PQT/VCP Public Report

Product Review Report

Insecticide Treated Nets Formulated with Pyrethroid+PBO and Pyrethroid+2nd Active

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Regulation and Prequalification Department (RPQ)

Access to Medicines and Health Products (MHP)

World Health Organization (WHO)

Contents

1. Background and Rationale for the Product Review

Bednets are intended to provide personal protection against insect vector-borne diseases to anyone sleeping under the bednet. Insecticide-treated nets (ITNs) are intended to provide enhanced personal protection as well as community protection by killing the insect vector, reducing the likelihood that people, whether protected by a bednet or not, will be bitten and thus reducing the rate of transmission of vector-borne diseases.

Increasing the use of ITNs resulted in decreased malaria incidence, malaria-related deaths, and parasite prevalence in many malaria-endemic areas between 2001 and 2015. Resistance to pyrethroids among vector populations has, however, grown due to reliance on this class of insecticides in both agriculture and vector control. In response to a growing incidence of resistance, in 2012 the WHO's Global Plan for Insecticide Resistance Management in Malaria Vectors (GPIRM) called for an increased focus on the development of new vector-control products to support resistance-management strategies.

A number of new ITN products have been or are under development in response to this call. The majority of the new products combine a pyrethroid insecticide with the synergist piperonyl butoxide (PBO), while some contain a combination of a pyrethroid insecticide and a second insecticide from a different Insecticide Resistance Action Committee (IRAC) mode of action functional class.

Prior to the establishment of the Prequalification Unit-Vector Control Product Assessment Team (PQT/VCP) the assessment of ITNs by WHO was the responsibility of the WHO Pesticide Evaluation Scheme (WHOPES). The creation of PQT/VCP and the resulting product assessment transition was enacted to ensure that the evaluation of ITNs (and other vector control products) is aligned with other health products, to enhance transparency in product evaluation, and to strengthen quality assurance. The transition was completed in June 2018.

2. Purpose of this review

During the conversion of WHOPES recommendations to product prequalification listings, ITNs containing a pyrethroid insecticide in combination with either PBO or a non-pyrethroid insecticide were identified as being supported by partial quality and efficacy assessments, which focussed on the pyrethroid component. While no safety concerns that would preclude conversion to prequalification listings were identified during the conversion action, PQT/VCP indicated, at the time, that a product review process to identify and address any gaps in the data supporting these products would be initiated. This review is the response to that indication.

A product review process is intended to address an issue which impacts a group of products sharing certain attributes. The process includes:

- Identification of a need for a review of information across multiple products sharing similar characteristics or a class of products
- Identification of the relevant products based on the issue
- Review of existing information
- Identification of new information/data gaps to be addressed
- Applicant submission of information based on the identified needs
- Evaluation of submitted information to inform next steps

This product review was first presented to stakeholders in April 2019 at the i2i Manufacturers Convening in Geneva, Switzerland. Further considerations were presented regarding the "Identification of new information/data gaps to be addressed" in December 2019 at the Joint UNICEF-UNFPA-WHO Manufacturers Meeting in Copenhagen, Denmark.

Two preliminary reports have previously been written summarising the chemistry (first report) and entomology (second report) aspects of the responses received by PQT/VCP to the calls for information and identifying gaps in the existing data. The purpose of this final report is to combine the findings from the first and second preliminary reports, to provide additional discussion of the gaps identified, assess their significance, and to provide recommendations regarding future actions.

It is important to reiterate that this product review is not intended to be a reassessment of these products for the purposes of retaining their prequalification listing. Rather, this is to obtain, for the purposes of strengthening and improving the science assessment of these products going forward, information about the data the manufacturers may have on hand to support their product's use as a vector control tool but was not previously required for a WHOPES evaluation. In addition, this review will inform PQT/VCP of data that is necessary to strengthen the current assessment and improve our understanding of these products.

3. Products and communication to relevant manufacturers

In early 2020 letters were sent to the manufacturers of all combination ITNs that had either been converted from WHOPES recommendations to prequalification listings or had received a prequalification listing directly. The products in scope are those containing a pyrethroid in combination with the synergist PBO, or in combination with a second active ingredient. The letters requested information pertaining to Module 1 (labelling of the ITNs, particularly statements of shelf-life, storage conditions, and wash intervals), Module 3 (quality aspects including current and historical formulations and manufacturing processes, supporting physical/chemical data, manufacturing sites, product development, and chemical content and residual bio-efficacy of products subjected to operational use), and Module 6 (Site Master Files). A more detailed list of the information requested is provided below.

