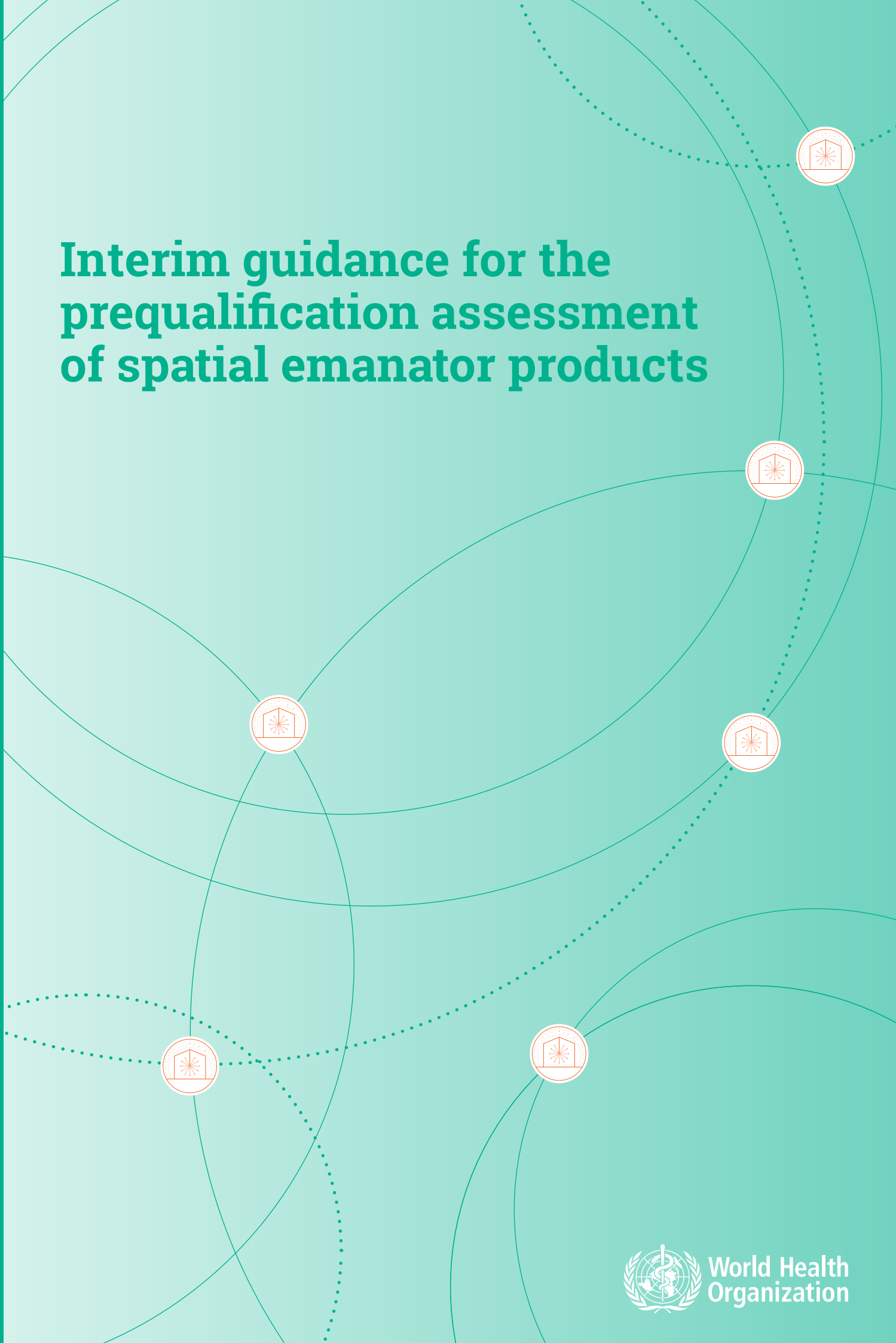
Interim guidance for the prequalification assessment of spatial emanator products

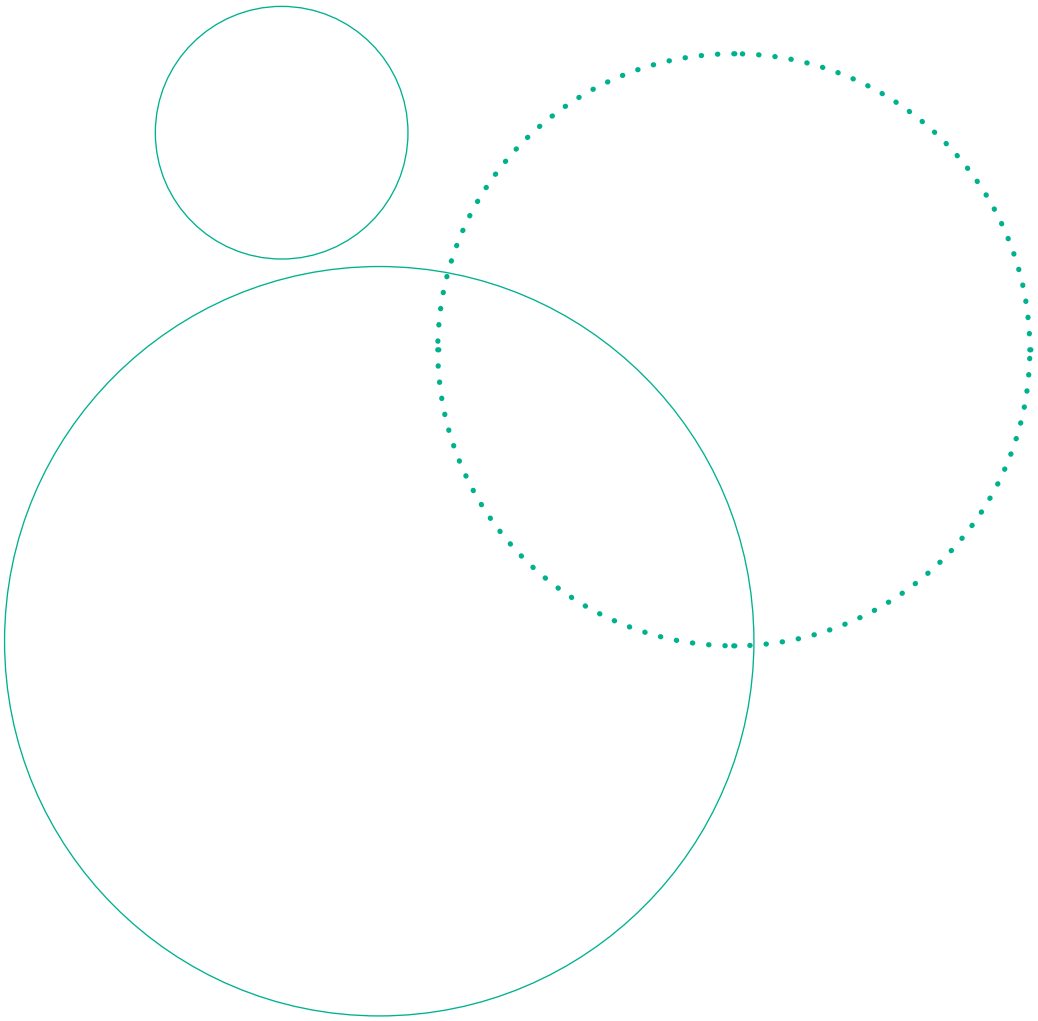


World Health Organization

Contents

Abbreviations

AI	active ingredient
DMP	Description of manufacturing processes
DMS	declaration of manufacturing sites
GLP	Good Laboratory Practice
GRAM	Generic Risk Assessment Model(s)
HSD	Health Systems, Access and Data Division
NRAs	National Regulatory Authorities
PQT/VCP	Vector Control Product Assessment Team
RPQ	Regulation and Prequalification Department
SOP	standard operating procedure
VCP	vector control product
WHO	World Health Organization



1. Introduction

The World Health Organization (WHO) prequalification assessment process for vector control products (VCPs) is coordinated through the Regulation and Prequalification Department (RPQ) in the Health Systems, Access and Data Division (HSD). These procedures are carried out by the Vector Control Product Assessment team in the Prequalification Unit (PQT/VCP).

