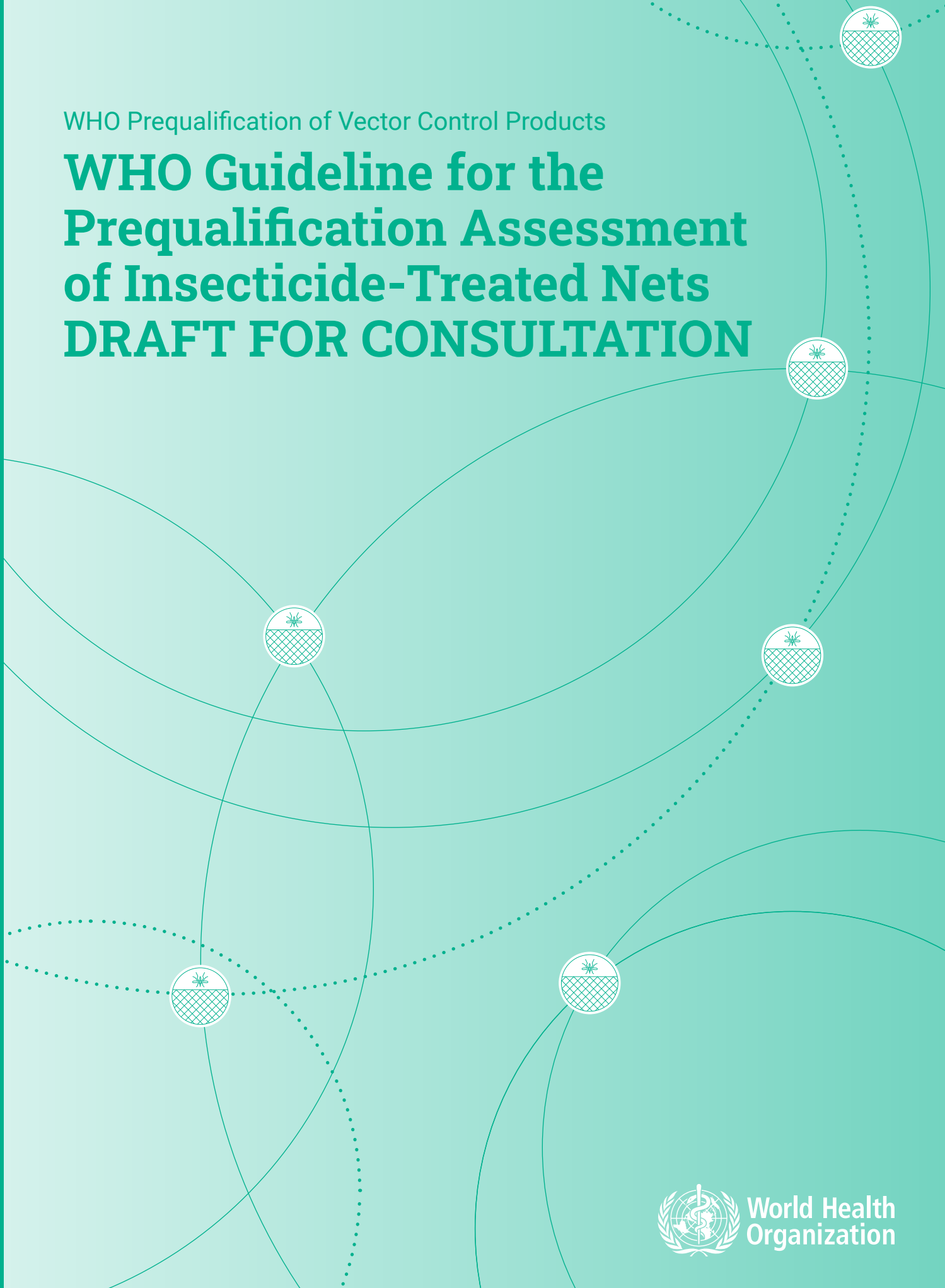
WHO Prequalification of Vector Control Products

# WHO Guideline for the Prequalification Assessment of Insecticide-Treated Nets DRAFT FOR CONSULTATION



World Health Organization

September 2022 - DRAFT FOR CONSULTATION

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Insecticide-Treated Net Guideline



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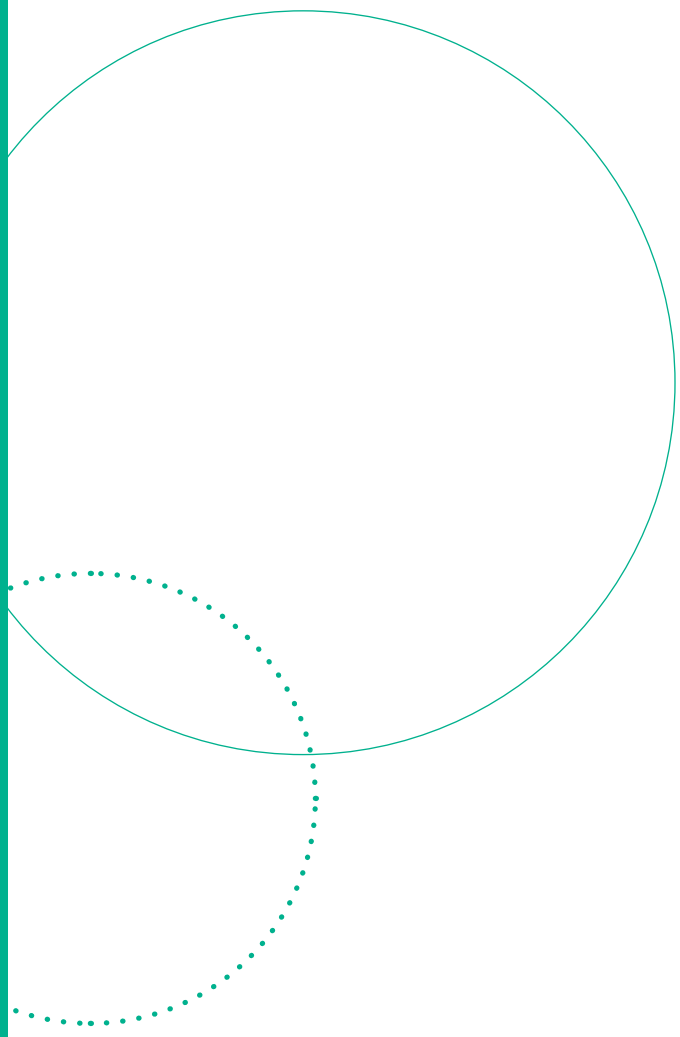
# Contents

# Contents

# 2. Introduction

World Health Organization (WHO) prequalification assessment process for vector control products (VCPs) is coordinated through the Regulation and Prequalification Department (RPQ) in the Access to Medicines and Health Products Division (MHP). These procedures are carried out by the Vector Control Product Assessment Team in the Prequalification Unit (PQT/VCP).

