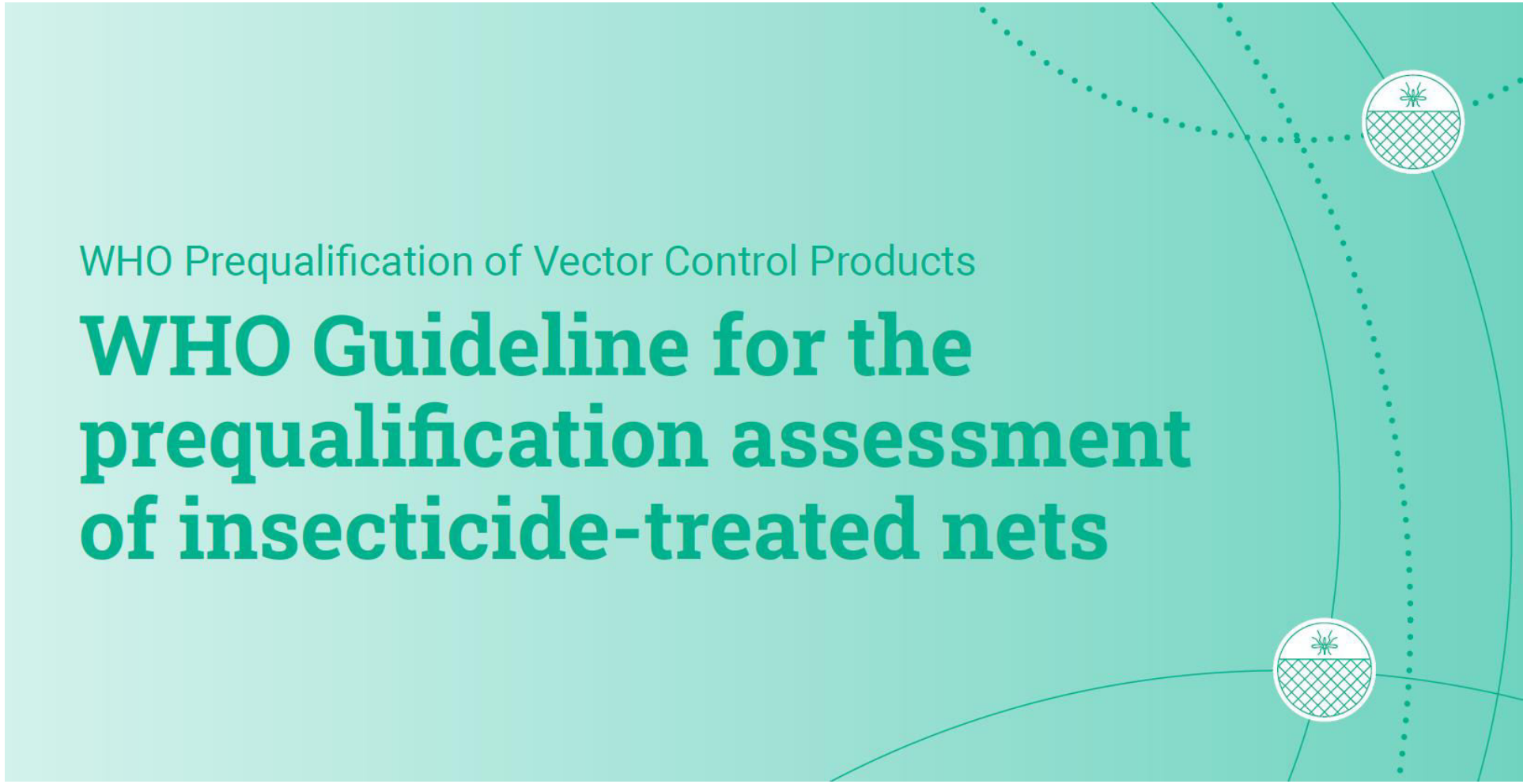
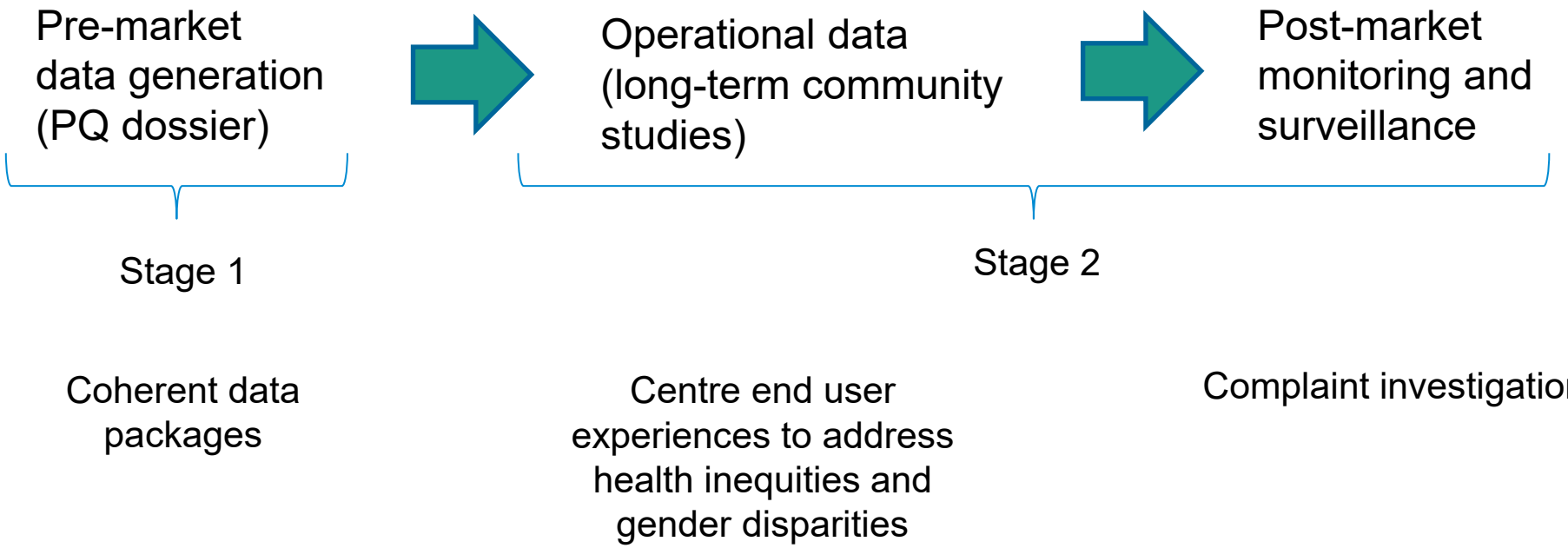


