidence interval of the statistical method, the manufacturer shall consider the risk analysis output and the risk resulting from the probabilities of not detecting shifts or discrepancies in the production quality and their implication on the patient or user health.

8.3 QC plan design considerations

The sampling procedure should detail the operations, authorities and chronology of the sampling process (points, location, operators etc.) for the collection of the specified size or number of specimens from the ongoing production process to determine the characteristics and the variability in those samples and compare their closeness to specified target values.
Validation of the sampling process methods should be established and documented to demonstrate the homogeneity inside a batch and support the representativity of the samples collected during the processes (formulation, lyophilization, oven drying, sterilization, incubations, stripping, spaying or coating processes, etc.) or according to specified criteria (per operator, per critical raw material, per run, per sequences, etc.)

All interpretation and equations needed for the calculation of the result should be specified or under validated computerised calculations. All tables used for the calculation and calibration curve used in analysing samples shall be traceable and recorded.

QC specifications and QC control records, at each level of the process shall reference approval, rejection, retesting or reprocessing decision chart criteria according to the design outputs and the validation of the process outputs. Acceptance criteria for derogation or reprocessing shall be described.

8.4 Traceability

The specifications of the sampling protocol must provide all information to unambiguously identify the analytical sample, subject matter of the QC procedure (activities, equipment or goods), and ensure traceability of the data.

Traceability of all the characteristics of the product (name, reference or catalogue number, batch or lot number, serial number, version reference, material, processing cycle or flowchart of production, the list of components and formula, production site, rooms, equipment, area, list of reference materials, etc., and the specification of the controls) shall be detailed to allow the assessment and the verification of the product and the operations to those detailed specifications.

In order to ensure an adequate sampling process, the status of the products during their progress in the process of manufacturing shall be unambiguously identified to the user, the operator or reviewer.
The status of the product prior to QC release, such as quarantined (when awaiting for reception, during investigation / sampling, labelling, returned goods under investigation, etc.), product under reprocessing, rejected products, or approved products shall be clearly recorded / displayed on the goods.

Samples must be identified clearly and indelibly, in a way to ensure traceability. Each laboratory analytical sample of the products shall be allocated a unique code specific to the quality control laboratory.

8.5 Analytical sample preservation

Before QC testing, samples must be stored separately from other products or other sources of potential contamination and stored under specified storage conditions (temperature, humidity etc.). When samples are transferred to the quality control laboratory for QC assessment, they are to be maintained at specified conditions during transit and storage to preserve their representative characteristics consistent with the remainder of the batch from which they were sampled.

The sampling process for the collection of retention samples of products under QC must be specified for stability (accelerated and real time stabilities) and regulatory purposes. The sampling process of critical raw materials, intermediates or fully packed finished products, with their packaging and labelling, shall be described.

Batch manufacturing records and QC records shall provide all information for traceability of the procedures, specifications, resources required and resources involved, status and identification of materials and equipment, records of operations, their conformity and check of verification and the decision of approval or rejection. All specifications, operations and results must be recorded and approved.
9 QC methods

9.1 QC specifications

QC specifications define the characteristics, descriptions, values, and storage intervals that the product should meet to conform to requirements. This can include specifications for raw materials, including water, semi-finished or finished goods, and reference materials that impact the final product. The specifications for the QC steps and the QC methods should be established according to the criticality of each product or criticality of the processes. All through production, criteria must be established to monitor the extent to which these products meet target specifications and control deviations.

All information required for the QC process should be included in the procedures and decision matrices. This information could include required infrastructure, equipment, instruments or other devices needed to perform the QC process, methodology, and required control samples and their distribution. All QC procedures used shall specify the authority and qualification of the operators needed for the test performance.

QC procedures shall be performed on maintained and qualified equipment which is usually identified in the production (batch) records. The calibration of the instruments needed to perform tests shall be described and documented. Specific procedures should be established for each type of measuring equipment, considering the type of equipment, the extent of use and supplier’s recommendations (e.g. checking pH meters before use or checking of balances) or according to international standards.