**The mandate of WHO vector control prequalification is to increase access to safe, high-quality and effective VCPs.**



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, as determined by WHO, the WHO prequalification requirements are included in the WHO list of prequalified VCPs.

The procedures of WHO prequalification are used to assess the safety, quality and efficacy of VCPs for the purpose of providing guidance to interested United Nations (UN) 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 safety, quality or efficacy.

This document, Guideline for the Prequalification Assessment of Insecticide Treated Nets, is the first of a series of Guidelines Documents which will be developed by PQT/VCP for VCPs. The development of this Guideline has been informed by the input of a number of experts as acknowledged above as well as knowledge gleaned from the science assessment of prequalification applications to PQT/VCP, the WHO PQT/VCP Product Review of Non Pyrethroid only ITNs, current research and ongoing work in the field, input from partners within WHO and relevant information from the revised 2013 Guidelines for Laboratory and Field Testing of Long-Lasting Insecticide Treated Nets. Stakeholders and partners were consulted widely on the guideline content, through a number of targeted focus group and a major consultation session which was open to all interested stakeholders.

# 3. Intent of the Guideline

The purpose of the **Guideline** is to provide information to stakeholders on ***what*** requirements are necessary for a complete prequalification dossier for ITN products.

This Guideline establishes the baseline for dossier requirements which are necessary to assess ITN products for the purposes of **WHO prequalification.** It is supported by **Implementation Guidance** documents which provide specific information and considerations for ***how*** applicants may approach the generation of supporting information and compilation of a complete product dossier.

A complete dossier includes:

- information to address all data requirements and,
- 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 Guideline describes the framework and approaches for prequalification assessment and decision making for ITNs. The decision to prequalify an ITN is based on the substantiation of a reasonable expectation of product performance as assessed using a weight of evidence approach.

In developing this Guideline, the existing prequalification guidelines and guidance related to the assessment of quality, safety and entomological efficacy of ITNs 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 Guideline supersedes the WHO Guidelines for Laboratory and Field Testing of Long Lasting Insecticidal Nets (2013).

| Engagement with all stakeholders | Process and decision-making | Broader impact |
|---|---|---|
| • Practice openness and transparency | • Action-oriented | • Embrace innovation and creativity |
| • Collaborate, engage and listen | • Evidence-based | • Apply a global perspective to meet varying geographic and disease needs |
| • Demonstrate integrity | • Adhere to established roles and responsibilities | • Monitor and evaluate current approaches to meet changing global needs |
| • Be respectful and demonstrate respect | • Transparent | |
| | • Timely | |
| | • Well-documented policies and decisions | |
| | • Continuous evaluation and process improvement | |

The guideline is intended to:

- Describe approaches for inclusion of consistent and reliable data generation
- Identify data requirements to support re-evaluation of current products, inform developers of new ITNs of the concepts and requirements for dossier development
- Establishes the framework and concepts upon which ITNs are assessed and the basis of decision
- Allow for flexibility to incorporate future evolution of methods and analysis as well as deviations from standardized guidance when justified
- Inform guidance on product testing for purposes other than prequalification assessment and QA/QC/QMS

The guideline is not intended to be:

- A guide for academic research
- A literature review of ITNs and related methodology
- Establishment of best practices and recommendations for use of ITNs
- Guidance for use of unsubstantiated, unproven, and unvalidated information/methods
- Guidance on GMP, NTD, nor VCAG requirements

All stakeholders should rely on this Guideline and the related Implementation Guidance documents to understand the characteristics of ITNs and the product life stages.

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

Procurement agencies should refer to these documents to assist with procurement decisions, including interpretation of available information for use in informing product selection.

Member States should refer to the Guideline and the related Implementation Guidance documents to:

- Understand WHO assessment approaches and data requirements for ITNs
- Inform the establishment or evolution of data requirements for registration by National Regulatory Authorities
- Support engagement with WHO for collaborative initiatives related to ITN product registration

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.

# 4. Bednets

For the purposes of this document, the term **bednet** has been used to describe the products to which this Guideline applies. The term bednet is intended to convey the use of the product in a manner by which the user is protected while within a space enclosed by the fabric, regardless of whether the user is indoors, outdoors, in a bed, hammock or other arrangement. Other documents may use the terms bednet and net interchangeably.

Bednets are an essential form of personal protection against mosquitoes which may transmit malaria. The bednet provides a physical barrier to prevent biting, thereby protecting the user. In some cases, bednets may also be used as interventions for other vectors which transmit diseases, such as sandflies. The information presented in this document is primarily considered within the context of the use of bednets as interventions for malaria. However, many of the concepts, principles, and requirements can be relied upon with minimal augmentation for consideration in the use of bednets as interventions for other vectors.

**Untreated bednets** are those products which provide a physical barrier to protect users from mosquitoes and/or other vectors and are considered by WHO as "Physical/device" VCPs. These products are typically not regulated as health products, nor pesticide products, due to the solely physical mode of protection. WHO may develop standards to inform preferred product characteristics or target product profiles which provide guidance to manufacturers, purchasers, and users on the characteristics to be considered in the design and construction of these products.

**Insecticide treated nets (ITNs)** are bednets which contain an **active ingredient(s) (AI)** which is intended to repel, kill, or mitigate the target vector so as to enhance the **personal protection** of the bednet as well as impart **community protection** through impacts on vector population, biting rates, and sporozoite infection rates.

An AI is a chemical which induces a biological response and in the case of ITNs, this typically involves insecticidal or insect regulating effects. For the purposes of this document, unless specifically identified, the use of "AI" also includes formulants which are intended to impart synergistic effects by means of amplifying the toxicity of an AI or mitigating detoxification of the AI in the target vector so as to increase the effect.

# 5. Characteristics and Product Life Stages of Insecticide Treated Nets (ITNs)

## 5.1 Defining an ITN product

An ITN product is defined by the declared formulation and manufacturing process of the **fabric**(s), and the declared **construction**.

In the assessment of a change application for a prequalified product, WHO considers the proposed change(s) to determine if the product is still supported by the available product dossier or if a new product application must be submitted.

TABLE WITH EXAMPLES?

## 5.2 Systems for classification of ITNs

For the purpose of WHO prequalification of ITNs, there is not a classification system for grouping ITN products. Each product is assessed based on the information provided to establish a **reasonable expectation of product performance** as assessed using a **weight of evidence approach**.

However, for other activities, ITNs may be classified based on various characteristics. The existing WHO recommendations for ITNs from the Global Malaria Program (GMP) rely on a classification system based on intended entomological modes of action of AI(s) formulated in ITNs and target vector characteristics.

