Questions from the chat during the RBM VCWG webinar on 'Addressing non-biological threats to the impact of ITNs towards improved ITN quality'

From Eric Ochomo: Geraldine, what is the motivation for increasing the number of semi field studies to 3?

The number of semi-field studies has been increased to three in recognition of the plurality of mosquito populations, combinations of resistance mechanisms, and differing resistance intensities in which ITNs are deployed.

We recognize that this is an additional data generation requirement, which is why we accept one closed-system semi-field study in addition to the two open-system studies.

From Graham Small: Could the PQ team say more about 'Module 7: Post-market information' of the guideline? What data will be used and how will this be gathered and evaluated by PQ?

Any information and/or data which address the data requirements for prequalification assessment, regardless if submitted prior to or after a prequalification decision, is incorporated into the relevant module of the product dossier. For example, if a manufacturer submits a Post PQ change (PPQC) application which includes:

- *Change to declaration of product formulation, this would be incorporated into Module 3 (Note: an update to the WHOPAR Part3 would be dependent upon the nature of the change)*
- *Change to include a new target vector, this would be incorporated into Module 5 (and potentially Module 3 if further product characterization is needed) and reflected in update WHOPARs for the relevant part(s).*

The long-term community studies are required as a post-PQ commitment and it is the responsibility of the legal manufacturer to generate and submit these data. Upon receipt and evaluation, the assessments of these studies are integrated into the WHOPAR Parts 3 and 5 as further information characterizing the performance of the ITN in operational settings.

Module 7, is defined in the guidelines as follows:

> *"Statement of intent*
>
> - *The intent of Module 7 for ITNs is for WHO to collect data and information about the stability and performance of the ITN in channels of trade and operational use. This information may be submitted voluntarily or at the request of WHO by the manufacturer, procurement agencies, or NRAs.*
>
> *Product specific post-market commitments and data requirement are determined based on the assessment of available information in relation to a new product application or change application. Additional information related to specific products may be received by WHO from*

submitters other than the manufacturer. This may include complaints/product issues related to pre-/post-shipment testing or observed performance in operational settings, published literature, or other available information. Based on the review of submitted information, additional information or data may be requested from the manufacturer."

As such, Module 7 allows for the compilation of additional information about an individual product. These data and information may be generated by or in agreement with the legal manufacturer, or by independent organizations. Generally speaking, PQT/VCP does not require manufactures to conduct post-market surveillance activities beyond those which are established within the declared and ISO-9001 accredited Quality Management System (QMS) employed to control the product production.

In some cases PQT/VCP may require specific data/information to be submitted by the manufacturer based on the assessment of pre-market and/or post-market data which is submitted to WHO. The inclusion of the specific requirements in Module 7, or elsewhere in the dossier is dependent upon the nature of the information requested.

Organizations or individuals may submit information about prequalified products to WHO through the complaint handling process. Information should be emailed to rapidalert@who.int as described here: https://extranet.who.int/prequal/vector-control-products/submission-complaints

WHO may become aware of issues pertaining to prequalified products by other means, for example scientific publications in peer reviewed journals or notices of regulatory action taken by National Regulatory Authorities. In such cases, WHO may request the submission of relevant information by the legal manufacturer and/or other organizations.

From Lucca Saettone: How about fabric durability?

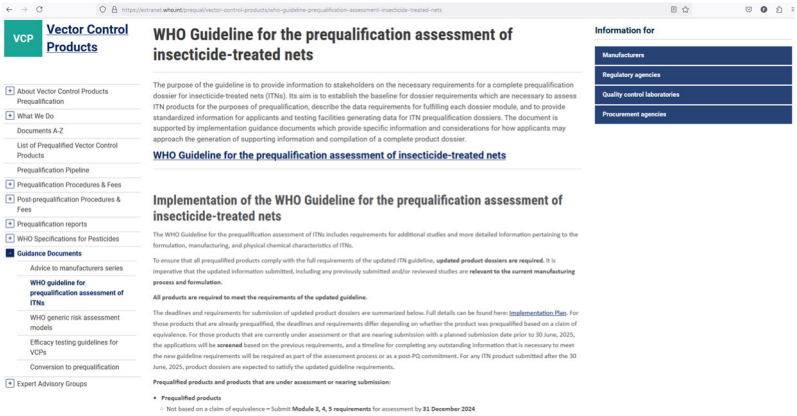
There isn't enough context to be able to answer this question completely, but in terms of fabric integrity measurements, these are conducted as part of the long-term community studies. Aspects of durability, such as appearance and dimensional stability, are assessed during the pre-market storage stability study.

