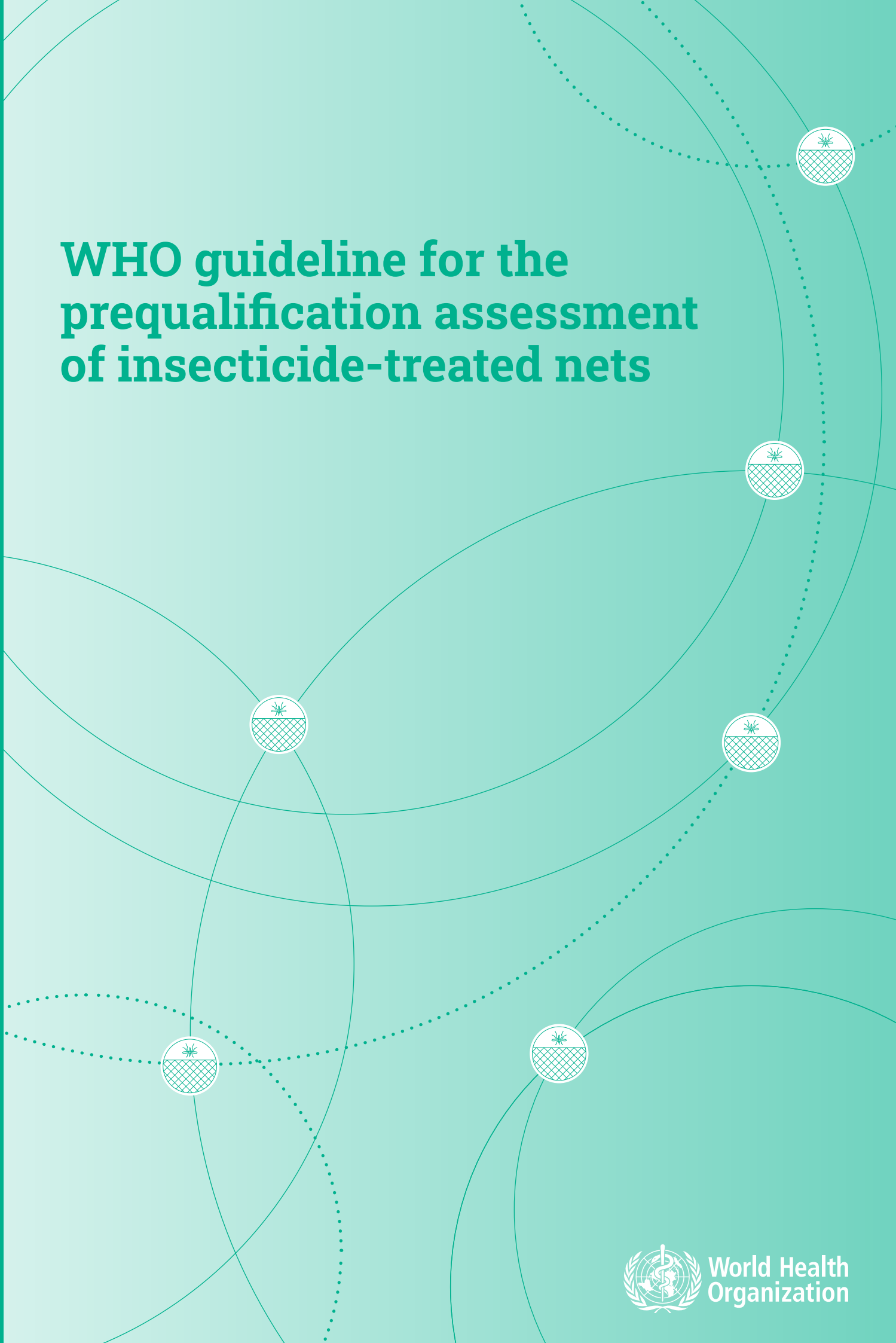
WHO guideline for the prequalification assessment of insecticide-treated nets