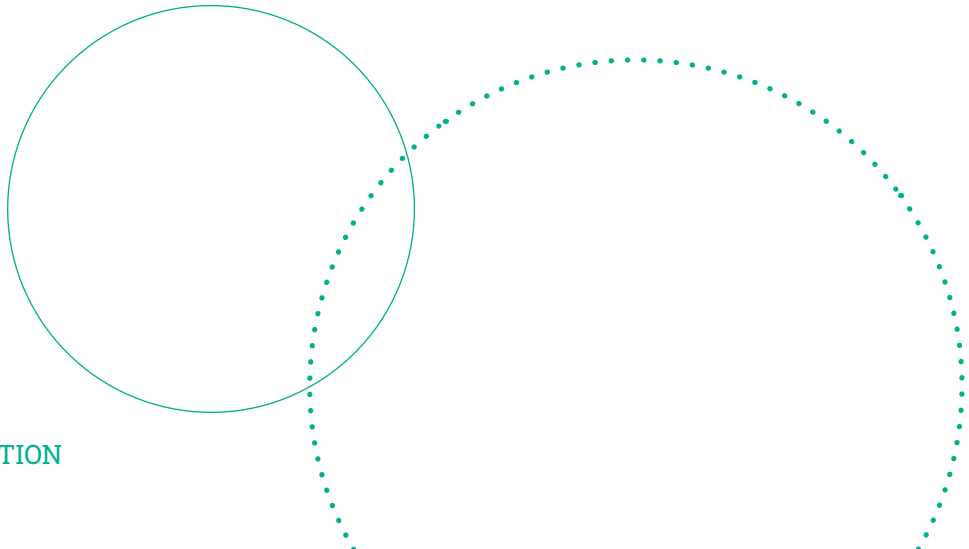
Stakeholders may rely on other classification systems as well. Some of these systems may inform product selection decisions within the specific environmental and vector population context.

## 5.3 Concepts for the development of ITNs

- Method of Application – describes the manner by which the AI(s) is applied to the integral components or pre-knitted fabric to produce the treated fabric
- Fabric Design – conveys the characteristics of the treated fabric used to form the ITN; for example, considering the yarn(s) and their properties and the knitting/weaving of the yarn(s) to form the fabric, or formation of fabric by other means
- Construction – describes the assemblage of fabric panels which form the final ITN; considering the potential for identical or different fabrics to be integrated into the final form, as well as methods/materials used for sewing

### 5.3.1 Method of Application

Bednets treated with an AI(s) which is intended to impart an effect on the target vectors, beyond the protective physical barrier, is what defines the regulatory scope and need for robust supporting information to evaluate the safety, quality and efficacy of these products. The ITN **method of application** describes the manner by which the AI(s) is applied to the integral components (e.g. yarn) or pre-knitted fabric to produce the treated fabric. Bednets may be self-treated or factory-treated.



**Self-treatment** of bednets is typically performed by the end user through a process of washing an untreated net in a prepared solution in order to **coat** it with the active ingredient(s). The solution is prepared by addition of a formulated intermediate (e.g. wettable powder, capsule suspension, solution concentrate, etc…) to a water bath, in which the untreated bednet is soaked. The formulated intermediate is referred to as an **ITN Self Treatment Kit**. Self-treated ITNs may require re-treatment.

**Factory-treatment** of ITNs has historically relied on one of two approaches.

- **Coating** the surface of a pre-knitted fabric, or preconstructed bednet, with a solution of AI(s) and **binder** formulants by means of a treatment bath or other application process, or
- **Incorporation** of the AI(s) into the yarn during the **extrusion** process prior to the formation of the fabric.

In many cases, when referring to ITNs, the descriptive term **impregnated** may be used and could refer to either incorporated or coated products unless clearly specified. Factory-treatment of ITNs is intended to apply a target **dose** of AI(s). Regardless of the method of application, the desired outcome is to produce a continuous and controlled release product.

The total content of AI(s) in/on an ITN is comprised of two parts:

- The **reservoir** is that portion of the AI content which is not exposed and thereby not available.
- The **surface concentration** is that fraction of the AI content which is exposed on the surface of the product.

For ITNs, a foundational step is establishing the reservoir of AI(s) whether within the fabric or bound to the surface. Thereby, the central characteristic of ITNs is the translocation of AI from the bound reservoir to the exposed surface. The characteristics of the release of AI, including the optimisation of the concentrations and biologically active physical presentation, is dependent on the formulation and manufacturing process.

The principles of the formulation development are the same, regardless of the method of application. AI(s) and other formulants, including the polyester or polyethylene (carrier), binders, adjuvants, stabilizers, colors, etc., are selected based on the intent of the product, its desired characteristics, and its use.

DIAGRAM TO BE DEVELOPED

### 5.3.2 Fabric design-integral components and formation

The fabric is both the formulation and the delivery mechanism. Each treated fabric will have its own characteristics, behaviour, and performance; these are primarily influenced by the formulation and the manufacturing process. One or more fabrics may be used as panels in the construction of an ITN.

The fabric design begins with the integral components, most often the **yarn**. Yarns can generally be characterized as being made from staple fiber, plies or filament (mono or multi). Historically, ITN fabrics have relied on **mono-filament** polyethylene or **multi-filament** polyester yarns. Such historical tendencies should not be viewed as standardized characteristics, as WHO has not established any limitations related to the production of the fabric or its integral components. WHO does not restrict the development of novel formulations and production methods relying on other polymer bases or fabric design concepts. The integral components of the fabric, e.g. the yarn and it's denier, directly impact the physical/chemical characteristics of the finished fabric.

The fabric design includes the formation of the fabric (e.g. **knitting**), completed prior to or after treatment. The formation may include uniform or differentiated integral components. Differentiated integral components are those which have differing physical/chemical characteristics. The pattern used for the formation of the mesh structure which becomes the fabric is a defining characteristic of the fabric as it directly impacts the physical/chemical characteristics of the finished fabric.

DIAGRAMS TBD

### 5.3.3 Construction

The **construction** of ITNs describes the assemblage of fabric **panels** which constitute the final form of the ITN.

A product is considered **homogenous** if the panels are made from the same fabric. Products which are constructed using two or more fabrics are referred to as **mosaic** ITNs.

In general, the following types of panels have been identified as potential parts of the construction of ITNs:

- Roof
- Sides
- Sides with Reinforced border
- Upright Barrier
- Other

DIAGRAM TBD

## 5.4. Production/Manufacture, packaging, and release of ITNs

For the purposes of WHO prequalification assessment, the manufacturing process includes the receipt of raw and/or formulated materials and ends with the release of the products to a third party.

The legal manufacture of the ITN is responsible for all aspects of the manufacturing process. The manufacturing process may be implemented in whole by the legal manufacture, by toll manufacturer(s), or a combination.

There are no international standards for delineation of batches/lots for the production of ITNs.

ITNs may be packaged individually in bags or without individual packaging in bales.

## 5.5 Post-production stages in the life of an ITN

### 5.5.1 Shelf-life prior to initiation of use (Storage, transport and distribution)

The **shelf-life** of an ITN product is the time from the date of production as declared by the manufacturer until the initiation of its use. During this time, ITNs would generally be transported and stored prior to distribution. There may also be a period of time after distribution to the end user before the product is used. The time from the date of production to the initiation of use can vary.