All appropriate calibration procedures should be described in the specifications, to ensure reliable qualitative or quantitative results.

As far as practicable, separate QC equipment can be dedicated to avoid cross-contamination between the product samples or the tests. Control material must be protected and preserved from any alteration or cross contamination from the samples themselves or from other standards or QC procedures.
9.2 Validation of QC methods

Validation shall be performed to provide evidence that the QC methods are fit for their purposes and achieve specified accuracy, precision, selectivity, sensitivity and reproducibility needed to verify the product that is being subjected to the QC process.

The method to determine the upper and lower QC limits, variability, interval confidence and the characteristics of the normal distribution of the result should be determined according to statistical principles. The ranges of acceptable variability of the process should be specified according to the characteristic of interest of the product under QC, the risk analysis output, the validation of the methods, statistical analysis of collected data and trends.

Potential interfering substances involving other manufacturing processes and other exogenous substances that could bias the QC results should be considered during the validation steps.

When there is a potential matrix effect, representative matrices may be used for a few steps of the QC but the verification of the performances of the product shall include, as a minimum, representative specified samples of each matrix to verify the performance of the product according to the intended use.

For the control of the sensitivity, trueness, precision and LLOQ, replicates can be required to verify the recovery and precision of the controlled samples at the targeted LLOQ or limit of the method and at least one other higher level.

The precision of an analytical method should be documented and the closeness of individual measures and the number of replicates defined.

9.3 Interpretation of the results

The interpretation of results and the final conclusions should be established under QC authority, reviewed, approved and signed off by the authorized QA representative.

Justification on the methods used, specifications selected for the verification of the product or the process, or any deviation from the prescribed procedure (eg. discussion about
discrepancies, false positive or false negative rate, calculations, slope, etc.), should be recorded and approved.

All rejected results (non-conforming) should be documented including the assessment of the failure. In case of failure, specifications for the retest should explain the reasons for reanalysing, inconsistent replicates, instrument failure and operator errors.

In the case of retesting, QC panel members should be tested in replicates. The retest or reintegration of results and their justification should be clearly documented. All units must be specified and expressed in international units where appropriate.

The decision, if the results or variability falls inside or outside specified limits, should be recorded as compliant or noncompliant and a decision matrix should define the further actions to be taken to stop or move forward in the manufacturing process. Further actions may require periodic review of cumulative results to ensure any changes, trending or drift over time are detected. Trending should be reported as an input into the risk assessment process and closely reviewed to determine if the problem is indicative of a more significant problem. Trending analysis and review process shall be included in the Management review process (2).

10 Conclusion

Quality control is an important and required process to detect whether or not performance requirements and quality objectives for an IVD have been met. Additionally, QC results can identify potential product risks and hazards and inform risk control measures to eliminate, reduce or mitigate identified risks and hazards to an acceptable level. A well designed QC plan (e.g., flowchart, detailing responsibilities and delegations of authorities, decisions making chart and product status) is an integral part of the quality planning and product realization planning activity phases.

The values assignment and the intervals of acceptable values for each calibrated reference material should be established through validated statistical methods in accordance to a
specified measured procedure. The number of reference panel members validated for
routine control should be maintained.

The minimum analytical sample size of the product to obtain meaningful results will be
established according to determined criteria for acceptable risk and confidence level. The
calculations and interpretation of results shall be detailed for each QC procedure. Records of
QC processes shall describe the values, acceptance and rejection criteria as well as decision
matrices.

Manufacturers have a responsibility to design and implement QC activities throughout a
product’s realization and post-production phases to identify defects and sources of failures
in the products they produce. A manufacturer’s QC activities, QA processes and QMS,
collectively, are intended to eliminate or minimize sources of defects and failures as much as
possible. Where these cannot be eliminated and residual risk remains, strategies for
managing them must be addressed taking into consideration the nature of the impact, the
IVDs capabilities, operator requirements and continuous monitoring. Manufacturers must
also decide, especially for unacceptable risks, how best to disclose residual risk information
to the user through labelling or other documents accompanying the product.
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