World Health Organization

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(WHO prequalification of vector control products)

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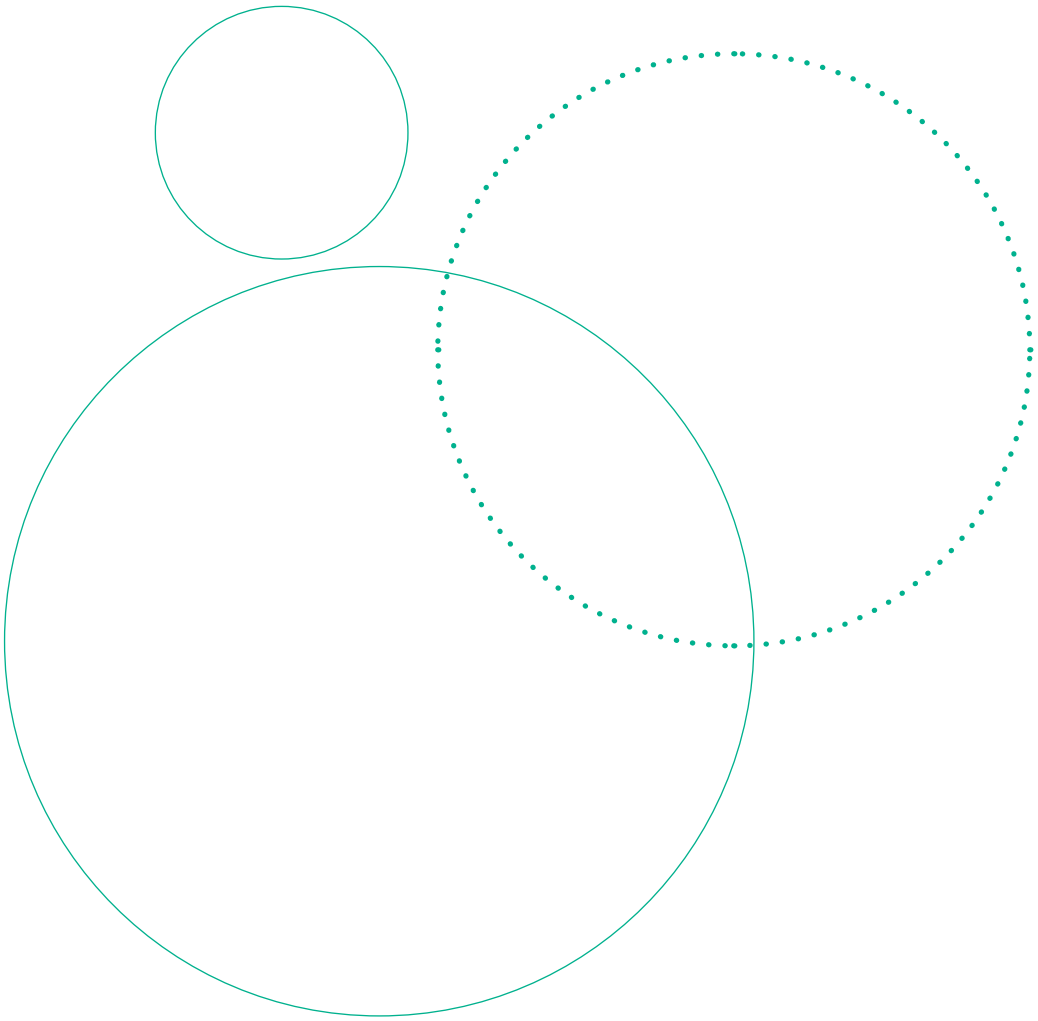
Abbreviations

AI	active ingredient
GLP	Good Laboratory Practice
ITN	insecticide-treated net
NRA	National Regulatory Authority
PQ	prequalification
PQT/VCP	Vector Control Product Assessment Team in the Prequalification Unit
QMS	quality management system
SMF	site master files
VCPs	vector control products
WHO	World Health Organization