WHO prequalification of VCPs is a comprehensive assessment of individual VCPs through a standardized procedure aimed at determining whether the product meets WHO prequalification requirements.

The prequalification assessment process includes the review of submitted product dossiers and inspection of manufacturing sites.

Products submitted for prequalification assessment that meet the WHO prequalification requirements, as determined by WHO, are included in the WHO list of prequalified VCPs.

The procedures of WHO prequalification are used to assess the quality, safety and efficacy of VCPs for the purpose of providing guidance to interested United Nations agencies and WHO Member States in their procurement decisions. WHO Member States may also recognize or rely upon prequalification decisions to support the registration of VCPs in their countries.

WHO prequalification does not imply any approval by WHO of the product and manufacturing site(s). Moreover, prequalification does not constitute any endorsement or warranty by WHO of the fitness of any product for a particular purpose, including its quality, safety or efficacy.

This document, *Interim guidance for the prequalification assessment of spatial emanator products,* was developed in response to the growing interest and requests for guidance on the prequalification dossier requirements for spatial emanator products. As interim guidance, this document is intended to convey the current assessment approaches employed by PQT/VCP for spatial emanators and identify the critical product information needed to conduct a prequalification assessment.

In developing this guidance, PQT/VCP relied upon the input of external experts as well as knowledge gleaned from the science assessment of prequalification applications to PQT/VCP, current research and ongoing work in the field, input from partners within WHO and relevant information from the 2013 *Guidelines for efficacy testing of spatial repellents* (1) and the *Guidelines for efficacy testing of household insecticide products – mosquito coils, vaporizer mats, liquid vaporizers, ambient emanators and aerosols* (2).

This document is an initial step in the development of a full guideline on the prequalification assessment of spatial emanator products. Stakeholders and partners will be consulted to generate feedback on this guidance during the process of guideline development.

The mandate of WHO PQT/VCP is to increase access to safe, high-quality and effective VCPs.

2. Intent of the interim guidance

The purpose of the interim guidance is to provide information to stakeholders on ***what*** requirements are necessary for a complete prequalification dossier for spatial emanator products.

This interim guidance establishes the baseline for dossier requirements which are necessary to assess spatial emanators products for the purposes of **WHO prequalification.** This guidance is supported by **implementation guidance** documents which provide specific information and considerations for ***how*** applicants may approach the generation of supporting information and the compilation of a complete product dossier.

A complete dossier includes:

- information to address all data requirements;
- information to enable the comprehensive assessment of the proposed product, including those characteristics or intended effects which may not be enumerated in the baseline requirements.

> The interim guidance describes the framework and approaches for prequalification assessment and decision-making for spatial emanator products. The decision to prequalify a spatial emanator product is based on the substantiation of a reasonable expectation of product performance as assessed using a weight of evidence approach.

In developing this interim guidance, the existing prequalification guidelines and guidance related to the assessment of quality, safety and entomological efficacy of spatial emanator products have been consolidated and updated. The entirety of the information herein has been developed within the guiding principles framework for the activities of WHO PQT/VCP. This interim guidance incorporates those aspects of WHO's *Guidelines for efficacy testing of spatial repellents (1)* which align with the identified dossier requirements for prequalification assessment.

The guidance is intended to:

- describe the dossier requirements for the prequalification assessment of spatial emanator products;
- describe approaches for consistent and reliable data generation for inclusion in product dossiers;
- establish the framework and concepts upon which spatial emanator products are assessed and the basis of decision;
- allow for flexibility to incorporate the future evolution of product designs/types, methods and analysis as well as deviations from standardized guidance when justified;
- inform product testing activities beyond the scope of prequalification by means of describing best practices for spatial emanator product testing.

The guideline is not intended to:

- be a guide for academic research;
- be a literature review of spatial emanator products and related methodology;
- establish best practices and recommendations for the use of spatial emanator products;
- provide guidance for use of unsubstantiated, unproven and unvalidated information or methods;
- provide guidance on requirements or processes for the development of WHO recommendations through the technical units responsible for vector-borne disease guidelines.

All stakeholders should rely on this interim guidance and the related implementation guidance documents to understand the characteristics of spatial emanator products.

Manufacturers/applicants should rely on these documents to inform the development of product dossiers for applications for prequalification assessment.

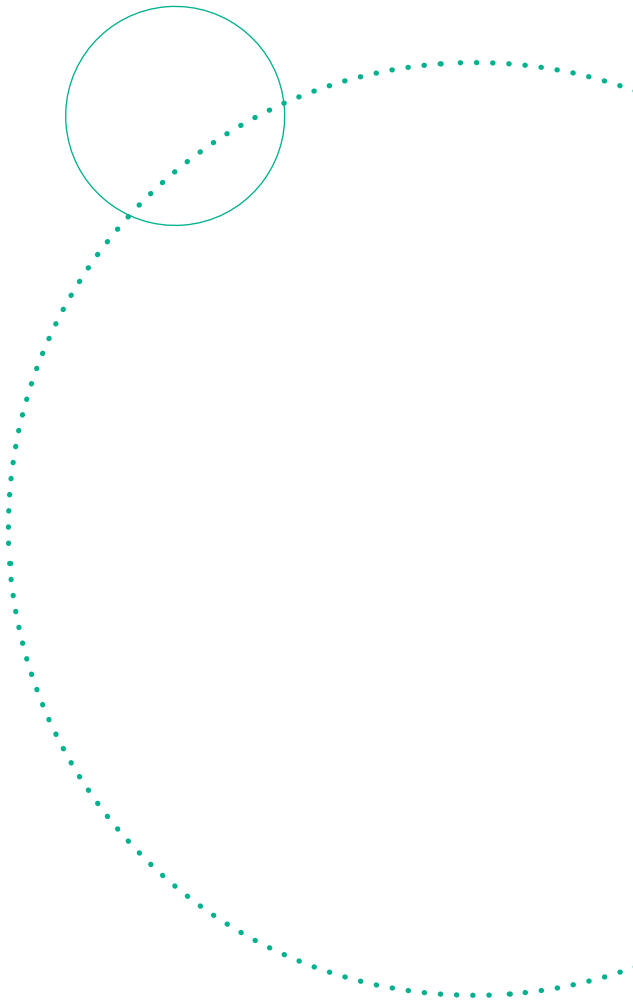
Contract research organizations should use these documents to inform their work with manufacturers in the generation of supporting data/information for the purposes of WHO prequalification assessment.

Procurement agencies and Member States should refer to these documents to understand WHO assessment approaches and data requirements for spatial emanator products, as this may assist with procurement decisions, including interpretation of available information for use in informing product selection.

Member States may also refer to the interim guidance and the related implementation guidance documents to:

- inform the development or evolution of data requirements for registration by National Regulatory Authorities;
- support engagement with WHO for collaborative initiatives related to spatial emanator product registration.

As stated in the *Overview of the WHO prequalification assessment of vector control products (3)*, once a product has been prequalified, it is included in the WHO list of prequalified VCPs and becomes eligible to participate in the procurement processes of United Nations agencies. WHO Member States are encouraged to use the WHO list of prequalified VCPs for their respective procurement decisions. Nevertheless, United Nations agencies and WHO Member States using information from the WHO prequalification assessment should not exclusively rely on WHO prequalification assessment and should make their own assessment before purchasing products included in the WHO list, including but not limited to steps such as ensuring the supplier's financing stability and standing, the ability to supply the required quantities of the product, the security of the supply chain, quality control testing and other relevant aspects.



3. Characteristics of spatial emanator products

3.1. Types of spatial emanator products

In the context of public health pesticides, the term spatial emanator refers to a class of products which are designed to emit active ingredients (AIs) into the air with the intent of repelling, disorienting and/or killing vectors, such as mosquitoes, so as to reduce vector biting of humans and thereby interfere in the transmission of vector-borne diseases. Spatial emanators may emit AI into the air through passive or active mechanisms. Globally, there are a wide variety of spatial emanator product types and designs which may be intended for indoor and/or outdoor use.