World Health Organization

Major changes in, and intent of, the revised guideline

Why update the guideline?

Data consistency and improved policy outcomes



WHO guideline for prequalification assessment of ITNs - status

- 2019 – 2023: Guideline for the prequalification assessment of insecticide-treated nets - Published December 15, 2023
  - Parent guideline document
  - 46 implementation guidance documents, including
    - Descriptions of methods and required studies
    - Templates/forms
      - Example filled templates and forms
    - Glossary
    - Index checklists for each module
    - Arranged on website by module
  - Some activities continued into 2024
    - Updated long-term community studies protocol
    - Development of guidance on post-market monitoring and surveillance

Intent of the updated guideline

- The intent of the WHO Guideline for prequalification assessment of ITNs is to prepare the way for the products of the future.
- Updated pre-market data requirements to ensure comprehensive baseline datasets on product specifications, fabric behaviour, active ingredient presentation and product performance in multiple settings

- Historically, products have been developed to ‘meet’ the requirements of the 2013 LLIN guidelines, instead of being designed for their intended use
- The updated guideline and data requirements ensures that product characteristics and performance are tied to the product intended use and duration of effect, not to ‘pass’ a guideline requirement

Intent of the updated guideline

- Generate baseline datasets for all existing products
- Revised pre-market data requirements set the baseline for updates to revised long-term community studies protocol and development of post-market monitoring and surveillance guidance

Summary of major changes from the 2013 guideline

1. Claiming equivalence to an already prequalified product
2. Increased availability of bioassay methods
3. Module 3 (quality) data requirements
    a. Full module 3 data required for each fabric
    b. Introduction of additional physical tests
    c. Real time storage stability study
    d. Regeneration study
    e. Manufacturing release specifications

4. Module 5
    a. Requirement for three semi-field studies

Claiming equivalence to an already prequalified product

- Differences in formulations and manufacturing processes, including equipment settings, create potential impacts on the physical and chemical characteristics and performance of an ITN
- Applications claiming equivalence to an already prequalified product will no longer be accepted
- Removal of the PQ301 product application code
- Full product dossiers are required for all new ITN products
- Manufacturers who are in the process of preparing an application claiming equivalence should request a pre-submission meeting
- Implementation plan for products that are currently prequalified on the basis of equivalence

Module 3 (quality)

Critical concepts and intention of major changes

Intention of the Module 3 major changes and critical concepts

The product, when it is put into use, should be the same or better than the product batches that were used in the efficacy studies

Instead of using the previous pre-established limits for physical and chemical characteristics, manufacturers should submit *product specific data* (with *product specific limits* as proposed by manufacturer) based on the physical chemical characterization of batches used in efficacy studies.

