Technical Guidance and Specifications

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Joint UNICEF, UNFPA and WHO meeting with manufacturers and suppliers of in vitro diagnostics, vaccines, finished pharmaceutical products, active pharmaceutical ingredients, contraceptive devices and vector control products
Copenhagen, Denmark
18 to 21 September 2017
Guidance: Prevention better than Cure

• The need for more detailed guidance is clear
• Inefficiency, costing time and resources:
  • Producing inadequate studies
  • Assessing inadequate studies
  • Repeating work
  • Reassessing…and reassessing…
• Communicate to manufacturers what is required
  • “…how many is enough?”
• Benchmark for both manufacturers and assessors
• Basis for producing dossier grading tool
New “Guidance and training” section on website

- Sample dossiers
- Technical Guidance Series
- Technical Specification Series

http://www.who.int/diagnostics_laboratory/guidance/en/
Sample dossiers

Fictitious IVDs
Provide examples of
• formatting and reporting details required
• how to complete an “Essential Principles” checklist
• risk assessment
Technical Guidance Series (TGS)

- The Technical Guidance Series is for manufacturers interested in WHO prequalification of their IVD.

- The series is intended to help manufacturers in meeting prequalification requirements by making process more transparent and improving quality of submissions.

Goal: to continue to create TGS in response to needs identified primarily in the dossier assessment phase of PQ.
## Technical Guidance Series

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| TGS annex | Establishing component stability for an IVD  
Case study: single-use buffer vials for rapid diagnostic tests |
| TGS ... | Risk management for manufacturers of IVDs               |
| TGS ... | Quality Control for In Vitro Diagnostic medical devices for WHO Prequalification |
| TGS ... | Use of Biological Reference Materials                   |
TGS -1 Standards applicable to the WHO Prequalification of IVDs

TGS 1 identifies international standards, global, national, and regional and industry standards and regulatory authority guidelines for the manufacture, verification, and validation of IVDs.

Manufacturers are encouraged to use appropriate international standards when demonstrating the IVD conforms to relevant Essential Principles.
TGS - 2 Establishing stability of an IVD

TGS-2 describes the requirements for WHO PQ in terms of stability testing and guidance on possible approaches.

It outlines the basic principles for stability testing including:
- Critical characteristics of the IVD
- Finalized product presentation
- Minimum number of lots
- Specimens in stability panels

The studies submitted should accurately reflect the expected environmental conditions and the normal usage conditions/methods encountered by the typical users where the IVD is used.
Annex to TGS - 2 Establishing stability of an IVD

TGS-2 describes the requirements for WHO PQ in terms of stability testing for components

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 RDT.

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.
TGS - 3 Principles of performance studies

TGS-3 identifies the key principles that apply when conducting and reporting the study design, results, and conclusion of analytical and clinical performance studies that support performance claims

• relates to the information requested in Section 7 of the product dossier.
TGS - 4 Test Method Validation for an IVD

Provides guidance on the validation of the test methods used in establishing the design, the development and manufacturing of an IVD

By using validated test methods, a manufacturer can have confidence that claims made regarding the quality and performance of an IVD are supported by objective evidence.
TGS - 5 Designing an IFU for IVDs

TGS-5 provides information to manufacturers on how to effectively communicate the product information to the intended user and ensure the safe use of the IVD

- Identifies the critical information to be included in an IFU for end users.
- Encourage manufacturers to use harmonized terms in labelling, and standardized format in presenting information and performance characteristics
TGS – 6 Panels for quality assurance and quality control of IVDs

Provide guidance to manufacturers on the
• Principles for developing QA/AC panels
• Selecting specimens for inclusion
• Maintaining the panels
• Relationship between assay claims and panels used
Technical Specifications Series (TSS)
Technical Specifications Series (TSS)

Summarize minimum performance requirements for WHO prequalification, to establish:

- appropriate performance evaluation and re-evaluation criteria,
- appropriate reference methods and reference materials.

Specific requirements tailored to types of infections, conditions, etc.

- Requirements that address needs of Member States in LMIC
- Requirements that relate to general performance characteristics

Clarify requirements:

- Manufacturers
- Assessors
Technical Specifications Series (TSS)

• Currently published or in preparation
  • TSS1: HIV RDTs
  • TSS2: G6PD RDTs
  • TSS3: Malaria RDTs
  • TSS4: DRAFT HPV NATs
  • TSS5: Cholera RDTs

• Planned to continue to publish for all IVDs eligible for PQ assessment
Technical Specifications Series (TSS) Overall Structure

Intended Use:

- Sufficiently detailed statement of intended use, including:
- Function of the IVD:
- Intended testing population and operational setting:
  - e.g. for professional use in a laboratory setting and/or POC/Near-Patient Testing, self-collection, self-testing
- Clinical indication
Technical Specifications Series (TSS) Overall Structure

Scope:

