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

Establishing component stability for in vitro diagnostic medical devices

Annex to TGS–2
Preface

WHO Prequalification – Diagnostic Assessment: Technical Guidance Series

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

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.

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. Countries in which WHO-prequalified IVDs are procured often have minimal regulatory requirements, and the use of IVDs in these countries presents specific challenges. For example, IVDs are often used by health-care workers who do not have extensive training in laboratory techniques, in harsh environmental conditions, in the absence of extensive pre- and post-test quality assurance capacity, and for patients with a disease profile that differs from the profiles encountered in high-income countries. Therefore, the requirements of WHO prequalification may differ from the requirements of high-income countries, or those of the regulatory authority in the country of manufacture.

The Technical Guidance Series (TGS) was developed following a WHO working group 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.

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 web site.
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The draft technical guidance document was posted on the WHO Prequalification website for public consultation on 19 September 2017. 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 two-month response period was provided.

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1 Abbreviations

FMEA  failure mode and effect analysis
IFU   instructions for use
ISO   International Organization for Standardization
IVD   in vitro diagnostic
QA    quality assurance
QC    quality control
QMS   quality management system
R&D   research and development
RDT   rapid diagnostic test
SOP   standard operating procedure
TGS   Technical guidance series

2 Definitions

For the purposes of this document, the terms and definitions given in TGS-2 Establishing stability of in vitro diagnostic medical devices (1) apply:

Component: Part of a finished, packaged and labelled IVD medical device (2)

NOTE 1: Typical kit components include antibody solutions, buffer solutions, calibrators and/or control materials (2)

Constituent: For this document, constituent refers to raw materials used to make a component.

A critical constituent has any of the following characteristics:

- a new constituent i.e. a constituent not already issued as part of a product already for sale
- any constituent or accessory that must be matched (titrated, adjusted or verified for ongoing appropriateness, beyond normal incoming goods inspection procedures) within an IVD
- any constituent containing a biological agent of a labile nature (antibody, antigen, synthetic peptide, recombinant protein, nucleic acid, biocide)
- any constituent or part thereof from a new supplier or from a supplier without ISO 9001 certification or equivalent

A critical component has the same definition as in the preceding paragraphs with the term “constituent” replaced by “component”.

Prequalification of IVDs
3 Introduction

This document was developed by the Prequalification Team – Diagnostic Assessment group in WHO in response to stability concerns found during post marketing surveillance of single-use buffer vials, which are used as a kit component for rapid diagnostic tests (RDTs). The recommendations in the document may be applicable to establishing the stability for any components for IVDs although the examples and emphasis is on the change from establishing stability for multiuse dropper bottles to that for single-use vials. The procedural steps for stability studies are presented in Annex 1 as a policy (3) for illustrative purposes. Precise standard instructions as would be expected in standard operating procedures (SOP) are not provided but rather a listing of what must be done.

The WHO prequalification requirements and basic principles of TGS-2: Establishing stability of in vitro diagnostic medical devices (1) apply equally to the validation of components, and this document is to be read in conjunction with the aforementioned document and TGS-4: Guidance on Test method validation for in vitro diagnostic medical devices (4).

4 Summary of the stages of a stability study for IVD components

4.1 Prepare a risk assessment based on the IVD design input documentation, the instructions for use (IFU) and the manufacturing specifications.

4.2 Prepare the study plan based on the information in the risk assessment.

4.3 Develop the protocols and any SOP required to fulfil the plan.

4.4 Select and store the materials.

4.5 Initiate the stability study.

4.6 Obtain and analyse the data as it is generated.

4.7 Prepare the report.

5 Planning and risk management

5.1 It is good practice to prepare, within the mechanisms of a quality management system (QMS), a plan for the investigation of all aspects of IVD stability. Planning is as important for components, and for changes to components, as it is for studies of the complete product. A well-developed study plan, with clearly defined objectives, responsibilities, and predefined pass/fail acceptance criteria must be developed, reviewed and internally approved in advance of testing.

5.2 Planning begins with defining the aims of the study, collecting all associated information and developing a risk management plan.

5.2.1 Careful forward planning contributes to ensuring that sufficient resources are made available, effective studies are performed and that both
experimental results and associated documentation are recorded in an appropriate manner.