The continuous and controlled release behavior of an ITN is apparent immediately after its production. In other words, the intended behaviour of the treated fabric, the translocation of AI and thereby reduction in the reservoir, commences. These processes are active throughout the shelf-life. Therefore, the storage and transport of ITNs must be viewed, in their own right, as factors affecting the potential performance of the product once in use and over the anticipated useful life. As part of the formulation, manufacturing and packaging, manufacturers may implement strategies aimed to control or limit changes to the physical/chemical characteristics, including the loss of AI, of the ITN prior to distribution.

During the shelf-life, ITNs are expected to maintain their physical/chemical characteristics, noting that some loss of AI and other minor changes may occur. Assuming that ITNs are transported and stored in appropriate conditions, those products whose use is initiated prior to the end of the declared shelf-life are expected to perform as indicated. Storage and transport of ITNs outside of the recommended storage/handling conditions may impact the performance of ITNs.

The stability of ITNs during the shelf-life is specific to the product and different ITNs may have different declared shelf-lives.

ITNs that have been in storage beyond the declared shelf-life, may still be functional. However, it is the responsibility of the implementing organizations to determine whether circumstances merit the use of these products and how to assess and confirm that the products remain fit for purpose.

For ITNs which have been stored in improper or uncontrolled conditions, or significantly beyond the declared shelf-life, implementing organizations may need to consider mitigative strategies for the distribution and potential replacement of ITNs.

To assist with these determinations, it is important to put in place the relevant processes and documentation to provide information on storage conditions.

### 5.5.2 In-Use life stage of ITNs

ITNs are typically used indoors. Users, and households, may have ITNs for individual sleepers or for multiple sleepers. The number of ITNs per household varies. ITNs may be hung in the afternoon/evening then taken down and stored during the day, or left hanging continuously.

ITNs are developed to carry the reservoir of AI(s) and release the AI(s) over time in order to provide the desired effect. As ITNs are continuous and controlled release products, a decrease in the total AI content over time is expected. In most cases, the loss of AI is predominantly a result of washing. The frequency and methods for washing ITNs is highly variable. For ITNs which are intended to maintain physical and chemical performance for 3 years, the recommended time between washes is roughly 54 days or 2 months, so as not to exceed 20 washes. More frequent washing can impact the performance of a product and the duration of its effective life.

ITNs may also be affected by other factors, such as sunlight/UV radiation when drying or other environmental factors. Prolonged exposure to direct sunlight can cause degradation of the AI and polymer matrix resulting in loss of AI, conversion of AI to inactive forms, and/or reduction in the physical durability of the fabric.

The physical durability of the fabric and constructed ITNs is critical in maintaining the additional benefits of the protection provided by the physical barrier.

ITNs should always be used and stored in a manner that reduces the risk of damage from open flame, heat sources, damage from animals, or excessive stretching.

To the extent possible, all holes should be repaired.

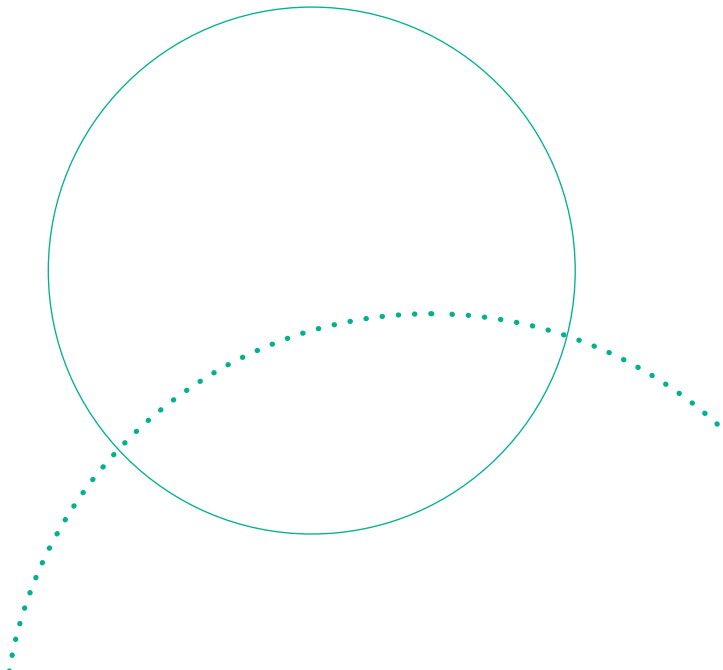
In situations where ITNs have been damaged and cannot be repaired, users should begin use of a new ITN, if one is available. If a new ITN is not available, users may choose to reinforce a damaged net with an untreated bednet for the purpose of continued personal protection until such time as a new ITN is acquired.

### 5.5.3 End of life and disposal of ITNs

Historical approaches to the generation of data for pre-market assessment of ITNs have focused on establishing and substantiating that the product can achieve a 3 year useful life prior to its disposal. In such cases, an ITN is considered to have reached its end of life, when it has been washed 20 times, in use for 3 years, or is no longer useable as a result of physical degradation.

Novel and innovative products may differ in their uses and therefore the associated time until the end of useful life.

Disposal of ITNs should always be done in accordance with regional, national, and local regulations.



# 6. Expectations of ITN performance

The product **performance**, and the establishment of a **reasonable expectation of product performance**, can only be assessed once the formulation and manufacturing process have been established. Product **performance** is demonstrated by an ITN's ability to perform the following functions:

- Provide continuous controlled release of the AI(s) to maintain the intended effects of the product on the vectors over the intended useful life of the ITN when used as instructed.
- Maintain physical integrity for the duration of the intended useful life when used as instructed and protected from damage (e.g, direct sunlight, open flame, animals/rodents, sharp objects, and excessive stretching).

**Bioassays** rely on living organisms in controlled studies to investigate the characteristics of a treated fabric by observing the behavioural responses of the test organism and the induced effect of exposure to the treated fabric (e.g., mortality or knockdown). Bioassays provide limited information about the potential **efficacy** of the product but are integral in investigating how a treated fabric behaves in response to washing/aging. Bioassays are further discussed and defined in section 8.2.3.

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

- **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
- **biologically available fraction** of the **surface concentration**, meaning the portion of the surface/exposed concentration which is in a form/presentation available for vector uptake from the treated yarns/fabrics
- ITN **construction**, referring to where AI(s) is present in the finished ITN product
- **uptake** of AI by free-flying target vectors exhibiting normal behaviour and interaction with the ITN
- handling and care of the ITN as recommended

Efficacy is further discussed and defined in section 8.2.5.

The **physical durability** is the ability of the treated yarn/fabric and constructed ITN to resist wear and deterioration from continual use. Physical durability is further discussed and defined in section 7.2.3.

**Effectiveness**, referring to how well an ITN 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, and
- use of the product as instructed

The pre-market assessment of ITNs 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.