Type of IVD

- Antibody RDT, Enzyme, RDT, Qualitative, Quantitative nucleic acid amplification technology)

Single analyte or multiple analyte IVD

- HIV, HIV in combination with Syphilis, HPV 16, 18 and so on
Aspects of TSS that reflect needs of Member States

Testing that reflects likely operational settings

- IVDs suitable in lower- and middle-income countries
- Risk assessment must take into consideration the likely operational setting and intended users
- Robustness, investigating deviations of temperature:
  - within those claimed in the IFU (lower, middle and upper extremes of claimed temperature range),
  - temperature ranges that exceed claimed operating conditions and cause test failure (incorrect/invalid results)
Aspects of TSS that reflect needs of Member States

Testing in a relevant specimen type

• Data must be presented to show the equivalence between specimen types used in performance studies.

• Clinical performance studies conducted using specimen types most likely to be used in resource-limited WHO Member States:
  • capillary whole blood
  • Oral fluid
  • Cervical swab, vaginal/cervical swab (self-collection), urine?
General Principles covered by the TSS

Testing relevant to IVD being assessed

• Performance studies must:
  • Use the specific final, locked-down version of the IVD intended for PQ
    (ongoing, minor design variations must be justified)
  • Use fully characterised specimens
  • Report results separately for analyte/species

• For detection of multiple analytes as a single test result:
  • Use specimens only positive for individual analytes
General Principles covered by the TSS

Testing relevant to IVD being assessed, cont…

• Evidence generated in a similar, related product may not be sufficient to support performance claims:
  • E.g. IVD-A: detects HIV only, previously submitted for assessment
  • IVD-B: based on IVD-A, but with addition of syphilis reagents for dual HIV/syphilis detection
  • Evidence from IVD-A testing to support IVD-A components in IVD-B may not be acceptable
Aspects of TSS That Reflect Needs of Member States

Testing that reflects diversity of users’ skills, training and experience

• Prequalified IVDs may be used by trained lay providers and/or health care workers
• These should also be considered as the intended user in addition to a laboratory professional
• Testing should be conducted:
  • at different geographical and epidemiological settings representative of intended users
  • by a variety of intended users
<table>
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<th>Specimen type</th>
<th>Analytical sensitivity</th>
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<td>Demonstration of equivalence between specimen types</td>
<td>Limit of detection</td>
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<tr>
<td>Demonstration of equivalence between specimen collection methods</td>
<td>Measuring range</td>
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<td>Specimen collection, storage and transport</td>
<td>Analytical specificity</td>
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<tr>
<td>Specimen collection, processing and stability</td>
<td>Potentially interfering substances</td>
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<tr>
<td></td>
<td>Endogenous</td>
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<tr>
<td></td>
<td>Exogenous</td>
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<td></td>
<td>Cross-reactivity</td>
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<tr>
<td>Precision of measurement</td>
<td>Metrological traceability of calibrators and control material values</td>
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<tr>
<td>Repeatability, reproducibility</td>
<td>Stability</td>
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<td>In-use stability</td>
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<td>Carry-over contamination</td>
<td>Flex studies</td>
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PART 2  Establishing clinical performance characteristics

Diagnostic sensitivity and specificity

PART 3  Qualification of usability (self-testing)

Qualification of usability (self-testing)
Label comprehension study
Results interpretation study
Observed untrained user study
Demonstration of IVD performance

- WHO Prequalification: **Clinical Validity**
- Does not cover **Clinical Utility**:

“...the effectiveness and/or benefits of an IVD, relative to and/or in combination with other measures, as a tool to inform clinical intervention in a given population or healthcare setting”
Usability...
Qualification of usability

Optimize the presentation of an IVD and the understanding of users in POC

Assessment of product design, instructions for use and usability of RDTs for self-testing

- Label comprehension study
- Results interpretation study
- Observed untrained user study
Development process for TSS and TGS

Each TSS and TGS relies on input from experts:

- Alignment with relevant standards, literature and best practice
- Aiming to strike balance between needs, alignment and practicability
- Series of reviews and consultation stages in drafting and finalization of documents
WHO PREQUALIFICATION PROGRAMME

Drafting
- External experts with relevant expertise (research, manufacturing, clinical use) and international regulators involved in peer review and drafting of initial document

Consultation
- Technical consultation on requirements for Technical Specifications, or consultation electronically within defined timeframe for Technical Guidance with technical experts, international regulators, R&D and IVD standard associations.

Public comment
- The documents are published on the PQ website for public comment and comments solicited from PQ stakeholders including manufacturers, industry associations, international regulators, IVD standard associations, experts

Finalization
- Finalization of the TSS/TGS including review of final document and comments by external experts.
Where to find information

Sign up to our mailing list to get updates of new TSS and TGS publications
• By emailing diagnostics@who.int

Find publications on our website
http://www.who.int/diagnostics_laboratory/guidance/en/