The information requested and considered in this review includes the following:

- Module 1. Administrative Information and Labelling
    - Cover letter
    - Table of contents for the submission
    - Declaration of labelling
    - Letters of authorization as required
- Module 3. Quality
    - Current formulation and manufacturing process
    - Historical formulations and manufacturing processes
    - Supporting physical/chemical data previously submitted to WHO for quality assessment and specification setting through the JMPS procedures
    - Current declaration of manufacturing sites
    - Product development information
    - Information on the chemical content and residual bioefficacy of products which have been subjected to operational use.
- Module 6. Inspection
    - Supporting site master file(s) if any changes have occurred

4. Approach taken to the review of product information and data

A working group was established comprised of expert assessors and WHO PQT/VCP team members familiar with the data requirements under both WHOPES and PQ, and with the ITN products themselves. These experts reviewed the information submitted by the relevant companies and considered the information from the perspective of the individual products, and collectively, in order to draw conclusions regarding appropriateness of the data for the purpose of evaluation and potential PQ listing, and any remaining gaps and/or areas for improvement.

The initial consideration for review of the submitted information was that the products for which data were submitted have met the current standards. They are prequalified products which have been shown to be safe and effective. The respective applicants have provided all required information at the time of WHO evaluation and maintained product dossiers in compliance with the established prequalification process.

The applicants who participated in this product review did so to assist WHO in analyzing the consistency of submitted information, identifying of gaps and key issues associated with the data packages, and ascertaining the availability of information which had previously not been requested by WHO and, as such, not submitted to WHO for evaluation. The findings from the complete review have been critical to develop substantiated proposals for enhancement of requirements for data to support the assessment of the products and for WHO to develop and disseminate meaningful guidance.

As an output of the product review, the working group developed recommendations for consideration by PQT/VCP. The analysis of the findings through which the recommendations were developed identified a critical factor: the majority of gaps and insufficient details were a direct result of the information having never been requested/required historically.

It is important to note that the Key Findings summarized below are the culmination of a detailed review of the data submitted in response to this product review. The data included an extensive volume of study reports, many of which contained confidential business information and/or confidential test data. Therefore, the complete analysis has been withheld from this final report in the interest of respecting the proprietary interests of the industry participants.

5. Key Findings

- The data presented in the dossier were often generated in a manner which deviated from the intent of the product, possibly in order to align with the standards/methods that were known and well established. A process must be implemented which allows for the flexibility to generate data which are linked directly to the intended use of the product and thereby used to substantiate product claims. Product testing should be conducted to support the use of the product.

- Encouraging and responding to innovative products, including novel/repurposed chemistries and formulation technologies, requires an openness to new methods and an assessment framework developed to incorporate and interpret additional forms of data.

- The complexities of ITN formulations and manufacturing processes can have a significant impact on the intended performance of the product. As the previous system did not incorporate a life-cycle approach to product oversight, subsequent changes to source materials, formulations and manufacturing processes may limit the usefulness of historical data.
- Often, ITNs are considered 'simple' products in comparison to other health products. However, an ITN is a complex product integrating the pesticide formulation (active ingredient) with the delivery mechanism (fabric/net), formulated and produced as a product which delivers continuous and controlled release of the active substance(s) of the formulation. ITNs are subjected to extremes in conditions before and during their extended useful life. Therefore, the directions for handling and use, often overlooked or considered as inconsequential/uncontrollable, are actually critical. For ITNs to perform as intended, for the duration intended, improved directions for handling and use of ITNs must be considered by the entire stakeholder community to maximize the potential impact of current products and inform the development of ITNs of the future.

6. Recommendations

The recommendations are presented in the following categories: Product Dossier and the established modules, WHO Specifications, and Assessment approach/process. The thoroughness of the data submitted by the respective applicants allowed for the development of recommendations beyond the scope of the information requested.

6.1. Product Dossier

With respect to general considerations and cross-cutting concepts within a complete product dossier, the working group recommends:

1. Further clarification and guidance about the intent of each module is required for improved understanding and compliance by applicants
2. Guidance be provided on acceptable methods of statistical analysis and presentation of results
3. Full details of formulations and manufacturing processes for all product samples used in the generation of data be declared.