# 7. Prequalification Assessment of ITNs

The application and assessment of ITN products follows the process, terms and conditions presented in the document Overview of the WHO Prequalification Assessment of Vector Control Products.

Manufacturers interested in the prequalification of an ITN are invited to contact WHO PQT/VCP prior to the submission of their application. PQT/VCP offers pre-submission 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 ITNs will be conducted as per the following criteria:

- Quality – Assess product formulation, manufacturing process and physical/chemical characteristics of the yarn(s), fabric(s), and constructed ITN(s).
- 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 vector(s) in conditions/settings applicable to the intended use of the product.

The inspection of manufacturing sites involved in the production of ITNs is overseen by the WHO PQT/INSP Team.

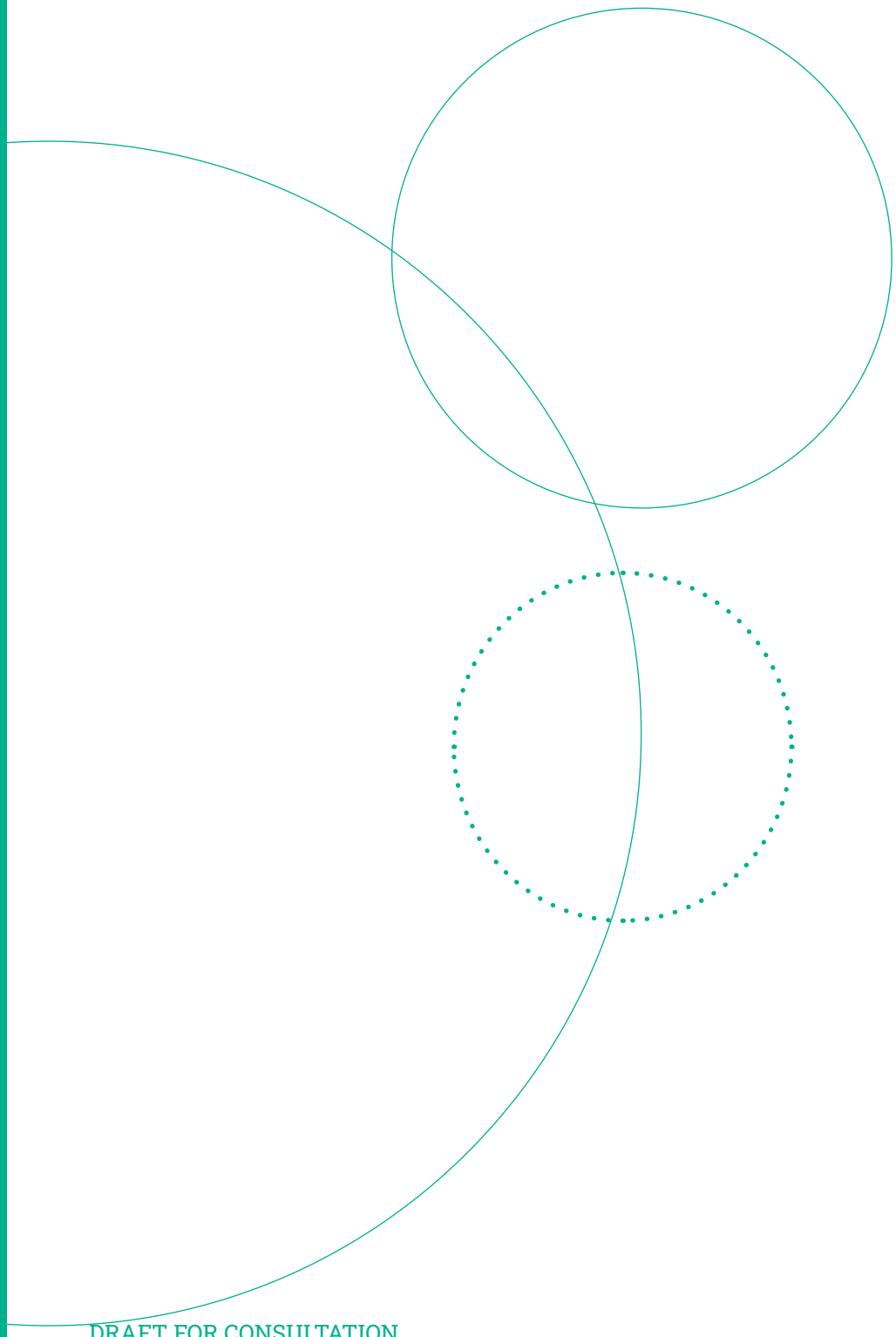
https://extranet.who.int/pqweb/inspection-services/vector-control-products

The **regulatory lifecycle** for vector control products, including ITNs, refers to the application/dossier preparation, submission, assessment, decision and change management of the product. For the purposes of WHO assessment and prequalification, the 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.

# 8. 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 ITNs, further information on the intent and description of data requirements is provided in this section.



## 8.1. Module 1: Administrative information and labelling

### Statement of intent

- The intent of Module 1 for ITNs is for manufacturers to provide WHO with information which demonstrate:
  - 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

1. Cover letter
2. Application form
3. Table of contents
4. Declaration of labelling

### Guidance documents

- To be populated – See "Relevant Guidance Documents"

## 8.2. Module 2: Discipline summaries

### Statement of intent

- The intent of Module 2 for ITNs is for manufacturers to provide WHO with information and summarized analysis which acts 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, 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, any anomalies across study reports and aid in the planning of the assessment.

### Description of requirements

1. Information regarding product development - e.g., the rationale for choosing specific ingredients in the formulation, their concentration informed by assessments of quality, safety and efficacy, their compatibility with the active(s) and polymers, optimization of the formulation and manufacturing process, etc.
2. Identifying information about Product Samples used in Testing – such as batch IDs, formulation codes, and manufacturing process for all product samples used in data generation and the corresponding studies.
3. Quality– Summary of data submitted in support of the product quality and interpretive analysis
4. Safety– Summary of risk conclusions in support of the product safety and identification of any recommended/required mitigative approaches for reducing potential risks
5. Efficacy– Summary of data submitted in support of the product efficacy and interpretive analysis across the available studies

### Guidance documents

- To be populated – See "Relevant Guidance Documents"