1. Introduction

The WHO prequalification assessment process for vector control products (VCPs) is coordinated through the Regulation and Prequalification Department in the Access to Medicines and Health Products Division. These procedures are carried out by 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 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, *WHO guideline for the prequalification assessment of insecticide-treated nets*, is the first of a series of guideline documents which will be developed by PQT/VCP for VCPs and is part of the collection WHO prequalification of vector control products. 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 insecticide-treated nets (ITNs); current research and ongoing work in the field; input from partners within WHO and relevant information from the revised *Guidelines for laboratory and field-testing of long-lasting insecticidal nets (1)*. Stakeholders and partners were consulted widely on the guideline content, through several targeted focus groups, and a major consultation session which was open to all interested stakeholders.

2. 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 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 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 *Guidelines for laboratory and field-testing of long-lasting insecticidal nets (1)*.

The guideline is intended to:

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

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 the use of ITNs;
- guidance for use of unsubstantiated, unproven, and unvalidated information or methods;
- guidance on Global Malaria Programme, Department of Control of Neglected Tropical Diseases, nor Vector Control Advisory Group procedures and 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.

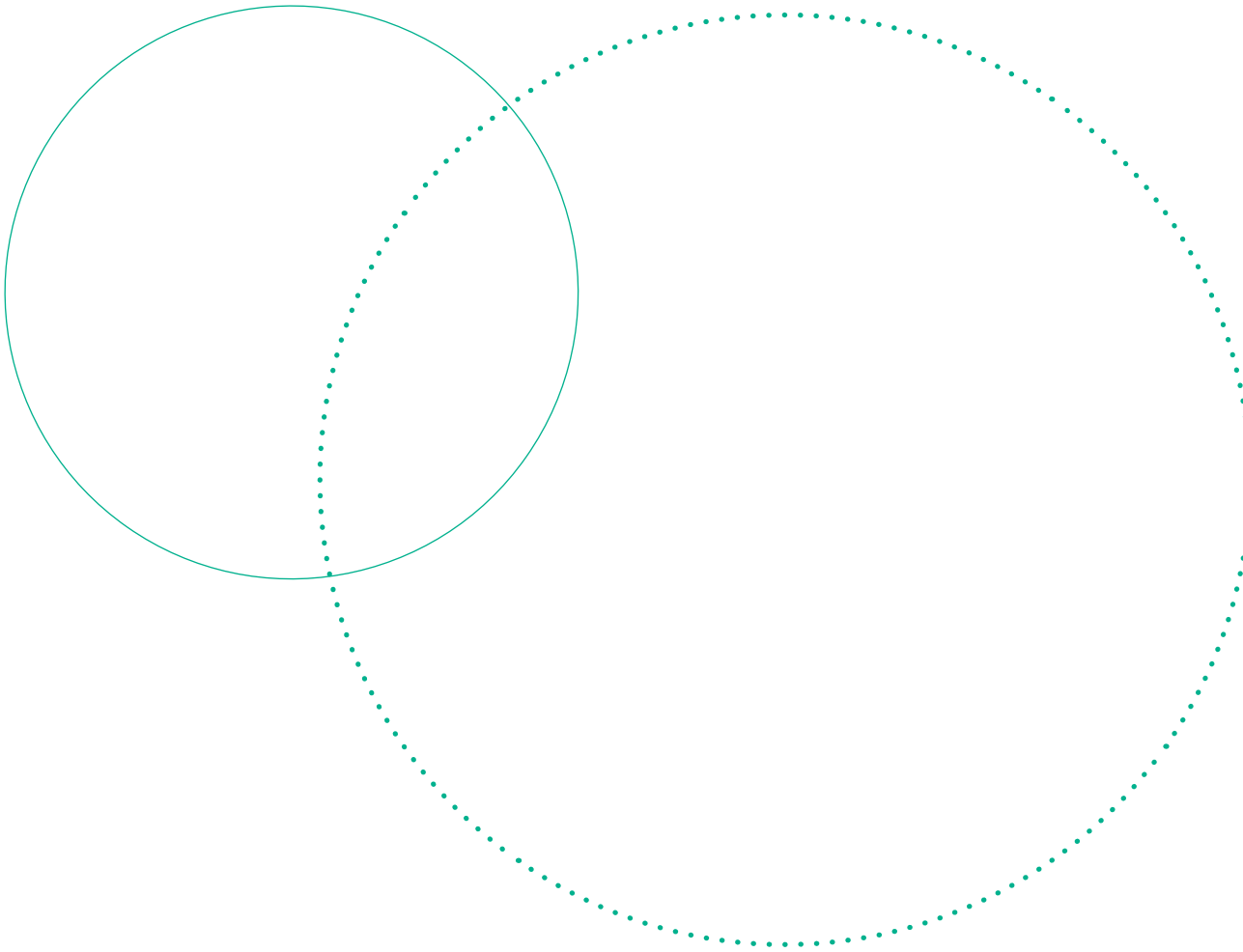
Contract research organizations should use these documents to inform their work with manufacturers in the generation of supporting data/information for the purposes of WHO prequalification assessment.

