PQT/VCP Public Report

Product Review Report

Indoor Residual Spraying (IRS)

Prequalification Unit – Vector Control Products Assessment (PQT/VCP)

Regulation and Prequalification Department (RPQ)

Health Systems, Access and Data (HSD)

World Health Organization (WHO)

6 August 2025

Contents

1. Background and Rationale for the Product Review

Indoor Residual Spraying (IRS) is the application of residual insecticide to the interior of houses or other buildings such that potential vector resting sites kill vectors before they are capable of transmitting diseases to humans.

Increasing use of preventative malaria control interventions contributed to a decline in clinical malaria cases between 2000 and 2015, of which 10% has been attributed to the use of IRS. Observed increases in pyrethroid resistance among vector populations led to a call in WHO's Global Plan for the Insecticide Resistance Management in Malaria Vectors (GPIRM) for an increased focus on the development of new vector-control products that can be used to support resistance management strategies.

A number of new IRS products have been developed or are under development in response to this call. The majority of these new products contain an insecticide from a different Insecticide Resistance Action Committee (IRAC) mode of functional class.

Prior to the establishment of the Prequalification Unit Vector Control Products Assessment Team (PQT/VCP) the assessment of IRS products 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 IRS 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

The World Health Organisation (WHO) *Guideline for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets* is being revised as part of the WHO PQT/VCP programme to update WHOPES guidelines. A preliminary review was conducted of historical IRS product dossiers to inform the guideline update. During the preliminary review, gaps in the data supporting these products were identified, which triggered the requirement to conduct a product review.

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

- Identification of the relevant products based on the issue
- Review of existing information on hand
- Identification of new information or data gaps to be addressed
- Call for Information
- Applicant submission of information based on the identified needs
- Evaluation of submitted information to inform next steps

The update of the IRS guideline was initially presented to stakeholders in November 2023 during the Joint UNICEF-UNFPA-WHO Meeting with Manufacturers and Suppliers held in Copenhagen, Denmark.

This final product review report contains the recommendations from the expert working group for updates to the existing guidance. It is important to note that this product review is not intended as a reassessment of products for the purpose of retaining their prequalification listing. Rather, it is intended to enhance the science assessment of these products through the development of updated

and modernised guidance. The findings from this review will inform PQT/VCP on the recommended necessary actions and help ensure that the prequalification of IRS products continues to reflect best practices and current knowledge in vector control.

3. Products and communication to relevant manufacturers

In early 2024 letters were sent to manufacturers of prequalified IRS products that had either been converted from WHOPES recommendations to prequalification listings or received a prequalification listing through the established PQ process. The products within scope were all currently prequalified IRS products.

The letters requested information pertaining to Module 1 (labelling of the IRS product, particularly identification, statements of usage instructions, storage conditions, and shelf life) and Module 3 (quality aspects including physical and chemical properties of substrates, selection of formulation type and formulants). A more detailed list of the information requested is provided below.

The information requested includes the following:

- Module 1
    - Cover letter
    - Declaration of Labelling
        - Surface type and characterisation
            - Target Application rate (mg/m^2)
            - Spray mix concentration (mg ai/ mL)
            - Volume of spray mix to be applied (ml/500m^2)
            - Residuality
- Module 3
    - Information pertaining to the development and design of IRS products which may be considered when identifying target substrates on which the product is intended for use
        - Data on the impact of the physical and chemical properties of substrates on product performance
        - Data on the impact of the physical and chemical variations within substrate types on product performance
    - Bioassay methods developed to support the demonstration of the characteristics of product performance
    - Chemical analysis methods developed to characterize the availability or presence of active ingredient(s) on surfaces

This information, in addition to the information contained in historical product dossiers, was considered in this review.

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 vector control products and the data requirements under both WHOPES and PQ. These experts reviewed the information submitted by relevant companies, and contained within historical product dossiers, and considered the information from the perspective of the individual products, and

collectively, in order to draw conclusions regarding the appropriateness of the data for the purposes of evaluation and potential prequalification listing, and any remaining gaps and/or areas for improvement.

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

Submissions were assessed on a product-by-product basis to identify gaps, outdated data and areas where further clarification would strengthen the prequalification assessment.

The applicants who submitted data to support WHO in undertaking the product review did so to assist in analysing the consistency of the submitted information, identifying 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.

As an output of the product review, the working group formulated recommendations for consideration by PQT/VCP. These findings from the complete review have been critical to develop substantiated proposals for updates to the technical requirements to support the assessment of the products and for WHO to develop and disseminate meaningful guidance.

It is important to note that the Key Findings summarised below are the culmination of a detailed review of the data submitted in response to this product review and of the historical product dossiers. The data included an extensive volume of study reports, many of which contained confidential business information and/or confidential test data. Due to the propriety nature of information, including confidential business information, study data and technical information, the full analysis has been retained by PQT/VCP. Only summary conclusions and regulatory recommendations are included in this report in line with WHO`s confidentiality practices.