3.1.1. Passive emanators

Passive emanators are those products which are designed to emit AI into the air without a source of power or external energy. These products generally rely on evaporation of the AI(s). Passive emanators are designed and engineered to release AI from a reservoir at a particular rate, referred to as the emanation rate. The reservoir content and emanation rate are critical factors in product design, as they directly impact the product's ability to reach an air concentration so as to induce the intended entomological effect over a prolonged period. For passive emanators, the emanation rate and lifespan of a product may be influenced by the environmental conditions, for example, temperature and humidity in which the product is deployed.

3.1.2. Active emanators

Active emanators are those products which are designed to emit AI into the air by means of controlled induced action affecting the AI reservoir such as increased temperature or air movement. Products that rely on heat for AI vaporization generally work either through combustion or non-combustion based heat transfer. Combustion based active emanators generally consist of a flammable AI reservoir which is ignited thereby inducing AI vaporization without degradation through pyrolysis.

For non-combustion based active emanators, there are generally two components, the formulated AI reservoir, for example treated disc or liquid cartridge, and a product specific device which generates heat to vaporize AI typically through an electrical input or a flammable liquified gas. In most scenarios, the formulated AI reservoir is inserted into the device which generates heat, and the AI is vaporized at the target emanation rate. Active emanator products that rely on increased air movement to drive AI vaporization generally work through a product specific device containing an electric fan that forces air through or across an AI reservoir. In most types of non-combustion based active emanators, the formulated AI reservoir can be replaced, and refill packages can be procured without needing to purchase another device.

3.1.3. AIs

Spatial emanator products may include the formulation of an individual AI or mixture of AIs.

3.1.4. Spatial emanator product types within the scope of this document

The following points are important for consideration by stakeholders, including but not limited to product developers, manufacturers and procurers.

For the purposes of prequalification assessments of spatial emanator products, this interim guidance is not intended to apply to:

- spatial emanator products intended for outdoor use;
- spatial emanator products intended for personal protection, for example, clip-ons, patches and bracelets;
- spatial emanator products which induce their effect solely through physical or non-chemical modes of action;
- combustion-based emanators such as, but not limited to, mosquito coils, candles and incense.

For active emanators, the product considered in

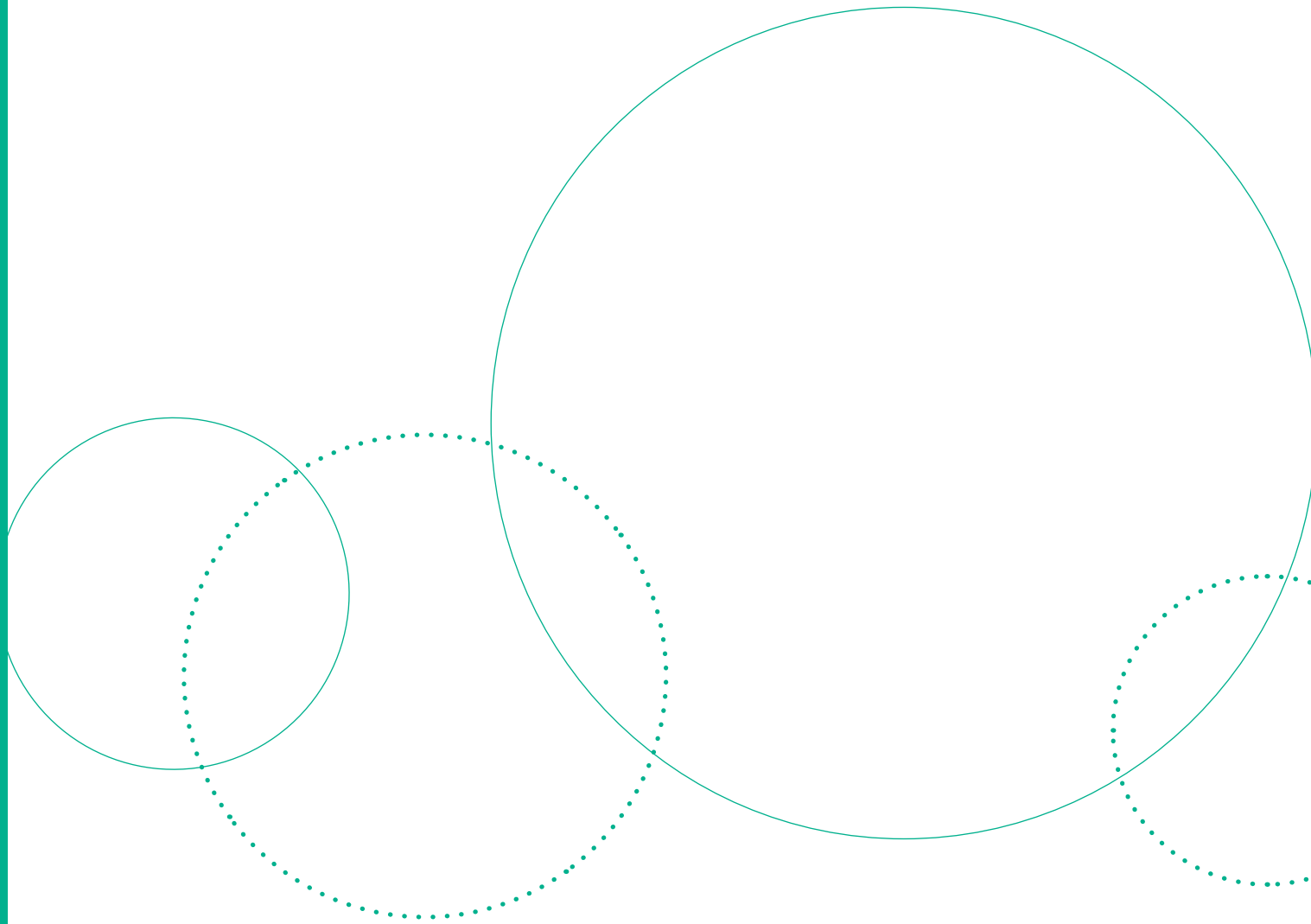
the prequalification assessment is the formulated AI reservoir. PQT/VCP does not assess the device(s) or equipment through which the formulated AI reservoir component is applied.

3.2. Defining a spatial emanator product

A spatial emanator product is defined by the manufacturer based on the declared formulation (including selection of raw materials), manufacturing process and those technical product specifications to which the product is declared to meet. If the product is an active emanator to be deployed in a product-specific device, the device and its identifying characteristics must be declared as part of the declaration of labelling.

In some contexts, spatial emanators may be referred to as spatial repellents.

For the purposes of this document, the term 'intended effect' is used to refer to any impact on either insect behaviour or characteristics induced by AI(s) in the air that results in a reduction in human-vector contact.



4. Indicators of spatial emanator performance

The prequalification decision is based on the substantiation of a **reasonable expectation of product performance.** Product performance can only be assessed after establishing and verifying the continuity of the product and its characteristics based on the declared formulation, description of manufacturing process and supporting batch production analysis. Product **performance** is demonstrated by a spatial emanator product's ability to perform the following function:

- Provide continuous controlled release of the AI(s) to maintain the intended effects of the product on target vectors over the intended useful life of the spatial emanator product when used as instructed.

Studies conducted in **free-flight rooms** rely on living organisms in controlled studies to investigate the characteristics of the treated product by observing the behavioural responses of the test organism and the induced effect of exposure to the released AI, for example, landing rate. These bioassays do not directly provide information about the potential **efficacy** of the product but are integral in investigating entomological responses of various vectors and continuity of AI emanation in response to ageing. The use of **free-flight room studies** is further discussed and defined in section 6.5.

The premarket assessment of spatial emanator products cannot reasonably ensure effectiveness of products under all operating conditions, nor in cases where products may be adversely impacted by transport, storage and use conditions beyond those recommended by the manufacturer and thereby assessed by WHO.