5.2.2 The risk assessment must cover all aspects of the IVD itself in addition to considering the components concerned.

5.2.3 Information must, as a minimum, come from the design input documentation for the IVD, the manufacturing specifications of the component, the IFU and any claims made in submissions to assessment bodies including the intended use, the intended users and the intended environments of use. Manufacturing specifications should include in-process and lot release\(^1\) quality assurance (QA) parameters.

5.2.4 The final risk assessment must define not only the parameters that require a stability study but also those necessitating re-validation (e.g. Table 1).

- For evaluation of single-use buffer vials the factors in Table 1 can be important but will be different dependent on the component, the intended use including regions of intended use of the IVD.

\(^1\) Lot release is the process of evaluation of an individual lot before giving approval for its release to the market.
Table 1: Parameters required for determination of stability of product components.

<table>
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| From the user inputs: likely storage and in-use environmental conditions in countries of use | **Temperature range:** at least 4 - 40°C, with cyclic changes  
**Consideration:** Many RDTs are stored in non-controlled temperature environments where temperatures range from cool temperatures overnight to hot temperatures during the day  
**Humidity:** a wide range  
**Consideration:** 25% relative humidity to mimic desert humidity and >85% to mimic tropical humidity  
**Pressure range:** sea level to 3000 metres.  
**Consideration:** air cargo-hold pressure, use on high mountains  
**Degradation:** in challenging environments of intended use  
**Consideration:** aggressive fungi, bacteria and high light intensity, plastic degradation  
**Transportation:** at least 4 - 50°C, with cyclic changes  
**Consideration:** temperatures are expected to be even more extreme than those experienced in storage by users, possibility of freezing  
**Mechanical stress:** physical shocks during transport and stresses from handling by users |
| From the user inputs: likely storage and in-use environmental conditions in countries of use | **pH:** as validated by research and development (R&D) department, end of life value important  
**Viscosity:** as validated by R&D department  
**Conductivity:** as validated by R&D department; good control of manufacture and changes on storage  
**Biocide functionality:** if required, biocides must remain potent  
**Labelling:** attachment and clarity  
**Consideration:** Glue leaching through the vial when exposed to extreme environmental conditions and compromising the solution within  
**Residual fill-volume:** dependent on plastic and leakage, humidity and pressure the fill-volume can vary with time |
| From manufacturing specification for solution contained within the vial | **Delivered volume:** when used as defined by IFU  
**Drop volume:** dependent on factors listed above, on plastic and on the angle at which the vial held. Drop volume can vary with dropper age and micropipette tips  
**Residual volume after use:** can vary with time  
**Flow time:** from specimen or reagent addition to completion of flow across the nitrocellulose membrane of flow RDT  
**Functionality:** with the stability testing panel\(^2\): all performance claims must be met |
| From QA/QC specification |  |

\(^2\) A panel is a collection of well characterised specimens and other materials that are used in quality assurance and quality control to monitor aspects of device and component function during stability studies, for in-process control, for some aspects of design validation and at lot release.
6 Validation and verification of changes to components

6.1 Verification of the stability claims of a new IVD should follow the expectations of WHO document TGS-2 (1).

6.2 If a prequalified IVD is modified or new components are introduced as a change (e.g. a change in configuration to single-use buffer vial from a multiuse dropper bottle) or if a component supplier is changed, then both re-validation and verification of stability claims must be undertaken, subject to risk assessment, as part of the change control (5, 6).

6.2.1 Changes to a prequalified IVD are required be reported to WHO according to WHO document "Reportable Changes to a WHO Prequalified In Vitro Diagnostic Medical Device" (7).

7 Product presentation for stability studies

7.1 Stability and validation studies of components must be performed using components made according to:

7.1.1 Validated manufacturing scales.

7.1.2 Finalized manufacturing specifications (8, 9, 10, 11):

- in their final packaging (including all labelling) in which the components will be made commercially available. If more than one presentation (e.g. fill-volume, bottle size) is to be provided each must be evaluated for stability,
- manufactured on qualified manufacturing equipment,
- meeting finalized and approved in-process quality control (QC) specifications.

7.2 If components are not made to final validated and documented manufacturing scale and specifications an attestation, with evidence, must be presented to the assessment body (e.g. WHO prequalification) that change of scale or documentation will not affect (11):

- any parameters of the product,
- any of the manufacturer’s claims.