5. Key Findings

- There is a significant gap in the knowledgebase of IRS products about how active ingredients interact with the variety of substrates to which they are applied and how the formulation of the product may influence such interactions and associated residual efficacy.
- Data requirements for IRS products must be aligned with the intended use pattern and acknowledge the variety of substrates upon which products may be applied. The guideline should be developed to establish clear data requirements and an assessment framework which remains flexible to enable the expansion and enhancement of formulation types and introduction of new classes of active ingredients.
- Strengthening the quality, consistency, and completeness of technical data is essential to support informed decision-making and confidence in establishing a reasonable expectation of product performance.

6. Recommendations

The recommendations are organized under the following categories: Product Dossier and its established modules. The comprehensiveness of the data submitted by applicants enabled the development of recommendations that extend beyond the scope of 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. PQT should consider whether IRS guidelines should continue to be combined with guidelines for net treatments.

2. PQT should consider introducing a requirement for all studies to be performed according to GLP standards.

3. Applicants should be required to submit all PDF files as searchable text rather than images and to include bookmarks to facilitate efficient screening and assessment.

4. The scope of the IRS guidelines should be expanded to include control of non-mosquito vectors of public health importance.

6.1.1. Module 1

The working group recommends:

5. PQT should consider whether an instruction to agitate the sprayer should be included in the directions for use for all IRS products or whether the need for this statement should be linked to the results for suspensibility testing in the physical/chemical characterisation studies. If an instruction to agitate the sprayer is included, a maximum time between agitations should be stated rather than a vague term such as “periodically".

6. Manufacturers should be required to declare a maximum storage temperature for their product and to provide evidence to support their choice of declared maximum temperature. Manufacturers should also examine whether the product in its container is sensitive to moisture and, if it is, to declare a maximum humidity as well as a maximum temperature.

7. Where there is evidence that product performance is affected by substrate, or reason to suspect that this may be the case, this should be stated clearly in the Declaration of Labelling.

8. The labelling information for IRS products should identify specific target species and insecticide resistance profiles. This information should be consistent with the species used in the efficacy studies provided for the product.

9. Products intended to be marketed for vector control purposes should not include information regarding potential use for other purposes (for example, domestic pest control) in the labelling information provided.

10. PQT should consider whether directions for use should be restricted to spraying of areas tested in the efficacy studies or whether inclusion of additional areas is acceptable.

11. Guidance on preparation of Declaration of Labelling documents should clearly state that recommended application rates must be consistent with those used in the efficacy studies provided in dossiers.

12. The IRS guidelines should include clear criteria for determining declared residual efficacy periods. PQT should consider what criteria are appropriate when different studies give different results. (For example, declaring the lowest residual efficacy period from the studies provided, declaring a range, or declaring different residual efficacy periods under different conditions).

6.1.2 Module 3

The working group recommends:

13. Guidance on quality aspects of IRS products, including formulation, manufacturing, physical/chemical characterisation, and quality control, should be added to the guidelines and suitable data requirements and Implementation Guidance documents should be developed.

Formulation

The working group recommends:

14. All formulants used in IRS products should be unambiguously identified, preferably by chemical name and CAS number. Where this is not possible, sufficient information should be provided to enable an assessor to confirm the identity of the formulant using publicly available information, such as product catalogues.

Manufacture

The working group recommends:

15. IRS product dossiers should be required to include both a flowchart and a narrative description of the manufacturing process. The narrative description should include individual steps, as well as details of process parameters and in-process controls applied.

Supporting physicochemical data

The working group recommends:

16. The requirement for physical/chemical characterisation of a minimum of three batches should be clearly stated in the guidelines for IRS products and applications not meeting this requirement should not be accepted for assessment.

17. All batches used in efficacy studies should also be included in the physical/chemical characterisation studies.

18. IRS dossiers should be required to include details of the physical state and particle size distribution of the active fraction, supported by suitable evidence.

19. PQT should consider whether additional physical/chemical testing should be performed on spray suspensions to confirm the results obtained under laboratory conditions.

20. PQT should consider introducing a requirement for IRS dossiers to include long-term storage stability studies performed under storage conditions either consistent with the declared maximum storage temperature (if this is included in the DoL for the product) or representative of storage conditions likely to be experienced by vector control products.

Specifications

The working group recommends:

21. Introduction of requirements for inclusion of tests for spontaneity of dispersion (or equivalent) in the specifications for wettable powder products and a test for particle size distribution of the active fraction in the specifications for all IRS products should be considered.

22. Limits in specifications should be based on the results reported in the physicochemical characterisation studies, especially those for the batches used in the efficacy studies. Any proposal for inclusion of limits wider than required by the reported results should be supported by a rigorous scientific justification including evidence or literature references to demonstrate that changes in the relevant parameter do not affect the performance of the product.