Efficacy data generated in various geographical settings and with a variety of vector species and/or strains provide important information about the consistency of a product's potential impact across use situations. Efficacy for spatial emanator products is influenced by the:

- **potency** of the formulated AI, meaning the amount needed to elicit the intended response (which may vary based on vector species/strain characteristics and resistance profiles);
- **emanation rate** of the product;
- **room volume** and the labelled directions for deployment of the number of products per room size;
- **air exchange** in the room and the maintenance of the target air concentration;
- handling and care of the spatial emanator product as recommended.

Efficacy is further discussed and defined in section 6.5.

Effectiveness, referring to how well the deployment of spatial emanator products in communities may perform in the real world in terms of both the intended entomological and epidemiological outcomes, is dependent upon:

- the design of the product and its potential efficacy;
- selection of an appropriate product for the cultural and entomological context in which it is intended to be used;
- consistent formulation/manufacturing;
- proper storage/transport/handling;
- use of the product as instructed.

5. Prequalification assessment of spatial emanator products

The application and assessment of spatial emanator products follow the process, terms and conditions presented in the *Overview of the WHO prequalification assessment of vector control products (3)*.

Manufacturers interested in the prequalification of a spatial emanator product are invited to contact PQT/VCP prior to the submission of their application. PQT/VCP offers presubmission meetings to ensure clarity and understanding of the prequalification process and data requirements, either generally or within the context of a particular proposed product.

All applications are screened for completeness prior to being accepted for assessment. The assessment of prequalification applications for spatial emanator products is conducted using the following criteria:

- **Quality –** Assess product formulation and construction (if applicable), manufacturing process and physical/chemical characteristics of the formulated product.
- **Safety –** Assess the hazard, exposure and risk based on the formulation and intended use of the proposed product.
- **Efficacy –** Assess information substantiating the impact of the product on the target vectors under controlled conditions and in multiple conditions/settings applicable to the intended use of the product, including chemical characterization of the samples used in efficacy studies.

The inspection of manufacturing sites involved in the production of spatial emanator products is overseen by the WHO PQT/Inspections team.

The **regulatory lifecycle** for VCPs, including spatial emanators, refers to the application/dossier preparation, submission, assessment, decision and change management of the product. For the purposes of WHO assessment and prequalification, PQT/VCP is the unit/team responsible for the assessment and decision for prequalification of vector control products.

Applications for WHO prequalification of VCPs are accepted only from the **legal manufacturer** of the products. The legal manufacturer of the VCP is the entity which is entirely responsible for the manufacturing of the submitted VCP. Legal manufacturers are required to ensure that all product dossier information on file with WHO is current and correct, including authorized points of contact. The legal manufacturer is ultimately responsible for ensuring that the prequalified product is manufactured in accordance with the information provided to WHO to support the prequalification assessment. This responsibility extends beyond the manufacturing of the product in facilities owned by the legal manufacturer and includes all contractual or toll manufacturing facilities. Legal manufacturers are also required to submit and maintain current information on the rebranding or supplemental distribution of their products to WHO.

Through the regulatory lifecycle of a product, there are often changes which may relate to the quality, safety and/or demonstrated efficacy of the product. In the assessment of such a change application for a prequalified product, WHO considers the proposed change(s) to determine whether the product is still supported by the available product dossier or if a new product application must be submitted.

6. Prequalification submission dossier format and purpose of each module

The modules which constitute a product dossier for prequalification applications to WHO are defined generically for their applicability across VCP categories and product types. For the purpose of spatial emanator products, further information on the intent and description of data requirements is provided in this section.

Implementation guidance documents that provide the relevant details for the fulfilment of data requirements for each module are available online.

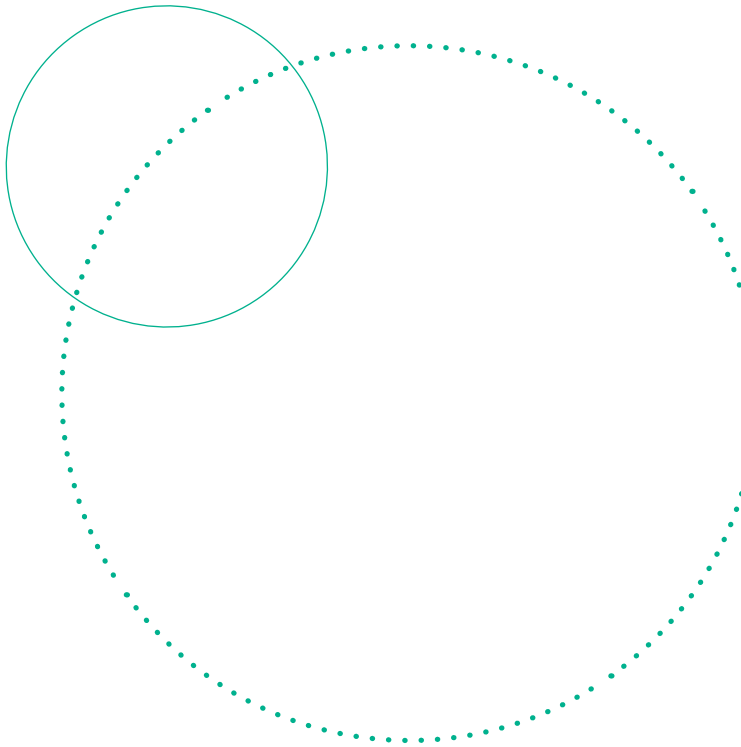
6.1. Module 1: Administrative information and labelling

Statement of intent

- The intent of Module 1 for spatial emanator products is for manufacturers to provide WHO with information which demonstrates:
  - establishment of the responsible company as the legal manufacturer/owner of the proposed product;
  - identification of authorized contacts;
  - formal request for assessment by WHO;
  - table of contents of all documents included within the application;
  - applicable label content to support the assessment of the product.

Description of requirements

- cover letter
- application form
- table of contents
- declaration of labelling, including:
  - any device or specialized equipment which is required to deploy the formulated product must be clearly stated in the declaration of labelling.
  - as spatial emanator products may be stored and deployed by end users, applicable Globally Harmonized System precautionary language and/or pictograms restricting the contact with and use of products by children should be included. This may be applicable to products in use and/or the storage of refills. Identification and implementation of necessary child-resistant packaging should be considered in accordance with national regulations in those countries where the product is intended to be deployed.