Procurement agencies and Member States should refer to these documents to understand WHO assessment approaches and data requirements for ITNs, 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 guideline and the related implementation guidance documents to:

- inform the establishment or evolution of data requirements for registration by National Regulatory Authorities (NRAs);
- support engagement with WHO for collaborative initiatives related to ITN product registration.

As stated in the *Overview of the WHO prequalification assessment of vector control products (2)*, 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 of VCPs process 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 financial 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. 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.

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(s), 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.

4. Characteristics and product life stages of ITNs

4.1 Defining an ITN product

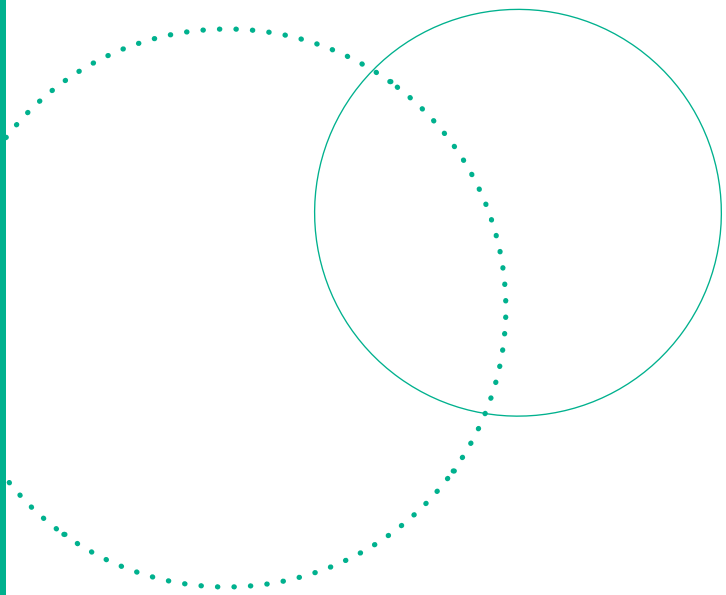
An ITN product is defined by the manufacturer based on the declared formulation (including selection of raw materials), manufacturing process of the **fabric(s)**, the declared final **construction**, and those technical product specifications which the product is declared to meet.

4.2 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 activities other than prequalification, ITNs may be classified based on various characteristics, including intended entomological mode of action of AI(s), chemical class, 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.



4.3 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 its 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.