6.1.1. Module 1

The working group recommends:

4. The current guidance on declaration of labelling be reviewed and enhanced to add critical information which is considered in the assessment
5. Guidance be provided on best practices of labelling of ITNs developed with input from member states, procurement organizations and other stakeholders
6. Specific consideration should be given to the recommended label content to be included on the sewn-on label tag, as well as consideration for the inclusion of mechanisms for practical wash counting by end users.

6.1.2. Module 2

The working group recommends:

7. Guidance be provided on the intent and structure of Module 2 to assist with the assessment by providing critical contextual information about the rationale for the product design/development and summaries of data, potentially including the following sections:

7.1. **Information regarding product development** - *e.g.,* the rationale for choosing specific ingredients in the formulation, their concentration informed by assessments of safety and efficacy, their compatibility with the active(s) and polymers, optimisation of the formulation or manufacturing process, etc.

7.2. **Summary of Product Test Samples** – declaration of the batches, formulation codes, and manufacturing process for all product samples used in data generation.

7.3. **Quality Summary** – Summary of available data across the supporting studies and analysis

7.4. **Safety Summary** – Summary of risk conclusions and analysis

7.5. **Efficacy Summary** – Summary of available data across the supporting studies and analysis

6.1.3. Module 3

The working group recommends:

8. Development of a statement of intent for Module 3 to clarify the purpose of the module
9. Introduction of a more granular structure to clearly identify and differentiate critical concepts and relevant information which are consolidated in the Module.
10. The PQ decision document should include reference to version-numbered formulation and manufacturing process documents which describe the composition and manufacture of the product to the level of detail specified in recommendations 11 and 14. Any changes to either of these should trigger a change application which should be supported either by data showing no effect on relevant properties of the yarn or ITN, or by a scientific justification citing literature demonstrating that the proposed change would not be expected to affect product efficacy or durability.

Product Composition and Manufacturing

Formulation

The working group recommends:

11. Guidance be provided requiring the complete formulation of ITNs including clear identification of all formulants (active and other). All ingredients must be unambiguously identified (preferably by chemical name and CAS Number, noting that only a proprietary name and either product code or catalogue number may be available in some cases). In the case of formulated intermediates such as masterbatches, a mechanism for ensuring that no unreported changes are made to the ingredient should be adopted.
12. All variants of a product that may be manufactured, including colour variants, should be identified separately in dossiers and in prequalification listings. The current guideline requirement to compare bioavailability curves of coloured ITNs with white ITNs of the same brand should be adhered to.
13. All declared formulations be identified using a unique code in order to support batch traceability of produced products over time.

Manufacturing Processes.

The working group recommends:

14. Data requirements and guidance documents should be updated to clearly state that manufacturing processes should be described in detail, with individual steps rather than summaries and with acceptable operating ranges for parameters such as times, temperatures, pressures, and others. The acceptable operating ranges should be supported by data generated during product development and/or manufacturing process validation studies.
15. The manufacturing process description should include details of the knitting and stitching patterns as these influence the ITN's physical durability.
16. Specifications, or an alternative mechanism to ensure batch-to-batch consistency of inactive ingredients, should be included in the data requirements.

Physical Chemical Data

The working group recommends:

17. The physical/chemical data requirements for ITNs should be reviewed with particular attention paid to meaningfulness/value of each current data requirement, gaps in information, availability of methodology, potential need for establishing attribute specific standards.
18. Requirement of a statement of approved storage conditions and maximum storage period for inclusion in the listing or decision document. This may require the addition of appropriate studies to the data requirements and validation of accelerated storage methods.

Chemistry

The working group recommends:

19. The focus of chemistry assessments should be shifted from total AI/synergist content to surface concentration and further that which is bioavailable. Total (i.e., reservoir + surface) content should be viewed as a secondary parameter. Method development for direct measurement of surface concentrations should be a longer-term goal with the use of modelling of expected surface concentrations until direct methods are available. Guidelines and data requirements should be amended, as necessary.
20. The presentation of all active substances (AI or synergist) on the surface of the yarn, including their physical states (amorphous or crystalline) and particle sizes and shapes, should be examined at appropriate points during product development and field testing. The effect of any changes in the bioavailability of the substance should be assessed.
21. Inclusion of data requirements that speak to formulation optimization for control of the active substance release from the reservoir, considering both the rate of release and potential maximal surface available concentration.
22. Data requirement and methodology for the Wash Resistance Index should be reviewed to consider the impact of selected wash intervals. This may require establishment of upper and lower limits to be defined and an analysis for linking the generated data to those data from efficacy trials.