7.3 Pre-production or pilot lots may only be used for stability and validation studies if these conditions are met.

8 Minimum number of lots

8.1 The conclusions from stability studies must apply to every lot of component and test device likely to be made during the commercial life of the product.

8.1.1 Sufficient numbers of different lots of component must be evaluated to give assurance that every future lot of the IVD will meet the stability claims.
• “different lots” requires different batches of critical constituents to be used in the components manufactured in different production runs.

8.1.2 Although standards (8, 9, 10) refer to the testing of at least three lots for shelf-life assignment and one lot for in-use stability, these numbers represent the minimum numbers. Testing of more lots may be necessary, depending on the lot-to-lot variance observed when different batches of critical constituents and components are used.

9 Stability of partly manufactured, bulk or stored components

9.1 Sometimes components of IVDs are prepared in bulk and stored for some time before being used in several different lots of a complete product. Some components are stored and then used in more than one product. Where such products are used in multiple assays, the remaining shelf-life or in-use life should be taken into consideration when being used as a component.

9.1.1 The design input documentation should define how long components are likely to be stored and whether the component will be stored partly manufactured or in its final configuration and packaging.

9.1.2 An IVD cannot have a labelled shelf-life beyond that of any of its components. Thus, the shortest labelled shelf-life for any component within a lot of the IVD will determine the overall shelf-life of that lot and this must be reflected on the labelling.

9.2 Considerations for components used in more than one product

9.2.1 The risk assessment prior to stability and validation studies must take into consideration each of the products in which the component will be used.
• the manufacturer must consider each factor and parameter for each product validated during R&D work and then specified in the manufacturing documentation;
• if validated parameters are different between products in which the component is to be used, the risk evaluation must identify those differences and ensure that the study plan will demonstrate proof of correct function in all products for all uses.

10 Quantitative reporting of stability results

10.1 Stability study results, like those for QA testing for lot release should be numerically quantified.

10.1.1 It is important to be able to demonstrate whether or not a parameter has changed during the course of a stability study and if so by how much it has changed. Any quantitative change can then be compared to the predetermined limits which are those within which the IVD will function.
• predetermined limits for the parameter will have been established in validation studies.
• the fact of a QC specimen being found reactive, or non-reactive, during stability studies is not informative unless there is a validated relationship to the claims of the IVD.
• WHO has observed that manufacturers use strong positive specimens in the panel which are reactive at the beginning and at the end of the stability study. However, this does not provide any indication of whether the component has lost activity and whether the potential decrease in activity is significant. QC/QA panel members should be prepared close to the limit of detection as suggested in CLSI EP12 (12).

10.1.2 Although many IVD are not intended to produce quantitative test results it is generally possible to make the reading of results objective by use of a scoring system.
• WHO recommends the use of scoring cards where intensity of the colour reaction (as noted on the scoring card) is scored either semi-quantitatively (e.g. −, +, ++, ++++, +++++) or quantitatively (e.g., a score of 0 to 5).
• some IVDs for antibody detection might stipulate that the strength of test result is not correlated with the antibody titre, although for any antibody the signal strength normally correlates with dilution of the antibody solution and with the relative activity of the IVD.

11 Monitoring specificity in stability studies

11.1 Specificity is among the most significant performance claims for an IVD with diagnosis as the intended use and is often ignored compared with the prominence given to sensitivity studies.

11.1.1 Specificity is influenced by the additives in solutions and diluents (detergents, chaotropic agents, cell constituents, masking proteins) thus monitoring the stability of these is an important function of the stability testing panels.
• it is recommended to collect a set of false reactive specimens as well as interfering specimen types (13) during the R&D phase of product design and to include these in the stability testing panel to monitor and control not only lot-to-lot variation but also stability. Changes in results for the stability testing panel members chosen to monitor stability should be investigated.

12 Zero time values and variance

12.1 The value of each measured characteristic at the beginning of the stability study and its variability over the study are important pieces of information.

12.1.1 Characteristics should be measured independently for each lot of material in the stability study to provide a “time zero” or benchmark value.
subsequent analysis of the stability data will indicate whether a statistically significant change has occurred to any measured parameter for any lot during the study. Although relevant practical allowable changes should have been predetermined in product or process validation, all statistically significant changes should be evaluated stringently to decide whether they may be representative of some otherwise undetected important change.