4.3.1 Method of application

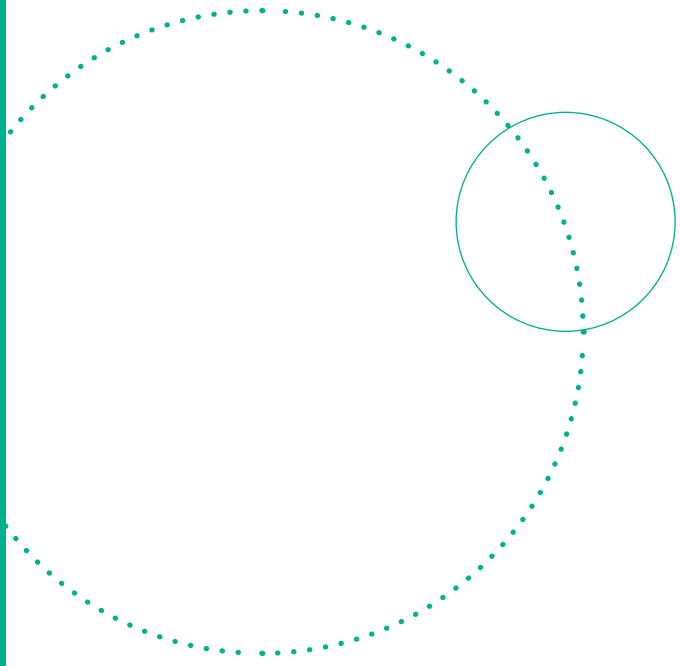
Bednets treated with an AI(s) which is intended to impart an effect on the target vectors, beyond the protective physical barrier, is what defines the regulatory scope and need for robust supporting information to evaluate the safety, quality and efficacy of these products. The ITN **method of application** 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 AI(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:

- **incorporation** of the AI(s) into the yarn during the **extrusion** process prior to the formation of the fabric (Fig. 1); or
- **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 (Fig. 2).

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 presentation of AI from the bound reservoir to the exposed surface. The characteristics of the release of AI, including the optimization of the concentrations and biologically active physical presentation, is dependent on the formulation and manufacturing process.

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. The dose, or total concentration applied to the product at the time of treatment, is not related to the efficacy of a product at a specific point in time.

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, colours, etc. – are selected based on the intent of the product, its desired characteristics, and its use.