Full module 3 (quality) data for each fabric

- Each fabric used in the construction of an ITN must be supported by a full module 3 data package
- Similar fabrics which have different deniers are considered different fabrics and must be fully characterised based on the requirements for Module 3.

- For mosaic nets (when the roof and sides rely on different fabrics), an appropriate sampling plan must be proposed by the manufacturer (IG to assist).

Introduction of additional physical tests

- Requirement for additional physical tests from five batches to be submitted as part of module 3 (quality)
  - Abrasion resistance
  - Snag strength
  - Resistance to hole formation
  - (Bursting strength)

- Results from each individual test will be published as part of WHOPAR part 3
  - Composite Resistance to Damage (RD) Index scores will not be published

Real-time storage stability study (1)

- Additional study that collects real time data on the storage stability of ITNs for 24 months
- Due to the amount of time required to generate sufficient stability data to support the assignment of a recommended storage period, this study should be started as soon as the formulation has been finalised and the manufacturing process has been developed to the point where only minor changes are likely to be required subsequently.
- Where the dossier does not include real-time storage stability data covering the full proposed duration of storage, a post-prequalification commitment for the applicant to supply the full data at the conclusion of the study will apply.
- Findings of the real time storage data should be used to provide guidance to procurers and stakeholders on the expectations of product stability when stored as recommended.

Real time storage stability study (2)

Tests to be performed and testing schedule

Tests	Months						
	0	3	6	9	12	18	24
Appearance/description	x		x		x	x	x
Mean AI/synergist content	x	x	x	x	x	x	x
Wash resistance index	x				x		x
Content of impurities	x		x		x	x	x
Netting mesh size	x				x		x
Dimensional stability to washing	x				x		x
Bursting strength	x				x		x
Snag strength	x				x		x
Abrasion	x				x		x
Resistance to hole formation	x				x		x

Regeneration study

- Incorporates chemical and biological time series analysis, using the before and after wash method to estimate surface concentration of AI(s)
- Results from chemical analyses used to select wash interval
  - Statistical algorithm used to determine stabilised surface concentration
- Bioassay results inform the resumption of biological activity but are no longer used to select the wash interval
- More informative method to use for artificial ageing of ITNs
- More realistic results from semi-field trials
- Implementation guidance for study and methods

Manufacturing release specifications

- Manufacturing release specifications will be published in Part 3 of the WHO public assessment report (WHOPAR).
- The manufacturing release specification focuses on those attributes proposed by the manufacturer, and assessed by WHO, for inclusion in Certificates of Analysis (COA) for product release.
- Stakeholders, including member states and procurers may require additional tests beyond those included in the manufacturing release specifications.
  - Part 3 of the WHOPAR contains the complete product specifications for all data requirements and analysis of inter- and intra-batch variability. These results and test methods may be used by stakeholders for further testing to confirm product compliance.

Manufacturing release specifications

- The primary purpose of the manufacturing release specifications is to ensure that key physical and chemical properties of commercial batches of an ITN are controlled to within ranges consistent with a reasonable expectation of acceptable efficacy and durability.

The manufacturing release specifications are distinct from the complete ITN product specifications, which include full characterization of the product based on the defined dossier and data requirements. In most cases, not all product specifications are necessary nor appropriate for quality control related product testing activities

Manufacturing release specifications

1. Tests to be included in the specifications

At minimum, attributes/tests for:

- Appearance;
- Identification, content, and wash resistance index for each AI/synergist;
- Content of any relevant impurities;
- Fabric weight;
- Netting mesh size;
- Bursting strength (fabric and seam).

Manufacturing release specifications

2. Test methods

- Methods published in standard references such as ISO or the CIPAC Handbooks
- “In-house” or other methods
  - Justification must be provided for the selection of the method(s), including the full description, supporting validation evidence, and be permissible for publication as part of the WHO Public Assessment Report.

Manufacturing release specifications

3. Setting of limits

- Limits for tests relevant to the physical durability of the ITN, such as bursting strength, should be proposed and justified based on the available batch data characterization included in the product dossier.

- Limits for tests relevant to entomological efficacy and the residuality of insecticidal activity, such as AI content and Wash Resistance Index, should be based on results for the batches used in the storage stability and semi-field studies initially, then either confirmed or amended when results for batches used in operational use studies are available.