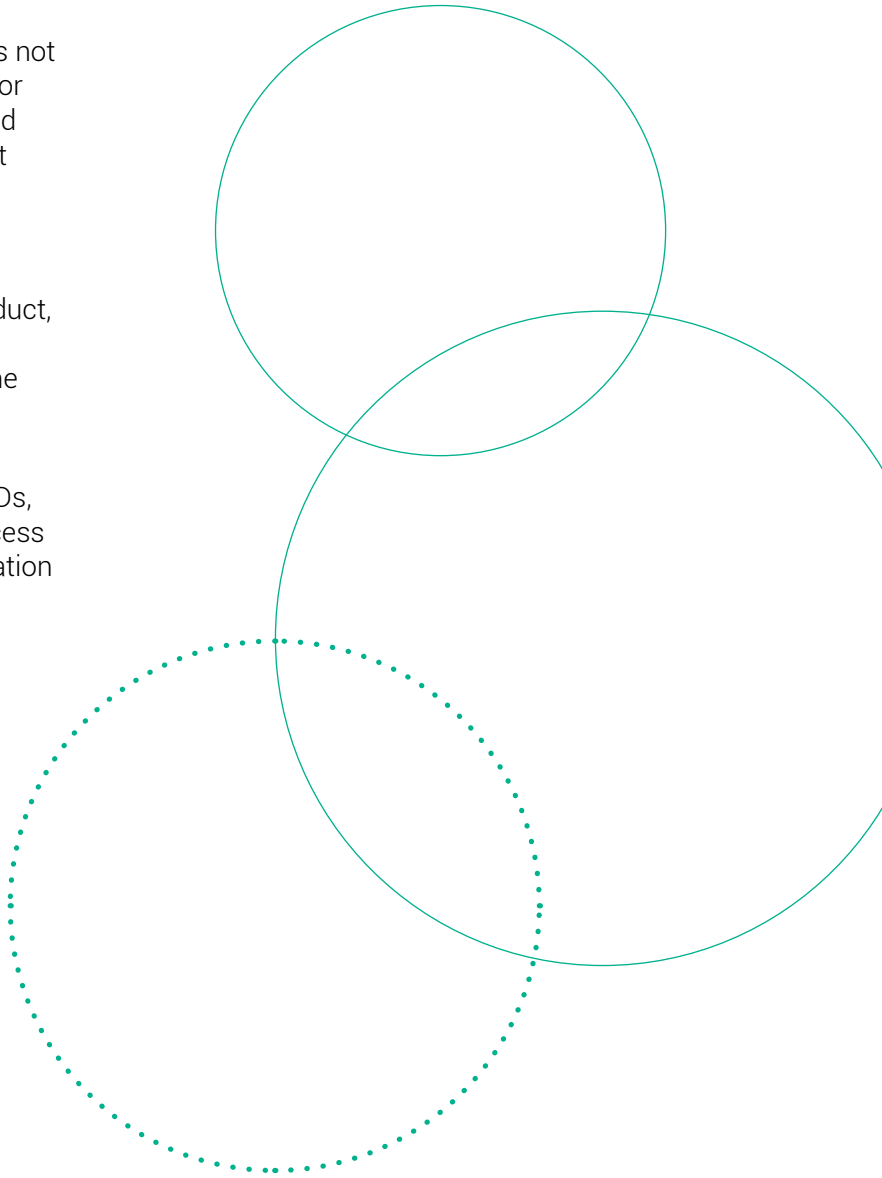
6.2. Module 2: Discipline summaries

Statement of intent

- The intent of Module 2 for spatial emanator products is for manufacturers to provide WHO with information and summarized analyses which act as a tool to assist with the full science assessment.
  - Whereas Modules 3, 4 and 5 contain the study reports, raw data and information, Module 2 allows for the presentation of the summary of relevant information, the applicant's interpretation of the available information, and supporting explanations for product characteristics or information which does not correspond to other modules.
- Module 2 is a tool to help assessors understand at a high level the product, the supporting data and any anomalies across study reports.

Description of requirements

- Information regarding product development – narrative description of the product development process which includes, but is not limited to, information about the rationale for AI and formulant selection, optimization and finalization of the formulation, development of the manufacturing process, scalability of manufacturing process to commercial production, etc.
- Product summary – description of the product, components/equipment for deployment, intended use pattern and justification for the claim of duration of intended useful life.
- Identifying information about product samples used in testing – includes batch IDs, formulation codes and manufacturing process for all product samples used in data generation and the corresponding studies.



6.3. Module 3: Quality dossier

Statement of intent

- The intent of Module 3 for spatial emanator products is for manufacturers to provide WHO with information and data which demonstrate:
  - the composition of the spatial emanator product;
  - the construction of the spatial emanator product, if applicable;
  - the manufacturing details of the spatial emanator product and the consistency of the production process;
  - the stability of the spatial emanator product formulation, including AI(s), and continuity of the release profile (passive or active emanation) throughout its intended useful life.
- In the context of the weight of evidence approach, the physical and analytical chemistry data in Module 3 typically have higher certainty given the controlled nature of the data generation for physical/chemical characteristics based on appropriate analytical methods. In so doing, the established baseline information has the effect of increasing confidence in the interpretation of other pre- and post-market data.

Description of data requirements

- The complete description, construction and formulation of the product (product composition and purpose of all formulants in intermediate formulations and finished fabrics).

  Note: All sources of AI (and synergists) must be supported by a current evaluation report confirming compliance with the established specifications.
- The complete product manufacturing details, including:
  - declaration of manufacturing sites (DMS);
  - control of starting materials;
  - batch delineation and formula;
  - description and control of manufacturing process (DMP).

    Note: A key difference between the manufacturing details in Module 3 and the information required in Sites Master Files for Module 6 is that the description of manufacturing process defines all equipment, settings/ranges, speeds and temperatures which must be followed in order to produce the product as intended. The quality management system, as presented in the site master file(s), is the system by which a manufacturer ensures that the declared process is followed.
- Declaration of construction, if applicable;
- Declaration of product sampling – defined sampling procedures for the individual product for the purposes of chemical and physical analysis;
- Description of device, if applicable;
- Chemical characteristics of the finished product;
- Emanation rate of the formulated product when used as directed by the label:
  - characterization of the range of emanation rates at different temperatures;
- Physical characteristics of any integral components (e.g. yarn), fabric(s), plastics and the finished product;
- Storage stability – physical/chemical data generated on product samples having been subjected to accelerated and real-time storage;
- Manufacturing release specifications, including methods and notes;
- Other related information as determined necessary based on the characteristics and design of the product.

6.4. Module 4: Safety dossier

Statement of intent

- The intent of Module 4 for spatial emanator products is for manufacturers to provide WHO with information and data which demonstrate that the product, as formulated and under intended use scenarios, does not pose an unacceptable risk to human health.
- In the context of the weight of evidence approach, Module 4 data have high certainty based on the conservative approaches to hazard assessment, selection of endpoints, and exposure scenarios by which risk is estimated. The supporting data are generated in controlled settings, and the available toxicological information of the AI has been reviewed by National Regulatory Authorities and international organizations.

Description of data requirements

- Reference to generated or publicly available AI hazard assessments which provide the basis for toxicological endpoint selection for use in the product risk assessment.
- Product risk assessment relying on the most current Generic Risk Assessment Model(s) (GRAM). In the absence of a specific GRAM for spatial emanator products, PQT/VCP has implemented the approach of relying on the *Generic risk assessment models for insecticide-treated clothing, skin-applied repellents and household insecticides* (*4*), which provides models to calculate health risks based on possible exposure scenarios of household insecticides.
  - the GRAM (*4*) provides a method to characterize inhalation exposure to mosquito coils or "other vapour-producing vector control products" using the ConsExpo "exposure to vapour" model (*5*). This inhalation exposure assessment calculates both applicator and residential inhalation exposure. Key parameters of the model include:
    - rate of release (emanation/emission rate) of AI from the product
    - room size
    - ventilation rate;
    - inhalation rate for different age groups.

    This model also includes exposure characterization for the revolatilization of the AI(s) from deposits on indoor surfaces which may lead to an increase in total air concentration of the AI(s).
  - for vapour-releasing products, the GRAM (*4*) does not include models for dermal exposure to AIs which may have settled on surfaces. In order to address this potential post-application dermal exposure scenario, the *Standard operating procedures for residential pesticide exposure assessment* (*6*) provides an appropriate approach to characterize the relevant exposure patterns. This SOP considers potential dermal contact from deposited residual AI(s) and provides a standard method to calculate post-application non-dietary ingestion hand-to-mouth exposure. Other models, such as the dermal exposure models of household space spray products (*4*) may also be applicable to characterize dermal exposure.
- Acute toxicology 6-pack.