Fig. 1. **Incorporated ITN**

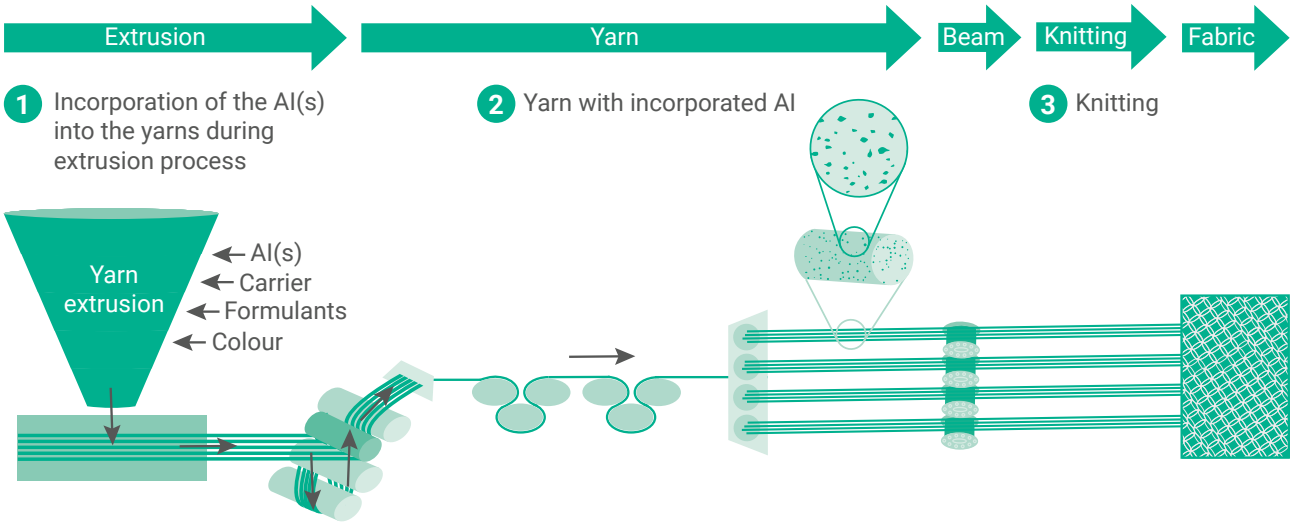
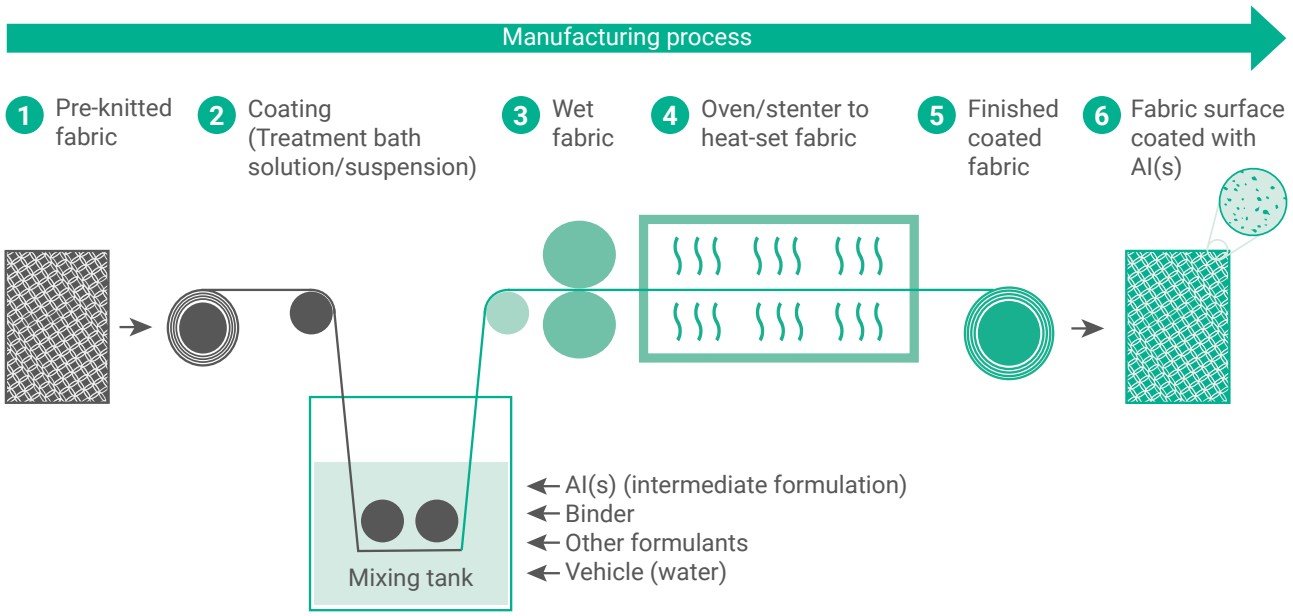