## 8.3. Module 3: Quality dossier

### Statement of intent

- The intent of Module 3 for ITNs is for manufacturers to provide WHO with information and data which demonstrate:
  - The composition of the itn
  - The manufacturing details of the itn and the consistency of the production process,
  - Stability of the itn formulation, including ai(s), and continuity of the controlled release characteristics throughout its life,
  - Physical durability, meaning the ability of the treated fabric and constructed itn to withstand physical damage when used as intended
- In the context of the weight of evidence approach, Module 3 data typically have higher certainty given the controlled nature of the data generation for physical/chemical characteristics based on appropriate analytical methods. In so doing, established baseline information has the effect of increasing confidence in the interpretation of other pre- and post-market data.
- In lieu of methods to quantify the surface concentration and characterize the form of AI(s) on an ITN, bioassays provide valuable information for characterising the chemical behaviour of the fabrics used in the construction of an ITN. Results from bioassays can be influenced by the following
- The product -
  - Properties of the fabric based on its method of application and design
  - Storage and handling of the product/ samples prior to utilization in studies
  - Preparation of product samples as per standard methods and for investigation of various life stages of the product (e.g. alignment with directions for use, artificial aging, in-use aging, accelerated storage, and/or real time storage)
  - Non-lethal effects of AI(s) which may reduce exposure (e.g., repellency/excito-repellency)
- The method -
  - Appropriateness of the selected method for the product being tested
  - Deviations from standardized procedures
  - Consistent use of the method within studies
- The organism -
  - Species/strain characteristics
  - Health and consistency of lab reared colonies
  - Test organism preparation
  - Test organism behaviour/responses (e.g., circadian rhythm)

The prequalification assessment has evolved from a framework for decisions relying solely on bioassays results meeting preselected thresholds, to the incorporation of expanded bodies of evidence. The results of bioassays provide an indication of the bioavailability of the AI of the tested product samples rather than predictions of efficacy. Bioassays provide critical information which characterizes the chemical behaviour of ITN fabric over its intended life. They are considered in the weight of evidence together with other available information to fully assess the product.

## Description of data requirements

1. The complete product composition and purpose of all formulants in intermediate formulations and finished fabrics
2. The complete product manufacturing details including:
   - •Declaration of Manufacturing Sites (DMS)
   - •Control of Starting Materials
   - •Batch Delineation and Formula
   - •Description 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, temperatures which must be followed in order to produce the product as intended. The SMF and QMS are the system by which a manufacturer ensures that the declared process is followed.
3. Establish defined sampling procedures for the individual product which ensure appropriate representation of the fabric(s) which comprise the constructed ITN for the purposes of chemical and physical analysis
4. The chemical characteristics of the treated fabric(s), and their integral components:
5. •Analytical Testing
   - » Verification of the target dose, homogeneity of the treated fabric, and consistency of production
   - » Characterize the behaviour of the treated fabric (translocation of AI from reservoir to bioavailable presentation) by means of:
   - » Determination and selection of appropriate wash interval for artificial aging – data, graphical visualization, and analysis of the amount of AI lost from fabric per wash in relation to various wash intervals [Example graphs to be provided]
   - » Wash resistance curve – data, graphical visualization, and analysis of the amount of AI lost in relation to a series of washes of the fabric(s) [Example graphs to be provided]
   - » Characterization of the physical presentation of AI(s) on the surface and potential changes in presentation over the intended life of the product to inform the assessment of other bodies of evidence. [For discussion as a pilot project]
   - » Wash resistance index
6. •Bioassays
   - » Regeneration time – data, graphical visualization, and analysis of observed and measurable effects on the vector(s) from exposure to the fabric(s), after depletion of surface AI by washing [Example graphs to be provided: x axis is days, y axis is the % response for selected endpoints]
   - » Bioassay wash resistance curve – data, graphical visualization, and analysis of the measurable effects on the vector from exposure to the fabric(s), following each wash in the determined series of washes [Example graphs to be provided: x axis is number of washes (0, 1, 3, 5, 10, 15, 20), y axis is the % response for selected endpoints)
7. The physical characteristics of the integral components (eg yarn), fabric(s), and constructed ITN
8. Storage Stability – physical/chemical data generated on product samples having been subjected to accelerated and real-time storage
9. Other related information

## Guidance documents

- To be populated – See "Relevant Guidance Documents"

## 8.4. Module 4: Safety dossier

### Statement of intent

- The intent of Module 4 for ITNs 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 available toxicological information of the AI has been reviewed by National Regulatory Authorities and international organizations.

### Description of requirements

1. Reference to generated or publicly available AI hazard assessments which provide the basis for toxicological endpoint selection for use in the product risk assessment.
2. Product risk assessment relying on the most current Generic Risk Assessment Model for ITNs.
   - In support of new product applications or change applications, applicants may include reference to published WHO Generic Risk Assessments for AIs typically used in ITNs. Applicants must determine if the design of their product or certain characteristics would require altering the presented risk assessment to properly reflect and assess the proposed product.
3. Acute toxicology 6-pack – The standard acute tox 6-pack required for VCPs and other pesticide products is generally relied upon to inform precautionary label language and directions for use. In the case of ITNs, in which the AI is formulated as part of the delivery mechanism, the generation of a complete acute tox 6-pack may not be necessary nor appropriate. Applicants should consider the requirements for countries in which the intend to register the product and the use of waiver requests based on known acute toxicological properties of the AI formulants.

### Guidance documents

- To be populated – See "Relevant Guidance Documents"

## 8.5. Module 5: Efficacy dossier

### Statement of intent

- The intent of Module 5 for ITNs is for manufacturers to provide WHO with information and data which demonstrate the product **efficacy** over the intended useful life.

  The **dose** of AI(s) in the treated fabric establishes the **reservoir** of AI(s) in the ITN which serves to replenish the **surface concentration** over the intended life of the product. It is not related to the efficacy of a product at a specific point in time.

  Efficacy studies focus on the impact of the constructed ITN on free-flying target vectors.