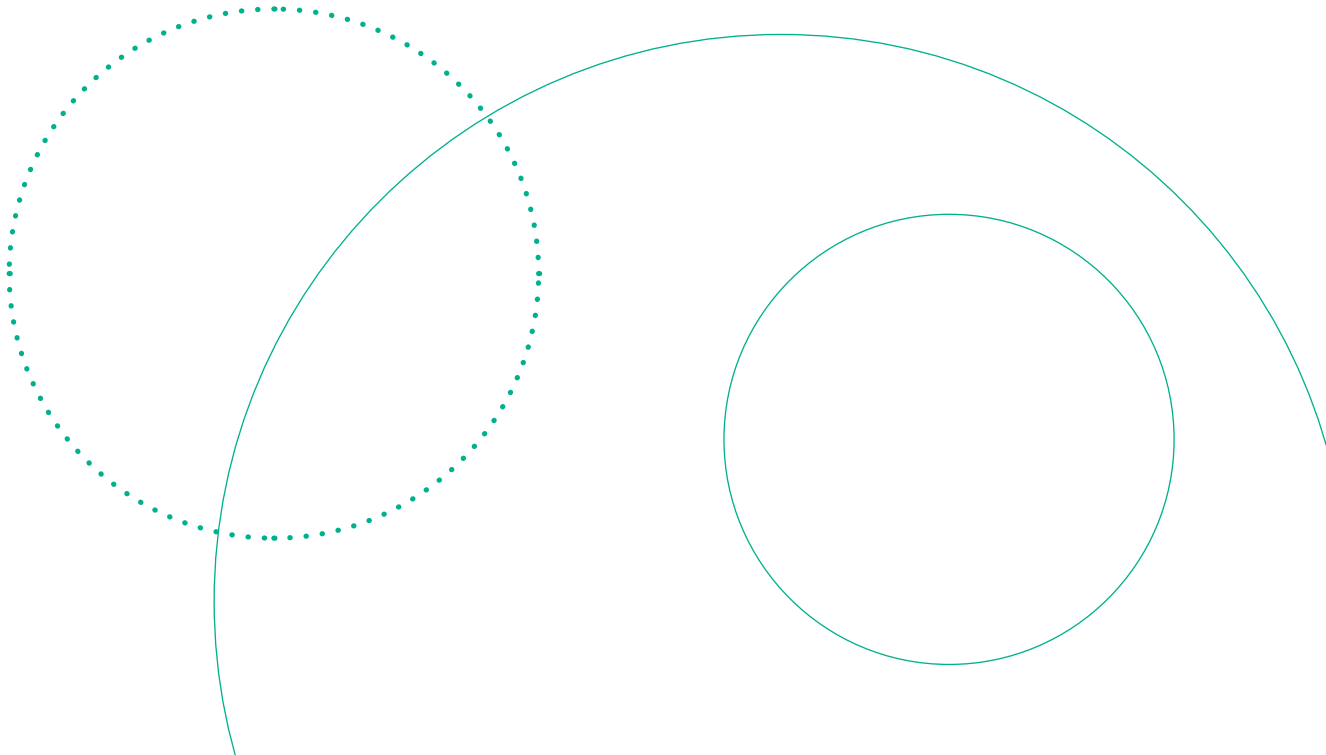
6.5. Module 5: Efficacy dossier

Statement of intent

- The intent of Module 5 for spatial emanator products is for manufacturers to provide WHO with information and data which demonstrate the product efficacy over the intended useful life, including:
  - the impact of the spatial emanator product on free-flying target vectors under controlled conditions before and after ageing;
  - the impact of the spatial emanator product on wild, free-flying target vectors before and after ageing;
  - depending on the test and the characteristics of the product, for example, the intended duration of emanation, ageing of product samples may include both artificial and operational ageing to characterize the reduction in the AI reservoir at which point the product no longer emits sufficient AI to induce the intended effect. This is referred to as the end-of-life of the product.
- The batches of all product samples used in Module 5 studies must be fully characterized as described in Module 3.
- Studies which include human participant exposure to spatial emanator products must be conducted in accordance with the applicable laws, regulations and ethical clearances within the regional, national and/or local context.
- Studies should include adverse event reporting as defined and required by the regional/national/local governing authority.
- In the context of the weight of evidence approach, Module 5 data can present varying degrees of uncertainty. Therefore, generating robust results requires the management of multiple factors which can contribute to uncertainty. Consideration must be given to:
  - the product:
    - assured quality of spatial emanator products used in studies;
    - storage and handling of the product/samples prior to utilization in studies;
    - preparation of the product as per standard methods and for investigation of the intended life of the product;
  - the method:
    - Good Laboratory Practice (GLP) compliance – documentation of methods, protocols, procedures and results;
    - selection of positive control(s) and related quality assurance;
    - selection of negative control(s);
    - appropriateness of the selected method for the product being tested;
    - robustness of the study design and implementation to support the appropriate statistical analyses of the generated data;
    - deviations from standard procedures;
    - consistent use of the method within and across studies;
  - the organism (test system):
    - species/strain characteristics;
    - health and consistency of laboratory-reared colonies;
    - test system preparation;
    - test system behaviour/responses, for example, circadian rhythm;
    - variability and heterogeneity in wild vector population; composition, abundance, structures, resistance profiles and behavioural characteristics in open system study designs, for example, experimental hut study.

Description of data requirements

- Description of the entomological mode of action of the AI(s), interaction with known mechanisms of resistance and potential for cross-resistance with other chemical classes;
  - free-flight room studies:
    - must be designed to allow for normal interaction of the target vectors, formulated product and bait animal (usually a human volunteer) and to collect data on the endpoints relevant to the intended impact of the spatial emanator product;
    - are conducted under controlled conditions that allow for the investigation of the characteristics of the product in response to ageing, for example, a continued induced effect on target vectors over the intended useful life of the product, against free-flying mosquitoes released in flight rooms. The investigation of additional, secondary endpoints may be achieved through the use of caged mosquitoes located in flight rooms;
    - endpoint(s) selected for use in flight room studies must be the same endpoint(s) as selected for use in the semi-field studies and be used consistently throughout the dossier;
    - sub-studies within a flight room study:
      - flight room study using fresh and aged products;
      - chemical characterization of fresh and aged products;
  - semi-field efficacy studies:
    - must be designed to allow for normal interaction of the target vectors, formulated product and bait animal (usually a human volunteer) and to collect data on the endpoints relevant to the intended impact of the spatial emanator product;
    - are conducted in open systems that allow for the assessment of the efficacy of the product against wild, free-flying target vectors. Open systems are considered to generate data that are closest to what may occur when a spatial emanator product is deployed in communities;
    - endpoint(s) selected for use in semi-field studies must be the same endpoint(s) as selected for use in flight room studies and be used consistently throughout the dossier;
    - sub-studies within a semi-field efficacy study:
      - experimental hut study using fresh and aged products;
      - chemical characterization of fresh and aged products;
- Further information to include in the assessment of the product and its potential performance in various settings. For example, efficacy data generated as part of clinical trials (epidemiological studies).



6.6. Module 6: Inspection dossier

Statement of intent

- The intent of Module 6 for spatial emanator products is for manufacturers to provide WHO with information which demonstrates:
  - the existence and implementation of an appropriate quality management system, accredited to the most current version ISO:9001, for all related manufacturing sites.

Description of data requirements

- SMFs must be submitted for all manufacturing sites identified in the Declaration of Manufacturing Sites form.
- In some cases, a single SMF may be submitted to support multiple manufacturing sites for which the activities, processes, and QMS are substantially similar. In such a case, site specific information (e.g. floorplans, etc.) should be aggregated and clearly identified.

6.7. Module 7: Post-market information

Statement of intent

- The intent of Module 7 for spatial emanator products is for WHO to collect data and information about the stability and performance of the spatial emanator product 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 national regulatory authorities.
  - currently, there are no data requirements in place for Module 7 and requirements could be different depending on the product.

Further information on the modules and specific dossier requirements, including implementation guidance documents, is available on the *PQT/VCP website (7)*.