Physical

The working group recommends:

23. Review of current data requirements and potential inclusion of additional data requirements which further characterize the physical durability of current and proposed products.

Methods and Test Parameters

The working group noted that there needs to be a defined distinction between bioassays for the purpose of characterization of quality related information about the products and testing to investigate efficacy. The following recommendations may be applicable to both Module 3 and Module 5.

24. Development of improved and expanded guidance on study designs for wash regeneration, wash resistance, and Experimental Hut Trials (EHTs). This should include considerations for appropriate statistical power calculations.

25. Development of improved guidance regarding the selection of mosquito strains to be used in bioassay and efficacy testing. Strain selection should consider resistance mechanisms, intensity, or other characteristics which are appropriate and relevant to the investigation of the intended action of the ITN.
26. Development of improved guidance regarding the selection of meaningful methods and endpoints which are appropriate and relevant to the investigation of the intended action of the ITN. This should include guidance on the weighting of different endpoints to improve the interpretation of the generated data.
27. Guidance be provided regarding the purpose of positive and negative controls in bioassays, as well as the interpretation of control data for informing the validity of the study and correction of test results (e.g., control corrected mortality).
28. Product specific sampling plans must be submitted by the applicant based on the design(s) and construction of the product.
29. Guidance be provided on the reporting of bioassay and efficacy data that captures the variability of test methods and products and standardises result reporting accordingly.
30. Guidance be developed to clarify the use of cone tests and tunnel tests, including considerations for the use of one or both methods in the generation of data for assessment.

6.1.4. Module 4

The call for information did not request information pertaining to Module 4 to be provided by applicants. It was determined by WHO at the outset of the product review process that based on the review of available information updated human health risk assessments could be developed relying on the revised 2018 Generic Risk Assessment Model for ITNs (GRAM 2018). WHO initiated the development of updated human health risk assessments focused on common pyrethroid active ingredients and PBO. The output of this effort is available on the WHO Prequalification website - Generic Risk Assessments for Insecticide-treated Nets.

Therefore, the working group recommends:

31. Development of a statement of intent for Module 4 to clarify the purpose of the module.
32. The direct citation or use of the WHO Generic Risk Assessments for ITNs, along with the existing GRAM. to inform applicants' development of human health risk assessments.

6.1.5. Module 5

The working group recommends:

33. Development of a statement of intent for Module 5 to clarify the purpose of the module. This should include differentiation of bioassay and efficacy data.
34. Characterisation of the local vector population at EHT sites, including insecticide resistance, intensity, and synergist pre-exposure (or genomic characterisation of metabolic resistance mechanisms) where appropriate should continue to be a requirement pre- and post-EHT.
35. Guidance be developed to inform the interpretation of data and potential for pooling of efficacy related results across sites and studies.

36. Guidance be provided regarding the purpose of positive and negative controls in efficacy studies, as well as interpretation of control data for informing the considerations of the validity of the study.

6.2. WHO Specifications for ITNs

The working group recommends:

37. A review of ITN specifications aimed at developing a template with clear guidance regarding the information required. This could include physical and chemical properties that are critical to efficacy and durability; and should examine how these properties can be controlled. Consideration should be given to development of testing to assess surface concentrations, which parameters are critical to physical durability, and whether a single measure of wash resistance is appropriate for ITNs.
38. Either the current single specification for LLINs should be replaced by a set of specifications applicable at different stages in the life cycle of the product (for example, manufacture, storage, in-use) or the specification should include different limits applicable at different stages for any parameters that would be expected to change over time.
39. The current wide limits for total content of active substances should be replaced with tighter limits for mean content and a separate measure of variability.

6.3. Assessment Approach/Process

The working group recommends:

40. In the absence of a clear rationale and evidence-based claims for changes, dossiers that are non-compliant with guideline recommendations should not be accepted for review.
41. Guidance be provided on the purpose and requirements of the long-term field studies conducted under operational use conditions which are identified as a post prequalification commitment. Distinctions should be made as to how the generated data inform or corroborate Modules 3 and/or 5.