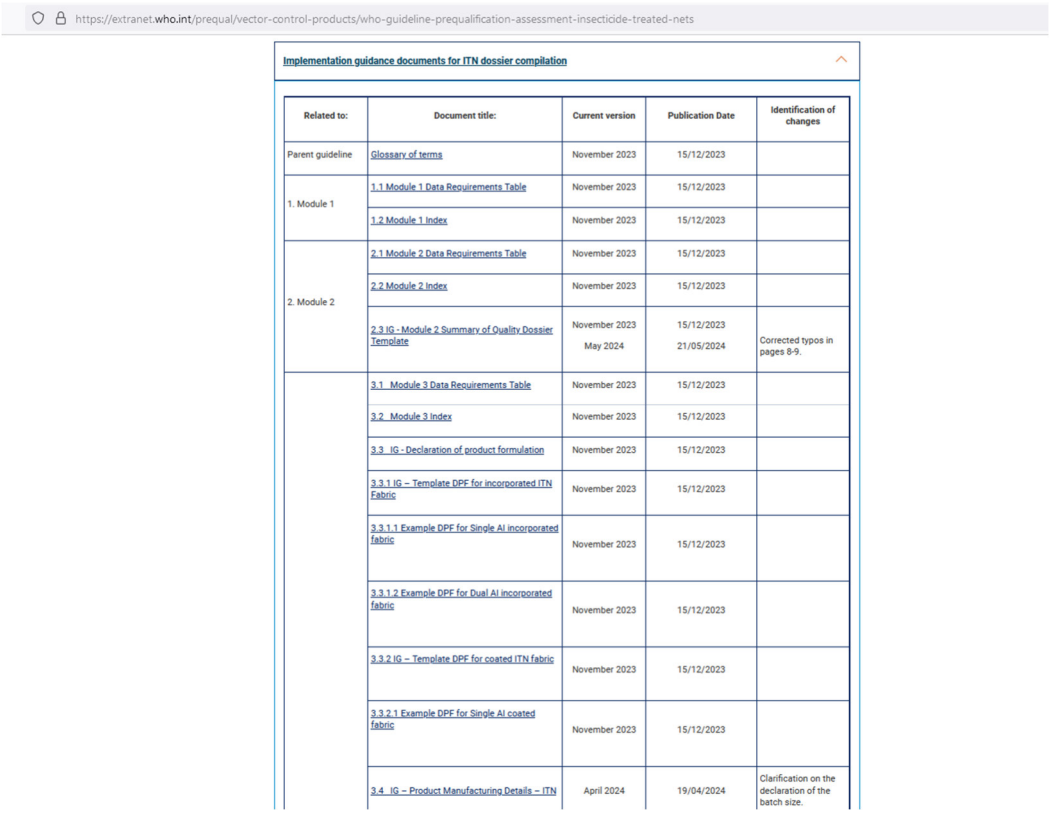
From Joseph Wagman: Replying to "Geraldine, what is t..." And as a follow-on to this question, will there be guidance on required differences among the semi-field settings (vectors, ecology, geolocation?)

At present, there are no specific required differences between semi-field study sites other than the requirement to be in diverse geographic locations.

From Dr. Poonam Sharma Velamuri, ICMR-RMRC NE, Dibrugarh: Any database management system / forms/ formats to have uniformity of results and tests from all centres.- for each tests, etc.

As part of the implementation guidance for the new ITN guideline, there are forms, templates and examples available https://extranet.who.int/prequal/vector-control-products/who-guideline-prequalification-assessment-insecticide-treated-nets