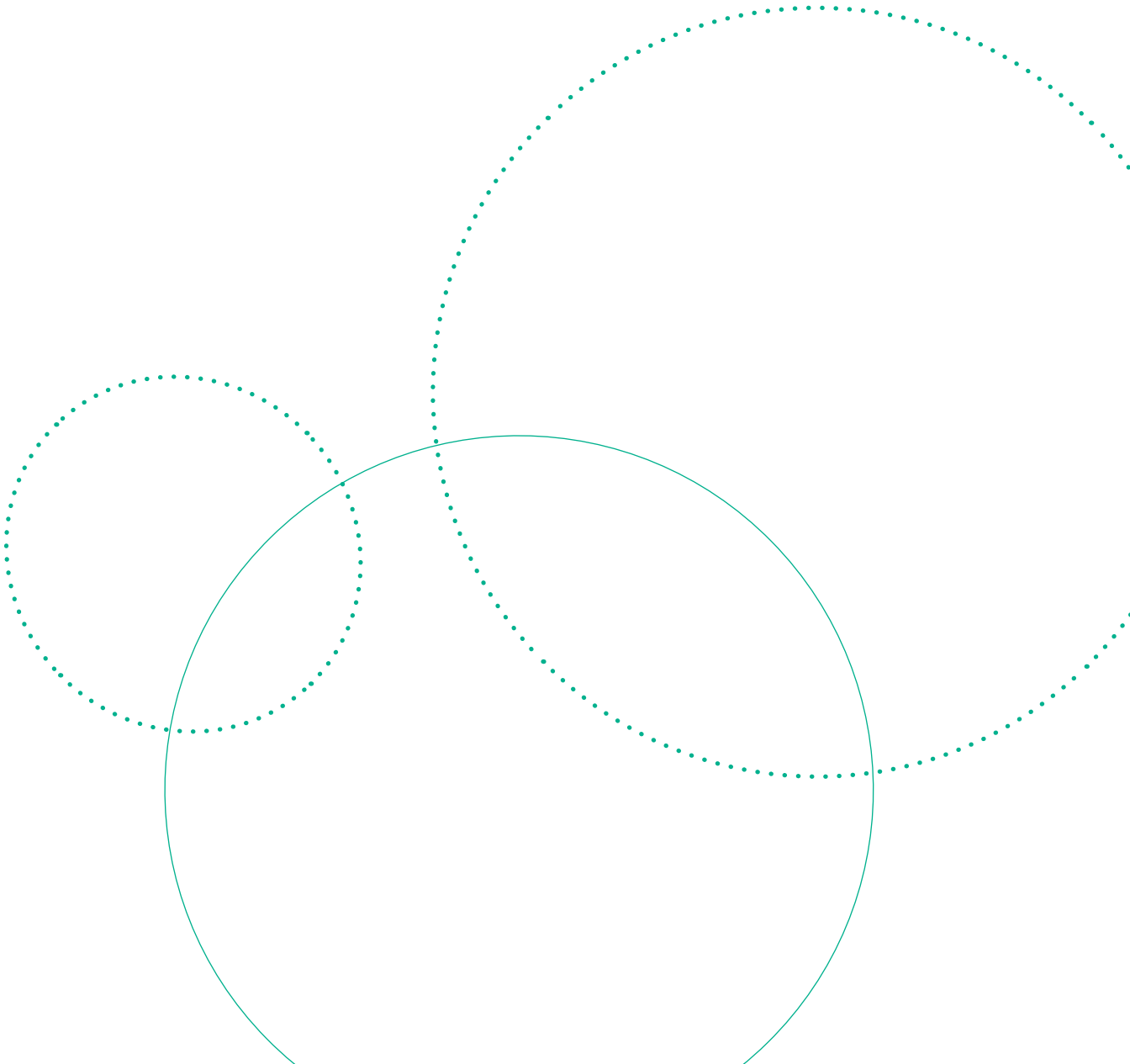
6.8. Importance of relying on the same production batches for generation of data for inclusion in both Modules 3 and 5

Ideally, all data generated for inclusion in Modules 3 and 5 should rely on the final product formulation and optimized manufacturing process, as compared to product prototypes or versions for research. If data are generated on prototype formulations, a scientific rationale for inclusion of these data in support of the final product is necessary.

In order to assess product performance, complete information on the batches used in data generation must be submitted. The same batches must be used for data generation to support both Modules 3 and 5.

A baseline understanding for controlling and assessing the quality of future production batches is established through the correlation of physical/chemical characteristics, chemical release behaviours and the analysis of intra- and inter-batch variability of the batches used in the efficacy testing. The inability to link data across modules, or if data are generated for Module 5 on samples which have been produced using different formulations or processes from those declared in Module 3, leads to significant uncertainty in the assessment of the product.

In the generation of data for Modules 3 and 5, product samples are prepared in a variety of ways to investigate the performance of the product across the relevant life stages. Samples should be prepared using standard methods which are relevant to the analytical/bioassay methods and intent of the study being conducted. Reliance on the same batches for data generation allows for improved certainty in the interpretation of results across different sample preparations.



7. Fulfilling requirements for all prequalification application types for VCPs, including spatial emanators

Applicants are encouraged to investigate the requirements of National Regulatory Authorities (NRAs) of the countries where the product is intended to be submitted for registration and other requirements related to the WHO recommendation development process led by the WHO Department of Malaria and Neglected Tropical Diseases. Identification of these requirements may influence the planning of data generation to ultimately be included in the submission to WHO in order to maximize the utility of the generated information.

In situations where a product is already available, that is, registered and distributed, applicants are encouraged to rely on information/data which have already been developed to support country or regional registrations. In compiling the dossier for submission to WHO, the applicant should review the available information against the WHO Prequalification requirements to determine if there are any gaps in information/data which may need to be addressed. An analysis of this investigation provides an opportunity to guide a presubmission meeting with PQT/VCP.

Applicants must fulfil all data requirements in the compilation of the supporting product dossier.

The available approaches include submission of data, waiver request and citation of publicly available literature.

7.1. Submission of data

- **Generation of new data –** involves the planning and conducting of studies on the proposed product for the purpose of incorporating the resulting reports and raw data in the submitted product dossier.
- **Reliance on existing data –** inclusion of previously conducted studies/information for which the submitter has full access. These data/information may have been used to support previous evaluations of the product.
  - A scientific rationale must be provided to support the inclusion of data generated on a different but similar product/formulation. The degree to which these data are included in the weight of evidence analysis is dependent upon the supporting rationale.
- **Bridging information –** bridging refers to linking existing dataset(s) to inform aspects of the product assessment in cases where:
  - there is little or no existing data;
  - similarities in the formulations of products tested can be used to scientifically justify inclusion of their data;
  - the results of the product being assessed from a particular setting can be applied to another similar setting.

Bridging information could be a supplemental study or scientific rationale.

7.2. Waiver request

Applicants may request waivers for data requirements. A waiver request must include a rationale for the request and may include supporting data as part of the justification. Waivers may be requested based on the specific characteristics of the product, conditions of its use, or mitigation which can be reasonably implemented. In certain cases, a waiver request for inclusion of non-GLP studies may be considered.

Deviations from standard testing methods or omittance of relevant study facets within individual studies should be documented and justified within the resulting study report.

7.3. Citation of publicly available literature

Applications for prequalification can include publicly available information/data/evidence to address specific data requirements. This is an accepted practice, as many of the AIs used in VCPs are older chemistries which are no longer protected under patents or data.

A number of regulatory authorities accept publicly available information and data to support a regulatory applicant, as it is acknowledged that generating more data to substantiate an already evaluated and known AI, product, use or claim can result in unnecessary generation of specific data, in particular toxicological and efficacy data.

The inclusion of appropriate and relevant publicly available data/information to support all or part of the following modules may be considered:

- **Module 4: Safety –** Examples include published WHO human health risk assessments from which applicable hazard conclusions for an AI(s) are identified as relevant and appropriate and/or toxicological data to support the safe use of the vector control product, for example, hazard and exposure data.
- **Module 5: Efficacy –** Entomological data to support the efficacy of the products may be included, but it is likely that this can only support certain aspects of the data package. Without access to complete descriptions of methodology and raw data, there are limitations in how such lines of evidence can contribute to the prequalification decision.
- Dossier modules that **cannot** rely on publicly available data/information:
- **Module 3: Quality –** As the chemistry and manufacturing data components are specific to each product, it is a requirement that this module be supported by data developed by the manufacturer.

The source of the information and quality of data in the public literature must be recognized by PQT/VCP assessors as reliable and appropriate to the submission and aligned with authorities and agencies which also rely on published data. Although PQT/VCP may accept a dossier including public data or evidence, the experts who are responsible for the review of the data have the final determination on whether or not this data can be used to support the submission. PQT/VCP reserves the right to request additional information from the applicant if the public literature does not fully satisfy the data that are needed to assure prequalification standards. The availability of supporting raw data may impact how such cited studies are considered within the weight of evidence for that discipline.