Manufacturing release specifications

Since some of the limits in the manufacturing release specifications will be based on the properties of the batches used in the semi-field and operational use studies, selecting the "best" batches for use in these studies may result in specifications that are difficult for commercial batches to meet.

Manufacturers are encouraged to select batches that are representative of typical production for use in the Module 5 studies to ensure that realistic and achievable specifications can be set based on the properties of these batches.

Inability of commercial batches to meet the requirements in the specification is not an acceptable justification for widening limits beyond what can be supported by results for the batches used in the efficacy studies.

Module 5 (efficacy)

Critical concepts and intention of major changes

Requirement for three semi-field studies

- Three semi-field studies required
- Two open system, e.g., EHT, in diverse geographic regions
- Third study either open, e.g., EHT, or closed, e.g., IACT
  - Demonstrate performance of ITNs against species/strains with specific characteristics
    - Pyrethroid-only ITNs
- IACT method can be used as a substitute for tunnel tests

Guideline implementation plan

Implementation plan (1)

- The WHO Guideline for prequalification assessment includes requirements for additional studies and more detailed information pertaining to the formulation, manufacturing, and physical chemical characteristics of ITNs.
- Hence, **updated product dossiers are required**.
- It is imperative that the information submitted, including previously submitted/reviewed studies are **relevant to the current manufacturing process and formulation**.

- During the product reassessment process, all products will remain on the prequalified list

Implementation plan (2)

- **Prequalified products**
  - Not based on a claim of equivalence – Submit **Module 3, 4, 5 requirements** for assessment by **31 December 2024**
  - Based on a claim of equivalence - Submit a **complete product dossier** for assessment by **31 December 2025**
- Proposed **products submitted after 30 June 2025** - Submitted product dossiers are expected to comply with the new guideline.

- WHO PQT/VCP will work with individual manufacturers to define timelines for data submission as required

Prequalified products not based on equivalence

Manufacturers of products which fall into this category will be required to submit the following for assessment by **31 December 2024**.

Module 3

1. Declaration of current formulation and manufacturing process
2. Phys/chem analysis on 5 batches (including additional physical tests)
3. Regeneration Study
4. Wash Resistance Study (using a wash interval based on the regeneration study)
5. Real-time storage stability (Interim results: minimum 6 months)

Module 4

6. Risk assessment based on current GRAM and/or citation of the available GRAs

Prequalified products not based on equivalence (2)

Module 5

1. No explicit requirement for generation of new semi-field studies.
2. Additional semi-field studies may be necessary. For each available semi-field study, the available phys/chem data (available from chemical analyses and/or QC data on production batches) of the test materials should be compared to the updated Module 3 data to justify the inclusion of the semi-field study in the updated submission
3. NOTE: Based on the results of the wash regeneration study, an analysis will be required to understand if semi-field trials are representative or if additional data are needed
4. If community studies have not been submitted, they are required by **31 December 2028**.

Prequalified products based on equivalence

- Manufacturers of products which fall into this category will be required to submit a complete product dossier for assessment by **31 December 2025**.

Proposed products submitted before 30 June 2025

- Applications will be screened based on the previous requirements
  - Allows applications to be accepted for assessment despite not necessarily fulfilling all data requirements as presented in the new guideline.
- Manufacturers are expected to rely on the updated forms/templates and provide all required information which does not require the generation of data.
- On a case by case basis, products may be prequalified in advance of receiving additional data and in such situations, the specific requirements would be included as Post-PQ Commitments.
- If a prequalification decision cannot be determined without additional data, a Request for Information (RFI) letter will be issued.

Proposed products submitted after 30 June 2025.

- For proposed ITNs which are submitted after 30 June 2025, manufacturers are expected to submit product dossiers which fully comply with the new guideline.

Road map

End 2023	Mid-2024	End 2024	June 2025	End 2025	End 2026	End 2028
Updated guideline published	Updated community studies protocol	Post-market monitoring and surveillance Updated dossiers for non-equivalent products	Transition period for dossiers ends	Updated dossiers for equivalent products All updated non-equivalent dossiers assessed	All updated equivalent dossiers assessed	Community studies submitted for all products

Stage 1	Stage 2	Stage 3	Stage 4
Pre-market data generation (PQ dossier)	Centre end user experiences to address health inequities and gender disparities	Product reassessments against new requirements	Consistent, robust public assessment reports available to guide product selection

Thank-you

Questions, comments, dialogue