Stability studies for in vitro diagnostics

Mark Lanigan
Dossier Assessments
Prequalification of Diagnostics Team
WHO
Presentation overview

• What is stability?
  – Why it is important; regulatory framework

• How is stability determined?
  – Types of stability studies
  – Experience of WHO Prequalification Dossier Assessment team
What is stability?

- In brief, stability is…

…the ability of an IVD (or its reagents) to maintain its performance characteristics over a defined time interval
Stability – regulatory framework

- EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline
- ASTM International D4169-14
Stability – WHO guidance

- WHO also recommends:
  - TGS-2 Establishing stability of in vitro diagnostic medical devices
  - Technical Specifications Series, e.g. TSS-3 Malaria rapid diagnostic tests
- But why are these necessary?
The WHO Prequalification Programme:

- WHO PQ identifies IVDs suitable in lower- and middle-income countries
  - Extremes of operating conditions
  - Diversity of user skills

Conditions not likely to be experienced where IVDs have been validated and regulated
The WHO Prequalification Programme:

- Very few stability studies take into account use of an IVD in LIMC
- Satisfactory to NRA
- Have not taken into account extremes of temperature and humidity and prolonged transportation times
How should stability be determined?

• What studies should a manufacturer perform?
• WHO experience with stability studies
Stability: three components

**Shelf life**
- How long the IVD can be stored
- Conditions of storage

**In-use stability**
- Stability of components reagents after opening, reconstitution

**Transport stability**
- Conditions experienced between manufacture and end-user
Stability: three components

Transport stability
Conditions experienced between manufacture and end-user

Shelf life
How long the IVD can be stored
Conditions of storage

In-use stability
Stability of components reagents after opening, reconstitution
A test kit and its components

- Antibodies/antigens,
- Colour-forming reagents,
- Stabilizers,
- Other reagents
Stability must be determined using the final product

Annex to TGS-2 Establishing component stability for an IVD Case study: single-use buffer vials for rapid diagnostic tests www.who.int
Stability: risk-based

• Stability studies should be based on risk assessment and take into account, as a minimum:
  – Variability of components
  – The users’ environment
  – Extremes of conditions during transport:
    • temperature, humidity, ambient pressure, vibration
Transport stability

- Conditions experienced between manufacture and end-user
Challenge at extreme conditions that simulate shipping

Transport simulation

High extreme
Temperature, humidity

Normal Storage Conditions

Determiner performance

Normal
Low extreme
Temperature, humidity

Return to Normal Storage Conditions

Determiner performance
Why not use a real shipping event?

• Actual transport:
  – Provides an indication of likely conditions
  – Conditions difficult to maintain and/or control
  – Conditions are often not recorded

• For example:
  – Kits loaded in insulated chest – freighted overnight in an air-conditioned train carriage
  – Does not reflect extreme conditions
Why not use a real shipping event?

- Actual transport is useful as a first step; however,
  - Shipping stability should be based on simulated transport challenge using controlled conditions
  - Kits should also be subjected to drop-shock testing
    
    [ASTM International D4169-14]
Other WHO PQ experiences…

• Transport conditions that do not reflect usage in resource-limited lower- and middle-income countries

• No end-of-life testing
  – Kits tested before and after transport challenge
  – But effect on shelf-life not determined

• Product performance determined using inappropriate testing panels
  – Specimens that would be unlikely to show that performance had degraded
Shelf life
• How long the IVD can be stored
• Conditions of storage
Determining Shelf life

e.g. “...the test can be stored at 5 - 35°C for 12 months...”

Normal Storage Conditions

Determine performance periodically, e.g.

35 ± 2°C

Does the IVD remain stable?

Shelf life = 12 months

Determine performance T=0

3-8°C

3, 6, 9, 12, 15 months
Does the IVD remain stable?

• Stability is…

…the ability of an IVD (or its reagents) to maintain its performance characteristics over a defined time interval
Does the IVD remain stable?

Time = at manufacture

Time = near the end of shelf life

Will the IVD will fulfil its intended use?

‘Positive’ specimen
What testing panel to use?

Low-reactivity specimen
*e.g. low concentration of target antigen*

Medium-reactivity specimen

Highly-reactivity specimen

Very high concentration of analyte
What testing panel to use?

- Depending on the IVD the testing panel should include:
  - A non-reactive [negative] specimen
  - Low-reactivity [positive] specimens
  - A medium-reactivity [positive] specimen

Control materials on their own may not be sufficient.
What testing panel to use?