23. Guidance on setting of specifications should include the potential for tighter limits at manufacture if stability studies identify changes in some parameters on storage.

Site Master Files

The working group recommends:

24. A requirement for Module 6 to be provided and to include Site Master Files covering all sites of manufacture of the finished vector control product should be added to the data requirements for IRS products.

6.1.3 Module 4

The working group recommends:

25. PQT should review existing information and available authoritative evaluations to develop new hazard assessments for active ingredients used in currently prequalified products.

26. The 2018 *Generic risk assessment model for indoor residual spraying of insecticides* 2nd Edition (GRAM 2018) should be relied upon in conducting updated human health risk assessments for indoor residual spraying products.

6.1.4 Module 5

Test methods

The working group recommends:

27. PQT should consider additional innovative approaches for assessing residual efficacy of IRS products and extend the guideline to include a greater number of chemistries with different modes of action.

Mosquito strains/species used

The working group recommends:

28. Guidance should require justification for vector population choice, proportion of major vectors to which the primary and secondary endpoint(s) are based on, including ecological relevance.

29. Detailed information on strain origin, number of generations, maintenance (both at larval and adult stages), climatic conditions (humidity, temperature) and resistance status (to a range of insecticides used for public health in each study site) and frequency of screening the colony for purity should be included in all studies in each study site.

30. The guideline should require inclusion of insecticide-resistant strains showing different resistance mechanisms and provide selection criteria for these strains in study sites generating data for dossiers for laboratory, semi-field and field studies.

31. PQT should consider asking applicants to include a diversity of species—particularly those that are epidemiologically important in their study areas—when generating bioassay data. Semi-field and field studies are increasingly providing data that reflect a broader range of vector strains at specific study sites.

32. Mosquito age and physiological status be standardised and reported consistently in all efficacy studies.

33. All studies must use mosquitoes of known age and physiological status, including both unfed and recently blood-fed individuals, and consider validating results with wild-type mosquitoes from local populations.

Test items

The working group recommends:

34. The study report should include exclusive detailed information regarding test items received at the test facilities including manufacture and expiry dates as well as batch numbers used in the studies.

Study Design

Insectary rearing conditions

The working group recommends:

35. Standardised rearing protocols should be used, including fixed food volumes, tray sizes, and larval density. Mosquitoes should be reared according to consistent procedures across dossiers (adapting to each to each study site and as much as is reasonably possible). Colony fitness (study system used in generating data for dossiers) should include fitness parameters such as weight and size.

36. Mosquito rearing follow standard operating procedures (SOPs) with clearly defined parameters, and that these be applied consistently across all studies conducted within each testing facility. This standardisation would enhance reproducibility and minimise confounding due to rearing-related variability

Pre/post exposure bioassay holding conditions

The working group recommends:

37. Bioassays should be conducted within defined environmental ranges, and actual conditions should be recorded and reported in all study reports.

38. Post-exposure holding conditions should be standardised and should be fully described in all study reports.

Controls (positive and negative)

The working group recommends:

39. Treatment and control replicates should be conducted in parallel—under identical environmental conditions—and using mosquitoes from the same cohort. This applies to both laboratory and experimental hut studies. Ensuring synchronisation helps maintain internal validity and improves the interpretability of efficacy data.

40. All IRS efficacy studies should include both a negative control and a positive control using a reference product. These should be run in parallel with test products under identical conditions, to support robust interpretation and comparability of results. Studies lacking a negative control (according to surface types) should not be accepted for assessment. Studies lacking a positive control should only be accepted for assessment if this is supported by a detailed and robust scientific justification.

Endpoints

The working group recommends:

41. The IRS guidelines should include the flexibility to select endpoints and acceptance thresholds appropriate to the mode and rate of action of the AI. The dossier should include a rigorous scientific justification for the selected endpoint, and the same endpoint must be applied consistently across all studies within the same dossier—including laboratory, experimental hut, and community trials. Where variations are necessary, appropriate justifications must be provided for the selection of alternative scoring endpoints.

42. The endpoints of excito-repellency and irritancy should be incorporated into the guidelines where relevant, to ensure a more comprehensive assessment of product performance.

43. WHO-PQT should consider removing the EIR as a required indicator in community studies. Instead, exposure risk can be effectively assessed using HLCs (or CDC Light traps or other host seeking sampling methods if IHL is not approved for a specific study site (i.e. dependent on each testing site ethical regulations) conducted both indoors and outdoors, complemented by measurements of indoor mosquito resting rates. These metrics can provide a reliable estimate of how an IRS product is impacting the vector population.

44. Study reports should include a justification for the chosen time points, based on product claims, expected decay patterns, or prior data.