13 Using data from accelerated studies

13.1 For the purposes of WHO prequalification, labelling should be based on real-time stability studies.

13.1.1 Accelerated shelf-life studies can be used in submissions to WHO prequalification, however, real-time studies must be initiated and ongoing. Labelling with respect to stability at the time of prequalification will be based on the findings of real-time studies.

13.1.2 Accelerated studies may sometimes be acceptable and may be of use in providing inputs to real-time studies.

- whenever accelerated data is used in the submission, real-time data must always be supplied to WHO prequalification as it becomes available.
- Appendix B in reference (8) exemplifies the minimum requirements and methods of calculation of a predicted shelf-life from accelerated stability testing data.
14 References


Annex 1: Example policy: Stability studies for IVD components

Introduction

The following section is written for illustrative purposes as an example of a policy (3). As a policy, it explains what steps are to be taken to generate acceptable stability data for components of IVD, in this case a change from multiuse dropper bottles to single-use dropper vials. It does not give precise, standard instructions as would be expected in an SOP. As a result, the process outlined in this policy could be completed in different ways for different IVDs and component.

A manufacturer is expected to have SOPs covering all its manufacturing activities, including: performing risk assessments, preparing testing plans, performing document and change control, selection and use of appropriate statistical methods and for operation of all instruments in its manufacturing facilities. These would also include precise instructions for all aspects of stability determination, for example: choice of reagents and test devices, conditions for storage of components, methods for linking design input requirements to the predefined outcomes of stability studies, etc.

For the purposes of this guidance and to illustrate this expectation, the planning described here will refer to such specific SOPs.

A:1. Summary

A:1.1 This example of a stability policy has been written in line with the requirements of ISO 23640:2011 (9) and CLSI EP25-A2 (8).

A:1.2 The policy outlines the procedures necessary for collecting the data required before a component shelf-life can be assigned but does not provide detailed guidance on how to assign that shelf-life.

A:2. Health, safety and the environment

A:2.1 No specific requirements for the use of this documentary policy but see paragraphs Appendix sections 5.1.1, 6.1.2 and 6.1.28.

A:3. Training requirements

A:3.1 Technical staff must be trained on all the instrumentation to be used, on the specific assays to be performed, and on the conduct and reporting of stability studies.

- Specific training is required before temperature monitoring and recording of those incubators, fridges, freezers and cold rooms used specifically for stability studies is commenced.
- Data analysis should be performed by qualified staff who have received specific training.
- For assays with visual interpretation, the staff should pass all required tests (e.g. for colour-blindness) to ensure consistent and accurate reporting.
A:4. Responsibilities

A:4.1 The R&D department is responsible for the development and documentation of a testing plan, including pre-determination of the requirements (required test outcomes) used for defining stability and the selection of materials and specimens to be tested.

A:4.2 The R&D department is responsible for obtaining required materials, putting them into the correct environments, conducting the subsequent testing, and validation and monitoring of equipment, unless agreed otherwise.

A:4.3 The R&D Project Leader is responsible for assigning the allowable component life from data generated in the study.

A:4.4 The R&D Project Leader, along with the QA manager, is responsible for investigating any excursion/deviation from expectation.

A:5. Develop the risk management documentation

A:5.1 Prepare a risk management document, normally as a failure mode and effect analysis (FMEA), with supporting documents to cover all the technical aspects of the component under evaluation. This would include at least the technical specifications, supplier details and acceptance criteria for the component, specifications for the manufacturing processes involving or leading to the component and the related QA and QC processes.

5.1.1 Evaluate all health, safety and environmental aspects of the potential studies.

5.1.2 Obtain and consider the input documentation of the product, particularly the intended use (environment of use and intended user), and the requirements from the manufacturing department provided as part of the design input requirements

- evaluate the overall conditions in which the product, and hence the component, will be required to operate and the extremes of conditions to be used in the stability study (e.g. temperature, pressure, light, humidity, microbiological contaminants, vibration) (1)

5.1.3 Consider the claims for the IVD and evaluate what it is that must be proven to be met at the end of the IVD’s assigned life, for example:

- detection of critical specimens, analytical sensitivity, precision,
- analytical and diagnostic specificity claims,
- time at which results must be read, flow times, drop volumes, stability of output reading.