Fig. 2. **Coated ITN**



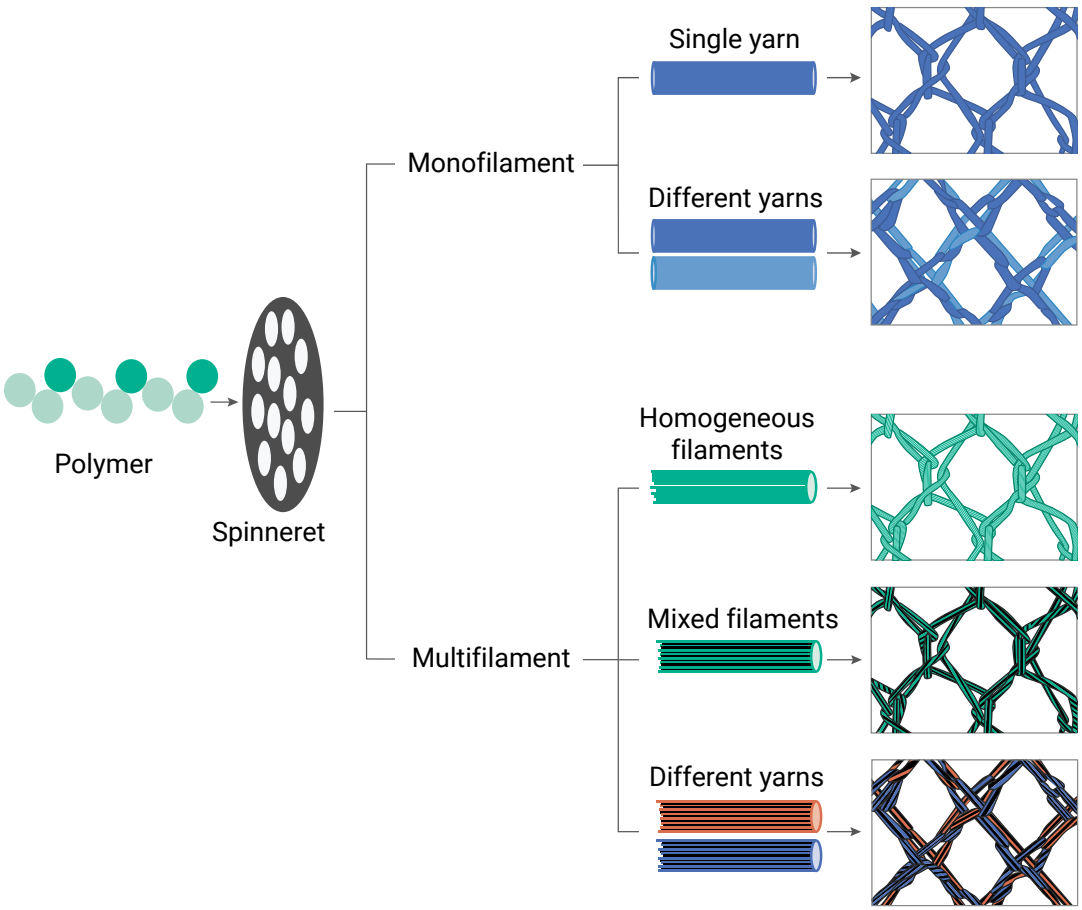
4.3.2 Fabric design: integral components and fabric formation

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 fibre, plies or filament (mono or multi). Historically, ITN fabrics have relied on **monofilament** polyethylene or **multifilament** polyester yarns (Fig. 3). 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 its 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.

Fig. 3. Visualization of monofilament, mulitfilament, and spun interwoven yarns



4.3.3 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 (Fig. 4).

Fig. 4A. Homogeneous rectangular construction: a single fabric used in the construction of the ITN

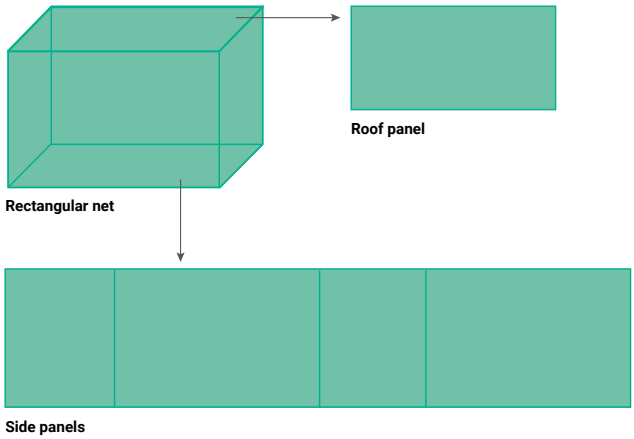


Fig. 4B. Mosaic rectangular construction: different fabrics used in the construction of the ITN