Sample size

The working group recommends:

45. PQT should specify a standard number of mosquitoes to be introduced to each cone for IRS bioassay residual efficacy assessment (lab, semi-field, and field studies) and consistency should be maintained across all study sites generating data for a dossier. Additionally, a consistent period for conducting bioassays should be clearly described and

all studies generated within each dossier should be in accordance with the circadian rhythms of the test system in each study site.

Substrate preparation and storage conditions

The working group recommends:

46. Study reports should include details of the environmental conditions (temperature, humidity and lighting) under which substrates were prepared and stored.

Laboratory studies

The working group recommends:

47. Guidance regarding studies intended to characterise the active ingredient should be removed from the IRS guidelines. Studies considered relevant to the application could be included in the dossier but should not be part of the requirements for dossier submission.

48. PQT should obtain advice from suitable experts on physical and chemical properties of substrates with the potential to affect the performance of IRS products, such as absorbency, adhesiveness, roughness, acidity/basicity, *etc*. This information should be used to design a set of standard substrates to be used in laboratory testing to characterise the effect of specific substrate properties on the product. The results of the laboratory studies should then be used to inform selection of substrates for use in semi-field studies to ensure that these are representative of the range of outcomes to be expected under real-world conditions.

49. The reference to spraying substrates using a Potter Tower should be replaced by more generic guidance regarding use of an automated spraying device capable of evenly delivering accurate, precise, and reproducible quantities of IRS products to substrates.

50. The IRS Guidelines should include a requirement for inclusion of filter paper assays in laboratory studies as a check on the accuracy and precision of the spraying procedure as well as clear acceptance criteria to be applied. Laboratory study reports should include a summary of the results obtained, with full results in either an appendix or an attached report, and an assessment of the results against the acceptance criteria.

51. PQT should consider developing laboratory studies to examine the effect of infiltration on the efficacy of IRS products.

52. The potential for use of different endpoints, such as time to 100% knockdown, rather than mortality in laboratory studies that aim to characterise the properties of the product should be examined.

Semi-field studies

The working group recommends:

53. Both laboratory and semi-field study reports should include full details of the preparation of the substrates, and semi-field study reports should also include details of how the huts were prepared for the study, including the date of application of the substrate to the walls. Studies not complying with the requirement for complete replacement of treated surfaces should not be accepted for assessment unless accompanied by a detailed scientific justification for not doing so.

54. IRS dossiers should be required to include a justification for the selection of substrates for use in the semi-field studies. This justification should include a discussion of the results of the laboratory studies, identification of the physical/chemical properties of substrates that affected the performance of the product, and details of key physical/chemical properties of the substrates selected for the semi-field studies. The substrates selected should include the substrate type identified as the expected worst case for performance and would ideally cover the range of expected performance outcomes.

55. The requirement in the guidelines to conduct a pre-trial assessment of hut attractiveness should be emphasised, and PQT should consider developing a clear Implementation Guidance document describing pre-trial assessment of the attractiveness of experimental huts. Studies that do not address this requirement should not be accepted for assessment.

56. Basic entomological surveillance be conducted at each site to characterise mosquito resting and feeding behaviours.

57. Acceptance criteria for the filter paper assay results should be added to the IRS guidelines. The criteria should be designed to control consistency of application, closeness to the target dose, and comparability between the test and reference products. Any studies not meeting the criteria should not be accepted for assessment.

58. PQT should consider removing the ease-of-use assessment from the guidelines and replacing it with determination of relevant physicochemical parameters such as suspensibility, foaming, persistence of suspension, clogging, consistency of spray rate, *etc*.

59. The number of application rates used in semi-field studies should be minimised to maximise the number of huts sprayed at each rate. (A maximum of two application rates is suggested.) Determination of optimum application rates should be one of the aims of the laboratory studies. In addition, the PQT should consider developing guidance on the maximum total number of arms included in semi-field studies on IRS products, including different substrates, application rates, and controls. The support of a statistician in developing this guidance should be sought.

60. Semi-field study reports should clearly state how live mosquitoes inside huts are treated in the analysis (that is, whether they are included as survivors, excluded, or analysed separately) and should include a justification for the approach chosen.

Field studies

61. PQT should consider requesting advice on these issues from statisticians and experts with broad understanding of study designs and field trials.

62. More detailed guidance on the design and conduct of community acceptability studies should be developed. For consistency with other product types such as ITNs, PQT should consider making these studies a post-market requirement for IRS products.

Data analysis

63. All studies should include a predefined statistical analysis plan clearly describing the statistical approaches to be used in the analysis of the results and the determination of the study outcomes and providing a rationale for the numbers of replicates, mosquitoes, and time points used.

64. Input from statisticians to support the development of standard statistical approaches to determining sample sizes, replicate numbers, and efficacy thresholds should be considered.