5.1.4 Obtain the list of the constituents (“bill of materials”) of the component and consider the physics and chemistry of each in terms of potential effects on stability, for example:

- plastics and stoppers from some manufacturers contain mould release agents. Remnants of these materials can affect product function.
- some adhesives (e.g. gum) from labels diffuse through plastic into the contents of containers.
- some plastics are porous to water vapour and to atmospheric gases
- some antimicrobial agents are unstable under some conditions of pH and ionic composition
• assess photostability for compounds whose photostability is not known and which will not be stored in lightproof containers

5.1.5 Obtain the manufacturing documentation for the component. Evaluate the importance of each of the parameters in the manufacturing specification, evaluate each of the specification requirements and consider which parameter might affect product function and which might change over time, for example:
  • “pH 6.7 – 7.1”
  • “required drop size = 30 ±4µL”
  • “fill-volume = 120 ±10µL”

5.1.6 Consider whether components made from new raw materials (detergents, biologicals, biocides) will have the same stability as those made from stored raw materials. For example:
  • some detergents generate peroxides on standing
  • some proteins change conformation on ageing

5.1.7 Consider the minimum number of lots of components required, composed of different lots of constituents, based on knowledge of likely inter-lot variability over the commercial life of the product. (See Minimum number of lots, page 8.)

A:5.2 Consider the applicability of accelerated stability studies. If necessary, consider appropriate methods for obtaining the Arrhenius constants and subsequent proof of their validity (See Using data from accelerated studies, page 11).

A:6. Develop the stability testing plan
A:6.1 Write a complete, detailed plan, according to which everything to be done will be fully documented and then approved - before starting any practical work.
  6.1.1 Prepare the plan, based on the risk assessment, including at least each of the following:

  The work environment

  6.1.2 Consideration of health and safety issues from the use of the new components and any planned test methods.
  6.1.3 The management structure, including competences and training requirements of technical staff performing the work.
  6.1.4 The precise schedule of testing.
  6.1.5 The precise instrumentation to be used, including storage facilities and validation, calibration, monitoring and servicing.
  6.1.6 The precise ranges of storage conditions to be used (Appendix section 5.1.2)
    • “room temperature” is inadequate: the precise temperatures to be used must be defined and subsequently recorded
    • the extremes of conditions used will define the extent of permissible claims
    • simulated transport stress conditions will almost always be required before setting those same components onto long-term real-time stability studies. Simulated transportation challenge should not be
replaced by actual transportation challenge. Actual transportation challenges often do not explore the full range of transportation conditions that could be encountered (including extreme values) (1, 8)

The items to be tested

6.1.7 The lot numbers of components to be tested, with justification for any manufacturing anomalies or excursions from finalized documented procedures.
6.1.8 The lot numbers of components not under investigation (ancillary reagents) but which are essential for the testing (all the other components of the product), see A:8 Selection and storage of ancillary components or accessories for the study, page 18.
6.1.9 The storage conditions of the ancillary reagents to ensure that any changes found in the tested component are not caused by changes in the ancillary reagents.
6.1.10 The number of units (bottles, devices) of each component to be stored under each condition.

The testing methods

6.1.11 The numerical criteria by which components will be judged satisfactory to be used, given the required shelf-life of the product.
   • Define and justify the expected value for each characteristic at the beginning and end (if different) of the component’s proposed shelf-life.
6.1.12 Any physical or chemical measurements to be performed on the components, separate from the test procedure according to the IFU. For example:
   • pH
   • viscosity
   • component initial and final weights
   • drop volumes, residual volumes
   • colour, turbidity
   • resilience of labelling
   • long-term efficacy of seals and thermal sealing
6.1.13 The test for overall functionality of the new component. This is usually that the product will meet all its claims for the intended use at the end of the assigned shelf-life, with the component at the end of what will be its assigned shelf-life.
   • Some components might have longer shelf-lives than the entire product but it is important to ensure that, while a lot of the product cannot have a later expiration date than the shortest dated component, the product will function as claimed with all components at the end of their stated shelf-lives.
6.1.14 The stability testing panel to be used (A:7 Selection and storage of stability panel members for the study, page 18), justifying each panel member’s inclusion and defining:
   • the volume and characterization of the bulk material to be used
   • the numbers and volumes of aliquots to be stored

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• the storage conditions for the panel members, or the method of obtaining, characterizing and validation of labile panel members such as whole blood for cell counts
• for buffer solutions: ensure that borderline reactive and false reactive specimens are included in the stability testing panel. (See Monitoring specificity in stability studies page 10)

6.1.15 The time points over the study duration at which each of the stability testing panel members will be tested.
• It may be the case that not every panel member needs to be tested at each time point (see reference 1 section 5.9).