Manufacturers should take the opportunity to discuss the inclusion of publicly available data as part of their submission with PQT/VCP at the presubmission meeting.

Acceptable sources of publicly available information/data

PQT/VCP will accept publicly available data, information and evidence to support an application for prequalification if the source is relevant to the submitted dossier, is consistent with scientifically established knowledge in the field and is from a credible, peer-reviewed publication such as:

- regulatory decision document from a WHO-recognized NRA;
- recognized peer-reviewed scientific journal or periodical. The journals that are considered acceptable should be recognized by PQT/VCP experts as well as the scientific community for their high standards and being leaders in their respective fields;
- recognized textbooks;
- WHO reports.

> Editorials, opinion publications and testimonials will not be considered in the WHO prequalification assessment of products.

7.4. Requirement for generation of data in compliance with GLP

All studies submitted to address dossier requirements for Modules 3, 4 and 5 must be conducted in compliance with GLP. Studies conducted outside of GLP may be submitted; these will be considered as supplementary evidence in support of the submitted GLP studies.

8. Decision-making

8.1. Framework

The decision to prequalify a spatial emanator product is based on the substantiation of a **reasonable expectation of product performance** as assessed using a **weight of evidence approach.**

8.2. Considerations of variability and uncertainty in decision making

Variability and uncertainty are concepts that are sometimes used interchangeably; however, there are differences, and both are inherent in data evaluation and risk assessment.

Variability refers to the inherent heterogeneity or diversity that occurs both within and between studies and the resulting data.

Uncertainty refers to a lack of data, the limitations to quantify or measure, or incompleteness of data which can impact the interpretation of the study.

The presence of both variability and uncertainty support the use of a weight of evidence approach to data evaluation and decision-making.

8.3. Weight of evidence

A weight of evidence approach is a method for decision-making that involves the consideration of multiple sources of information and lines of evidence. This approach avoids sole reliance on any one piece of information, line of evidence or indicator. A robust assessment is one that considers multiple lines of evidence to support a conclusion.

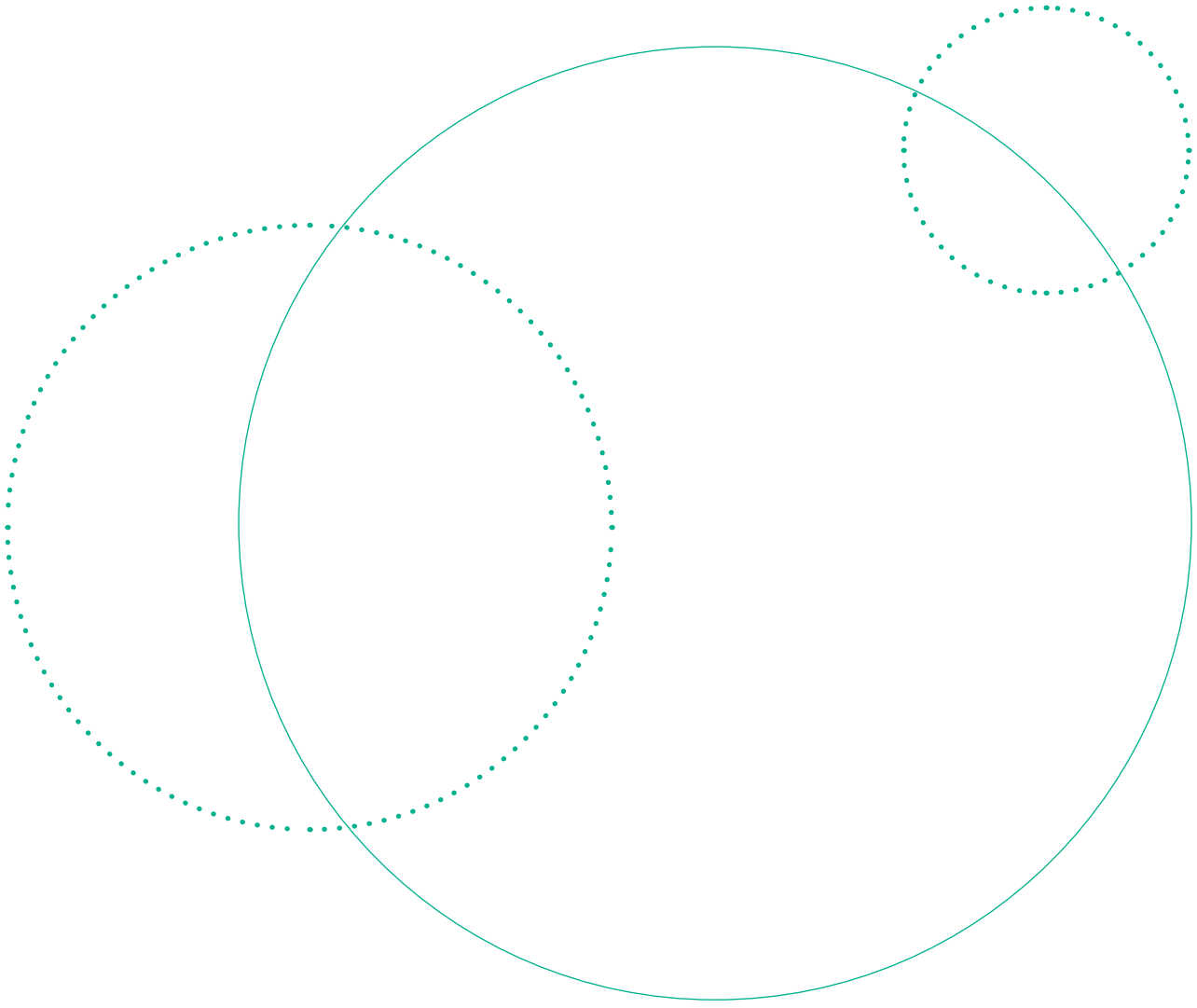
A weight of evidence approach is used in the prequalification assessment to evaluate the quality of each study and to consolidate results across multiple lines of evidence to support the interpretation or conclusion.

In assessing the information submitted within a product dossier, the scientific validity and appropriateness of the information in relation to the proposed product is determined in order to ensure that reliable lines of evidence are used in the decision-making process.

The decision places greater weight on stronger and more relevant lines of evidence but will also take into consideration those studies which may indirectly contribute to the overall weight of evidence.

9. Claiming equivalency to an already prequalified product

At this time, dossiers for spatial emanator products claiming equivalence to a currently prequalified product are not accepted by PQT/VCP.



10. References

1 Guidelines for efficacy testing of spatial repellents. Geneva: World Health Organization & WHO Pesticide Evaluation Scheme; 2013 (https://www.who.int/publications/i/item/9789241505024, accessed 24 July 2025).

2 Guidelines for efficacy testing of household insecticide products – mosquito coils, vaporizer mats, liquid vaporizers, ambient emanators and aerosols. Geneva: World Health Organization & WHO Pesticide Evaluation Scheme; 2009 (https://www.who.int/publications/i/item/WHO-HTM-NTD-WHOPES-2009.3, accessed 24 July 2025).

3 Overview of the WHO prequalification assessment of vector control products. WHO Prequalification of Vector Control Products. Geneva: World Health Organization; 2020 (https://extranet.who.int/prequal/sites/default/files/document_files/WHO_PQT_VectorControlProducts_June2021.pdf, accessed 24 July 2025).

4 Generic risk assessment models for insecticide-treated clothing, skin-applied repellents and household insecticides. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/330143, accessed 24 July 2025).

5 ConsExpo [website]. National Institute for Public Health and the Environment; 2024 (https://www.rivm.nl/en/consexpo, accessed 24 July 2025).

6 Standard operating procedures for residential pesticide exposure assessment [website]. Washington (DC): United States Environmental Protection Agency; 2025 (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide, accessed 24 July 2025).

7 Vector control products [website]. Geneva: World Health Organization; 2023 (https://extranet.who.int/prequal/vector-control-products, accessed 24 July 2025).

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