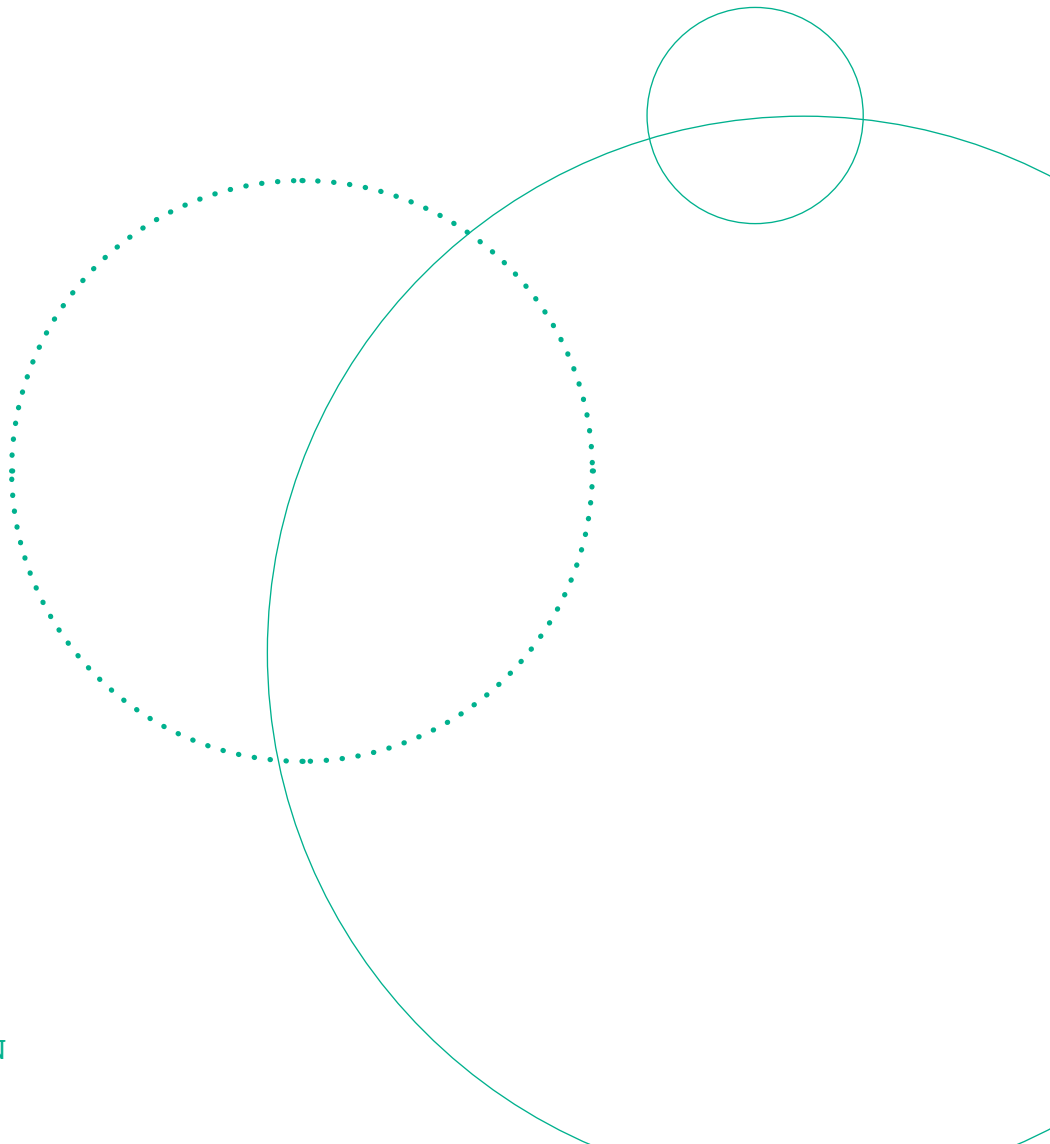
- In the context of the weight of evidence approach, Module 5 data can present varying degrees of uncertainty. Managing uncertainty, and thereby enhancing the interpretation of results in efficacy studies requires consideration be given for the:
  - Assured quality of itns/samples
  - Appropriate preparation of itns/samples for use in studies
  - Glp compliance – documentation of methods, protocols, procedures, and results
  - Inclusion/choice of positive control(s) and related quality assurance of itns/samples
  - Inclusion of negative control(s)
  - Robustness of the study to support statistical analysis of the generated data
  - Variability and heterogeneity in wild vector population structure (species/strains), density and behavioural/resistance characteristics in open system study designs (e.G., Experimental hut study)
  - Colony health and consistency of lab-reared vectors for used in closed system study designs (e.G, ambient chamber test)

### Description of requirements

1. 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
2. Semi-field efficacy studies may be conducted in closed and/or open systems. They must be designed to allow for normal interaction of the target vectors and the constructed ITN and collect data on the endpoints relevant to the intended impact of the ITN.
   - The batches of all product samples used in semi-field studies must be fully characterized as described in Module 3.
3. 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).
4. Adverse Event reporting – Studies which include human participant exposure to ITNs must be conducted in accordance with the applicable laws, regulations, and ethical clearances within the regional, national and/or local context. Each submitted study should include an appendix which reports documented adverse events as defined and required by the regional/national/local governing authority.

## Guidance documents

- To be populated – See "Relevant Guidance Documents"



## 8.6. Module 6: Inspection dossier

### Statement of intent

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

### Guidance documents

- To be populated – See "Relevant Guidance Documents"

## 8.7. Module 7: Post-Market Information

### Statement of intent

- The intent of Module 7 for ITNs is for WHO to collect data and information about the stability and performance of the ITN in channels of trade and operational use. This information may be submitted voluntarily or at the request of WHO by the manufacturer, procurement agencies, or 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 are available on the PQT/VCP website (insert link).

## 8.8. 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. The inability to link data across Modules, or if data are generated for Module 5 on samples which have been produced using different formulations/process as to 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.

# 9. Fulfilling requirements for all prequalification application types for VCPs, including ITNs

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. 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 (e.g. 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 pre-submission meeting with PQT/VCP.

Applicants must fulfill 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

## 9.1 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 on the product for which the applicant has full access to the study and supporting raw data or can provide WHO with a letter from the owner of the data stating that the data can be accessed to support the product submission. These data/ information may have been used to support previous evaluations of the product.
- **Bridging information** – Bridging refers to linking existing data set(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, or
  - Where 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.

## 9.2 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.

## 9.3.Citation of publicly available literature

Applications for prequalification can include publicly available information/data/evidence to address specific data requirements as it is acknowledged that generating more data to substantiate an already evaluated and known active ingredient, product, use or claim, can result in unnecessary generation of specific data.

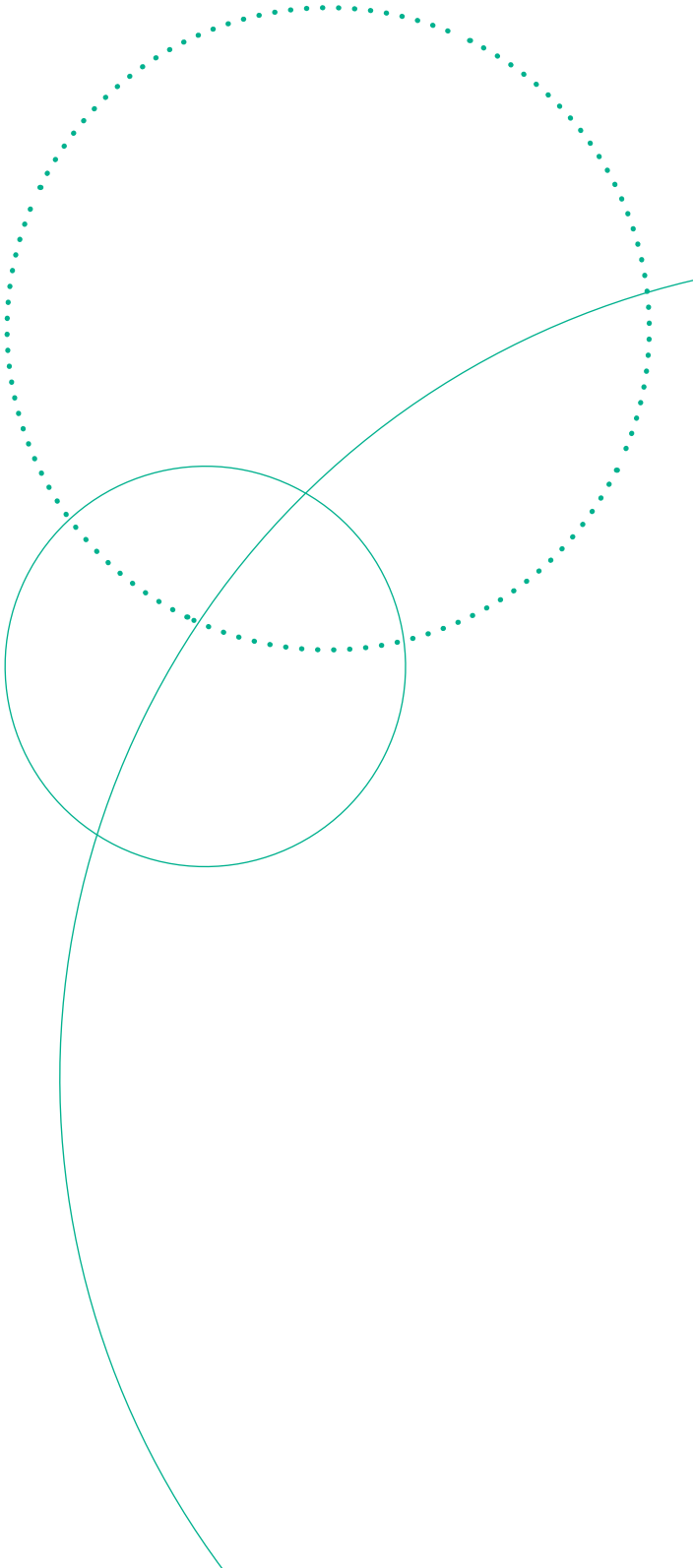
The source of the information and quality of data in the public literature must be recognized by PQT/VCP assessors as reliable and appropriate to the submission and aligned with authorities and agencies which also rely on published data. Although PQT/VCP may accept a dossier including public data / evidence, 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 need to assure PQ's standards.