6.1.16 The replication (at least in duplicate) of each stability testing panel member at the times at which it will be tested.

Methods for data evaluation

6.1.17 If the product itself does not give a quantitative result consider how to quantitate stability data (see Quantitative reporting of stability results, page 9).
• stating a criterion without a numeric value (e.g. “must be positive”) is rarely acceptable since unrecorded changes might then occur

6.1.18 Define and justify the statistical techniques to be used in data analysis, in assessing variance and in assigning shelf-life.
6.1.19 Define methods for detecting and disposing outlying values
• outliers must always be recorded and must never be omitted, even if repeat testing is within specification

6.1.20 Develop and validate (15) any data capture or analysis in worksheets.
6.1.21 Prepare the graphs (paper or electronic) to visualize the performance of each parameter, physical, chemical or stability testing panel related over the course of the testing time
6.1.22 Define and document methods to ensure that any change apparently found in the component under test is not caused by changes in other components of the assay system.
6.1.23 Define methods for approval of proposed deviations from the plan and for evaluation of any unexpected events during practical work

Approval for the plans

6.1.24 Justify any planned deviations from this policy
6.1.25 Obtain authorization of the plan before starting any work.
6.1.26 Establish managerial control and review of the progression of the planned study

Preparation of specific SOP required for the stability study

6.1.27 Prepare protocols and any specific SOP for the testing
6.1.28 The outcome of the risk management and planning (outlined in the previous paragraphs) will be a set of test methods that the manufacturer will perform
to collect the stability data. The following points should be considered for all procedures:

- Ensure and document that technical staff are aware of any hazards involved in the planned study.
- Ensure that SOPs are in place for each of the testing methods to be used.
- Ensure that any new test methods or panel members are valid for the intended purpose.
- Ensure that any instruments to be used are validated for that specific purpose.
- Ensure that protocols are in place to be assured that sufficient numbers of all reagents, stability testing panels, ancillary components and other supplies are collected, labelled and stored appropriately for the whole of the study (e.g. a 25% excess over that required).

A:7. Selection and storage of stability panel members for the study

A:7.1 Use only well characterized specimens from which to prepare the stability testing panels.

A:7.2 Select stability testing panel members or physical methods to test all the functionalities of the component (4) identified in the risk assessments.

- For stability or changes to buffer solutions known false reactive and potentially interfering specimens and borderline specimens must always be included unless there is clear evidence that they are not needed.

A:7.3 Set aside sufficient volume in aliquots to allow for the testing on each occasion specified in the plan (but not so large of volume as to waste materials).

- Use the same lot of panel members throughout the testing period.

A:7.4 For panel members known to be stable over the planned period of the study:

- Store the stability panel member to prevent loss of activity, for example in aliquots below the eutectic point (e.g. at -80°C if antigen or nucleic acid).
- Do not repeatedly freeze and thaw aliquots of stability testing panel specimens.

A:7.5 Ensure that a complete set of panel members is kept at ≤80°C or other conditions under which it is known to be stable so that

- The panel can be life extended, if that is found necessary.
- Unexpected results can be checked against a separately stored, unused panel.

A:7.6 For panel members known to be labile (for example CD4 or oral fluid specimens) ensure that replacement specimens will be available to monitor the critical claims and that such specimens are fully characterized by acceptable methods.

A:8. Selection and storage of ancillary components or accessories for the study
A:8.1 Set aside sufficient components or accessories so that the study can be completed using the same “match” at each testing point.
- non-critical or interchangeable components and accessories (as defined by the risk assessment) need not be designated in advance although it is prudent to do so
- bear in mind that several lots of the component being tested will be used and the objective is to obtain data not only on stability of the component but on any variability in stability between lots (Appendix section 5.1.7)

A:8.2 Store such ancillary materials under conditions known to provide maximum stability as defined in the stability plan.
  8.2.1 Store the selected items securely.
  8.2.2 Do not allow the selected ancillary components and accessories set aside for stability studies to be used for any other purpose.