- Depending on the IVD this should include:
  - All claimed analytes
    - e.g. *Plasmodium falciparum* and *P. vivax*
  - Whole blood specimens
    - Preferably capillary whole blood
Ongoing concerns with shelf life studies...

- Claimed shelf life studies:
- Not provided for all kit components
- Did not testing using whole blood specimens
- Tested only a single claimed analyte
  - e.g. *Plasmodium falciparum* but not *P. vivax*
- Used highly-reactive specimens
- Inappropriate claims:
  - “…stored at room temperature…”; “10-30°C”
  - “…stable for at least 2 years…”
In-use stability

- Stability of components reagents after opening, reconstitution
The opened test kit
Test cassette

Stored for e.g. 1 hour at claimed operating conditions

Determine performance

Stored for e.g. 2 hours

Determine performance

... 

Stored for e.g. 24 hours?

..., etc.

Determine performance
Buffer in bottle

Open at Time = 0
Determine performance, recap and return to storage

Reopen at e.g. Time = 3 months
Determine performance, recap and return to storage

Time = 12 months open, recap, test

Time = 15 months open, recap, test
In-use stability claim

- How does in-use stability of kit components affect overall performance of the IVD?
- e.g. buffer tested to only 2 months
  - Is there sufficient buffer to cover the claimed shelf life of the product (e.g. 12 months)?
In-use stability claim

• Is in-use stability reflected in the Instructions for Use?
  – e.g. “...the cassette should be used immediately after opening...”
  – e.g. “...Assay buffer is stable after opening until the end of shelf life...”
Ongoing concerns with is-use stability studies...

- In use stability studies do not reflect actual routine use of device
  - Buffers only opened once
- Studies not provided for some components (e.g. test cassette)
  - “Unnecessary” for single use devices
  - Not provided for reagent bottles/buffers
- Inappropriate instructions:
  - “...use buffer immediately after opening...”
Reporting requirements

- Each study should include:
  - Detailed testing protocol
  - Both summary and detailed results
  - Clear acceptance criteria and conclusion(s)
  - Semi-quantitative scoring of results
    
    e.g. -, w, +, ++, +++

    Reporting “positive” or “negative” or “10/10 positive” etc. not sufficient

- Preferably photographic records of results
PQ guidance, sample dossiers and technical specifications: Technical guidance series

**TGS 1** - Standards applicable to the WHO Prequalification of in vitro diagnostic medical device

**TGS 2** - Establishing stability of in vitro diagnostic medical devices

**Annex to TGS 2** - Establishing component stability for in vitro diagnostic medical devices. Case study: single-use-buffer vials for rapid diagnostic tests - **Draft**

**TGS 3** - Principles of performance studies

**TGS 4** - Test method validation for in vitro diagnostic medical devices

**TGS 5** - Designing instructions for use for in vitro diagnostic medical devices

**TGS 6** - Panels for quality assurance and quality control of in vitro diagnostic medical devices

**TGS 7** - Risk management for manufacturers of in vitro diagnostic medical devices - **Draft open for public comment**
PQ guidance, sample dossiers and technical specifications: Sample dossiers

Sample Product Dossier for a CD4 IVD
Sample Product Dossier for an IVD intended for HIV self-testing
Sample Product Dossier for a qualitative nucleic acid-based testing technology for HIV-1 and HIV-2 to detect HIV-1 and HIV-2
Sample Product Dossier for a quantitative nucleic acid-based testing technology to measure HIV-1 RNA
PQ guidance, sample dossiers and technical specifications: Technical specifications series

TSS 1 - Technical Specification Series to WHO Prequalification - Diagnostics Assessment: HIV rapid diagnostic tests for professional use and/or self-testing

TSS 2 - Technical Specification Series for submission to WHO Prequalification - Diagnostic Assessment: IVD to identify Glucose-6-phosphate dehydrogenase (G6PD) activity

TSS 3 - Technical Specification Series for submission to WHO Prequalification – Diagnostic Assessment: Malaria rapid diagnostic tests

TSS 4 - Technical Specification Series for submission to WHO Prequalification – Diagnostic Assessment: IVDs used for the detection of high-risk Human Papillomavirus (HPV) types in cervical cancer screening

TSS 5 - Technical Specification Series for submission to WHO Prequalification – Diagnostic Assessment: Rapid diagnostic tests used for surveillance and detection of an outbreak of cholera
Thank you

Any questions?