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

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

## 9.4.Requirement for Generation of data in compliance with GLP

Statement under development



# 10. Claiming equivalency to an already prequalified product

Manufacturers submitting an application claiming equivalence to a currently prequalified product must provide a dossier which includes complete Modules 1, 2, 3, and 6.

The manufacturer must identify the specific product to which they are claiming equivalence. This is referred to as the reference product. The reference product cannot have been prequalified based on an assessment of equivalence.

The product dossier must establish that the product is substantially similar to the reference product for all characteristics, including those determined by means of bioassays.

Prequalification decisions for products based on an assessment of equivalence may be cancelled in the event of changes to the reference product and/or delisting.

# 11. Decision making

## 11.1.Framework

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

## 11.2. 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 weight of evidence approach to data evaluation and decision making.

## 11.3. Weight of evidence

A weight of evidence approach is a method for decision-making that involves 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 multiples 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.

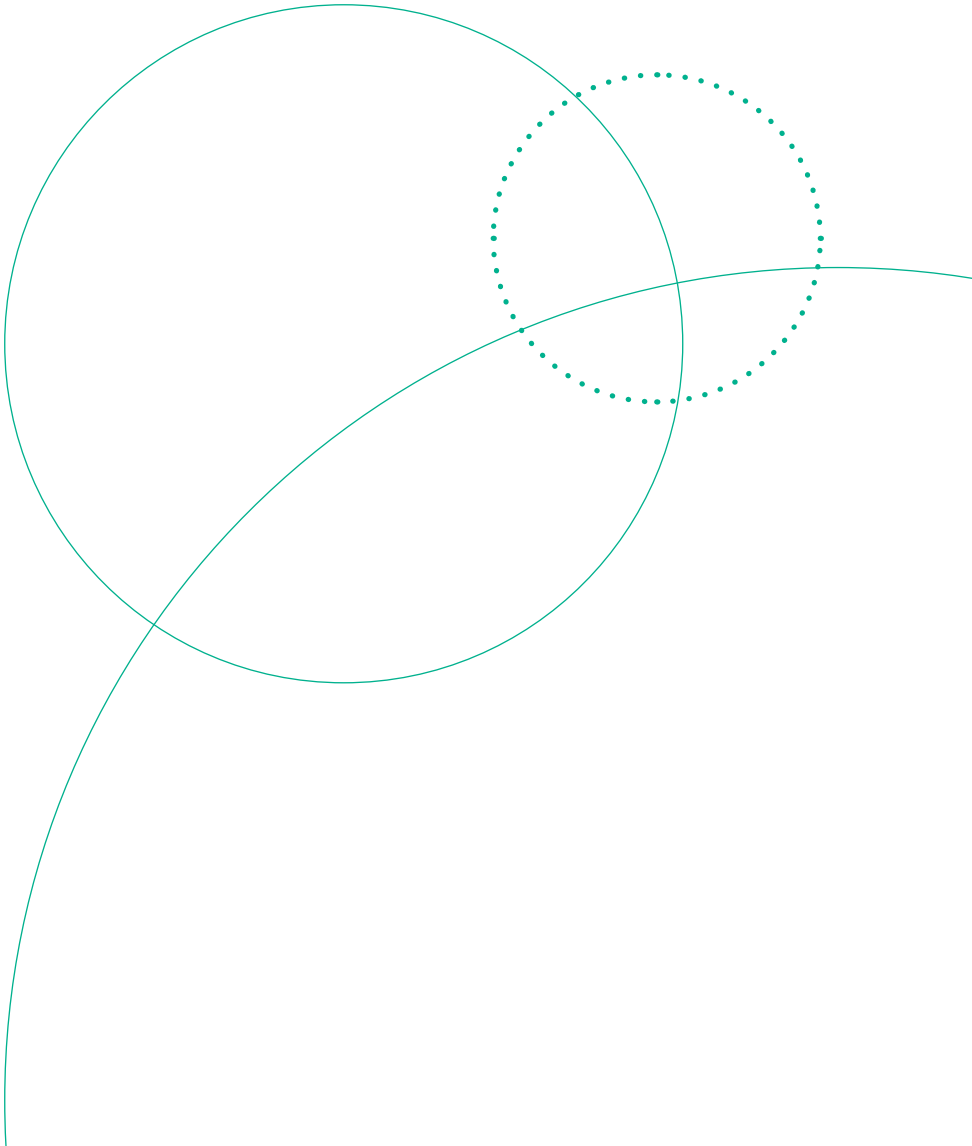
The decision places greater weight on stronger and more relevant lines of evidence but will also take into consideration those studies which may indirectly contribute to the overall weight of evidence.

# 12. Other relevant documents

The WHO has published several documents containing details regarding the application process, data requirements, risk assessment methodology, etc. associated with vector control products. While the present document includes this information, additional details may be found in the following references.

Overview of the WHO Prequalification Assessment of Vector Control Products. WHO Prequalification of Vector Control Products.

Norms, standards and processes underpinning development of WHO recommendations on vector control. WHO 2020.



# 13. Appendices

Content in development


World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

WHO Prequalification of Vector Control Products:
https://extranet.who.int/pqweb/vector-control-products