A:9. Storage of the components to be tested
A:9.1 Store the component so that liquid constituents are in contact with all the immediate packaging materials.
- if a liquid can come into contact with more than one type of material (e.g. a solution in a polystyrene vial with a neoprene stopper) then orientation of the component during storage i.e. upright versus inverted or horizontal should be such that the liquid comes into contact with all types of material.
- vibration of the stored components might be necessary on occasion

A:9.2 Record the temperature and humidity of each storage location daily.
- nominate a member of staff to do this as a critical part of their job
- ensure warnings are disseminated if storage conditions are outside the designated ranges or are showing unacceptable trends

A:10. Collection of the stability data
A:10.1 General expectations of data collection
  10.1.1 Data collection methodology must be defined in the plan for each specific study.
  10.1.2 Raw data must be collected and stored in a secure and traceable manner.
    - traceability of the data to date, operator (by name and signature), equipment
    - any worksheets used for collecting, calculating or presenting results must be formally validated, or verified by independent methods
  10.1.3 Testing is not done before the defined times
    - Additional testing is permitted but the rest of the original schedule must always be followed except with approved deviation from the plan
  10.1.4 Recording of the lot and item numbers of each component and test device tested.
  10.1.5 Recording of any unexpected events noticed while the test is being performed, for example:
• change in the physical state of the component, packaging or labelling
• change in smell or turbidity, which could indicate microbial growth
• change in viscosity or formation of precipitates
• change in colour
• leakage

10.1.6 Approval of proposed deviations from schedule. The following have proven appropriate in practice but must be evaluated for each study:
• test at the specified time for scheduled intervals of less than three weeks
• test no more than three days after the scheduled date when the intervals between testing dates are three weeks to two months
• test no more than 14 days after the scheduled date when the intervals between testing dates are greater than two months

A:10.2 Specific technical expectations of data collection
10.2.1 Establishment and recording of a time zero value (the value when the study is started: when the component is moved from optimal storage to the conditions under study, see Zero time values and variance, page 10)
• for each lot separately
• for all the parameters being evaluated
• on sufficient occasions to establish a time zero value with its variance
“Sufficient occasions” must be defined in the risk assessment and should cover all the variation that might be expected during the study due to factors such as the work environment, operator and equipment etc.

A:10.3 Specific expectations of data review during collection
10.3.1 The results are compared with the criteria in the stability plan (see appendix section 6.1.11) immediately after the test procedure is completed.
10.3.2 The testing is immediately repeated if any criteria are not met.
• a method to investigate a first failure is documented and followed but not necessarily before the repeat testing
• the original data is kept along with a record that repeat testing was done
• if the repeat assay also fails to meet criteria the project leader is alerted but a third repeat is not performed without prior investigation

A:11. Establishment of the expiry dating of the component
11.1 Establish the expiry dating for the component from real-time data only unless the relationship between accelerated data and real-time has been established.
11.1.1 Subject to prior risk evaluation it is usually safer to launch a product with a restricted life, which can be extended as real-time data is collected, than to use accelerated data. (See Using data from accelerated studies, page 11)
11.1.2 For the purposes of WHO prequalification, labelling should be based on real-time stability studies.
11.1.3 Consider lot–to-lot, user-to-user and test-to-test variation when setting the expiry dating.
A:11.2 Set the expiry date as the last date, minus a safety factor (usually one or two months for products with lives greater than 12 months and as agreed via risk evaluation for test devices and components with shorter lives or for in-use, opened or “on-board” stabilities), at which the component meets all the end of life criteria necessary for the claimed functionalities with at least 95 % confidence.

A:11.3 Ensure that real-time stability data is collected to support any dating from accelerated stability data.

11.3.1 Ensure that QA, manufacturing and marketing departments are made aware of any discrepancy between real-time and accelerated stability data as soon as possible.

**A:12. Prepare the stability report**

A:12.1 Prepare the report in accord with the QMS and document control but include at least the following in the report:

- an executive summary
- the testing plan
- lot numbers involved and the location of the manufacturing documentation
- criteria for all the testing, including physical, chemical and the stability testing panels at start and end of the assigned life of the components
- location of the records of all original testing data and storage conditions
- results obtained - present data in tabular and in graphical form
- summary and conclusions regarding stability
- an authorized statement of the component shelf-life
WHO/MVP/EMP/RHT/PQT/2019.03

The Technical Guidance Series for WHO Prequalification – Diagnostic Assessment is intended to assist manufacturers in meeting WHO prequalification requirements for their IVD. For further information on this guidance and other TGS documents email: diagnostics@who.int