Related to:	Document title:	Current version	Publication Date	Identification of changes
Parent guideline	Glossary of terms	November 2023	15/12/2023	
1. Module 1	1.1 Module 1 Data Requirements Table	November 2023	15/12/2023	
	1.2 Module 1 Index	November 2023	15/12/2023	
2. Module 2	2.1 Module 2 Data Requirements Table	November 2023	15/12/2023	
	2.2 Module 2 Index	November 2023	15/12/2023	
	2.3 IG - Module 2 Summary of Quality Dossier Template	November 2023 May 2024	15/12/2023 21/05/2024	Corrected typos in pages 8-9.
	3.1 Module 3 Data Requirements Table	November 2023	15/12/2023	
	3.2 Module 3 Index	November 2023	15/12/2023	
	3.3 IG - Declaration of product formulation	November 2023	15/12/2023	
	3.3.1 IG – Template DPF for incorporated ITN Fabric	November 2023	15/12/2023	
	3.3.1.1 Example DPF for Single AI incorporated fabric	November 2023	15/12/2023	
	3.3.1.2 Example DPF for Dual AI incorporated fabric	November 2023	15/12/2023	
	3.3.2 IG – Template DPF for coated ITN fabric	November 2023	15/12/2023	
	3.3.2.1 Example DPF for Single AI coated fabric	November 2023	15/12/2023	
	3.4 IG – Product Manufacturing Details – ITN	April 2024	19/04/2024	Clarification on the declaration of the batch size.

From Joseph Wagman: Can you clarify if all physical durability data must be generated with nets incorporating the final AI concentrations and formulations?

All data for submission to PQT/VCP must be generated using the final formulated product.

From Lucca Saettone: Are durability results included or will be included in the LLIN specifications?

The results of studies submitted will be reflected in Part 3 of the WHOPAR along with the rest of the phys/chem characteristics of the products.

Currently, it is not the intention of WHO nor recommendation that these properties be included in manufacturing release specifications. Following the submission of product specific results and international standardization, this recommendation may be revisited.

From Dr. Poonam Sharma Velamuri, ICMR-RMRC NE, Dibrugarh: In chemical analysis why only AI conc. Be determined, we should also see any biodegradation of the AI molecule could be due to any environmental factors.

The chemical analyses focus on the total AI concentration so as to quantify the available reservoir or total content of AI. It is important that the available enforcement analytical methods reflect the necessary sensitivity to differentiate potential forms of the AI, especially those which may be less active. As an example, the reference method for quantification of deltamethrin allows for the separation of [αS,1R,3R]-isomer (also known as the S-isomer) and the non-active [αR,1R,3R]-isomer (otherwise known as the R-isomer).

WHO would welcome the development of methods and further research into the mechanisms of AI loss.

From Lucca Saettone: How about loss due to evaporation in the field as compared to 20 washes plus regeneration studies? How will you assess for 3 year AI evaporation rate in the field?

We agree that evaporative loss is an important indicator to be measured. There are no currently available validated methods for measuring evaporative loss. If such methods were to be developed and validated, these could be added as indicators to the long-term community studies.

From Joseph Wagman: Is there a scenario in which PQ would revisit a qualification decision based on the results of a post-market study?

If a stakeholder conducts a post-market monitoring study, the results of which indicate that the product is not performing as expected, then those results should be submitted to rapidalert@who.int. This allows WHO to launch an investigation. The potential outcomes of such an investigation can include suspension and/or delisting of a product.

From Mark Hoppé : Is there sufficient global capacity to generate the new data required for existing listed products, plus ongoing development of 'innovative' products, by end 2025?

Data generation for the new data requirements is already underway. We are working with manufacturers on a case-by-case basis to understand any specific challenges that they may have in terms of balancing product development vs. meeting the new guideline requirements in a timely manner.

From Stephen Poyer: Will updated public-facing dossiers be released on a rolling basis over 2025/2026 (as new and re-submissions are assessed) or will there be batch releases at certain time points?

Each WHOPAR is published as soon as the assessment for the product is complete.

From Keith Esch: Thank you for this presentation and all the great work. For forthcoming ITN community study guidance, will PQ define standards for insecticidal efficacy (i.e. bioassay endpoints and cut-offs) and chemical residue testing? Same question for the forthcoming post-market monitoring surveillance guidance.

One of the updates to the new guideline was the removal of three factors with regards to the assessment of entomological testing results: 1) the threshold of 80% mortality/95% KD in a cone test (and equivalent for tunnel tests), 2) the ability to use the results from one endpoint, e.g., 95%KD, to outweigh suboptimal results from another endpoint, e.g. mortality, and 3) the ability to use the results from one bioassay method, e.g. tunnel tests, to outweigh suboptimal results from another bioassay method, e.g. cone tests.

Manufacturers are now required to select a single primary endpoint by which the entomological consistency (laboratory bioassays) and entomological efficacy (semi-field studies) of their product can be demonstrated. Manufacturers are also required to select a single bioassay method for use, except in those circumstances where two different methods are required to demonstrate the action of two different treatments on a dual-AI ITN.

With this in place, the guidance for entomological cut-offs to be used for the interpretation of results are now focused around the demonstration of the consistency of the induced biological effect, rather than meeting a defined threshold. For example, the guidance for the difference between unwashed and 20 washed nets in a laboratory bioassay is that the difference in the primary endpoint should not be more than 5% of the odds ratio of the washed/unwashed ITNs. Similar standards will be defined in the community studies protocol regarding the acceptable difference between the operationally aged ITNs and artificially aged ITNs.

For the post-market monitoring and surveillance guidance, PQ cannot dictate the endpoints and cut-offs that stakeholders use to determine whether a product is performing as expected. However, use of the bioassay method(s), endpoints and cut-offs that were used for the pre-market data generation and PQ assessment will enhance the interpretability of the data generated during post-market monitoring.

From Lucca Saettone: I think the criteria is 80% mortality after 36 months, is this correct?

This was the criteria used by WHOPES in the previous 'Phase III' studies, yes.

From Zoe Zhang: Compared with JMPS specification, dimension stability, falimability, accelerated storage stability are not included in the current manufacture release specification. What is the requirement and suggestions of PQ for manufactures when make

a release test during production? Will manufacture need to include them or exclude them when do the release test during production?

The published manufacturing release specifications in the relevant section of WHOPAR Part 3 convey those properties which are recommended for inclusion in certificates of analysis and QC management plans.

When considering the data requirements for product assessment, it is not necessary that every physical/chemical characteristic be considered in the manufacturing release specification. As such, member states and procurement agencies may require fewer or additional tests when confirming product quality of production batches. All supporting information about the phys/chem characteristics are published in Part 3 and can be used as a point of reference if needed.

From El Hadji Amadou Niang: Realizing that the storage conditions of ITNs can vary from one country to another. How could the WHO PQ standardize to take these different conditions? Because it has been documented that storage conditions may influence the physical and chemical quality of ITNs.
And for the Post-Market surveillance, is it possible to integrate it?

We completely agree that storage conditions have the potential to influence the physical and chemical characteristics of ITNs. In terms of generating data for the real-time storage stability study, this must be conducted under the manufacturer's recommended storage conditions. This is the only way to generate data on the chemical and physical characteristics of stored ITNs without introducing additional variability that may be introduced during transport and shipment.

As part of the development of the long-term community studies protocol, we have integrated the some of the same tests that are conducted during the storage stability study into the periodic evaluations of the operationally used ITNs. The intention of this is for the data generated in the long-term community studies to function as a bridge between the pre-market storage stability study and any post-market monitoring and surveillance that may occur.

In terms of integrating these concepts into post-market monitoring and surveillance, we recommend that as much relevant background data as possible are collected, for example, certificates of analysis, pre/post-shipment testing reports, denier version of the distributed product, etc., to enhance the interpretability of the post-market monitoring results.

From Dr. Poonam Sharma Velamuri, ICMR-RMRC NE, Dibrugarh: For PQ of an ITN, will they be supported by any biochemical assays, genetic and intensity assays of the vectors in the study area selections.

Studies for submission for PQT/VCP as part of a product dossier are required to be conducted with characterized mosquito strains that are appropriate for the chemical treatments on the investigational ITN, e.g., a strain carrying metabolic resistance mechanisms for a product containing a pyrethroid and PBO. This includes characterization of the local vector population at the semi-field sites, resistance intensity, and calculation of LC_{50}/LC_{90}.

As part of the data requirements for the submission of entomology data, manufacturers are required to complete the Matrix of Mosquito strains template, summarizing all available data for the colonised mosquito strains and local vector populations at semi-field sites.

Link to MSMS template: https://extranet.who.int/prequal/key-resources/documents/ig-template-msms

Link to MSMS instructions: https://extranet.who.int/prequal/node/29922

Link to mosquito strain selection guidance: https://extranet.who.int/prequal/node/29921

From Lucca Saettone: Yes, it can be predictive but not necessarily a good indicator.

Apologies, but we cannot identify which part of the presentation prompted this comment.

From Nam Le: Regarding the method validation of the new 3 durability method: Does WHO plan to conduct a comparison of the new physical durability test methods among multiple international laboratories to verify? Like CIPAC collaboration for chemical testing methods.

WHO is not an accreditation body for testing methods. With the inclusion of these tests in the requirements, there is the opportunity for stakeholder engagement and partnership to advance the international standardization of these methods.