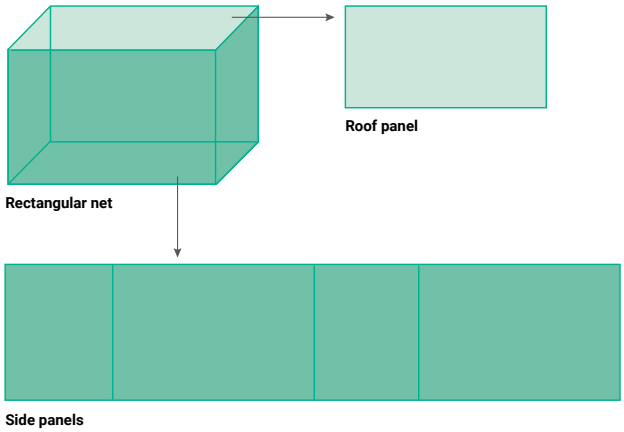
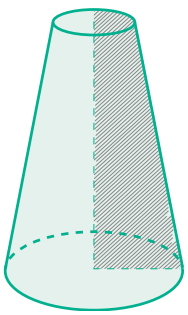


Fig. 4C. Conical construction



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

There are no international standards for delineation of batches/lots for the production of ITNs. Manufacturers are responsible for the development of such approaches as part of their quality management system (QMS).

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

4.5 Post-production stages in the life of an ITN

4.5.1 Prior to initiation of use (storage, transport and distribution)

The continuous and controlled release behaviour of an ITN, including the presentation of AI and thereby the reduction in the reservoir, is apparent immediately after its production. Therefore, the post-production storage and transport of ITNs must be viewed as factors that may affect the potential performance of the product once in use and during the anticipated useful life.

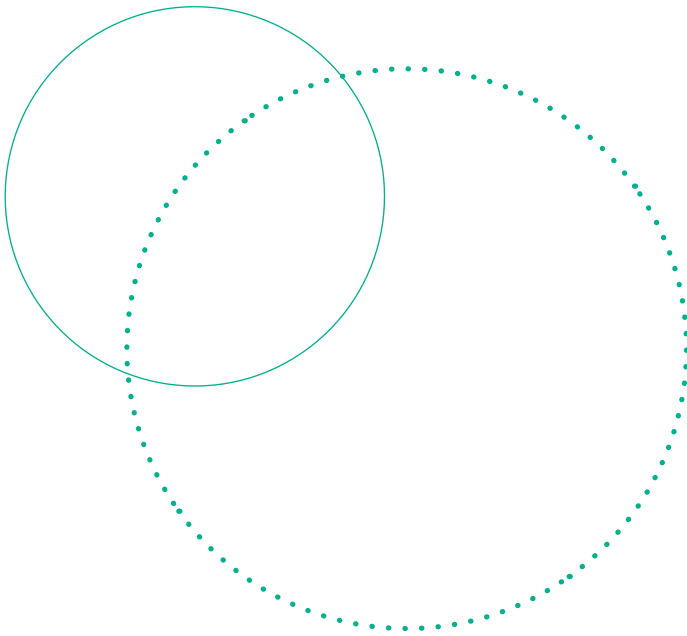
As part of the formulation, manufacturing and packaging of the product, manufacturers may implement strategies aimed to overcome, control or limit changes to the physical/chemical characteristics, including the loss of AI from the ITN prior to distribution.

Prior to the initiation of use, ITNs are expected to maintain their physical/chemical characteristics, noting that some loss of AI and other minor changes may occur.

The manufacturer-recommended storage conditions should be followed at all times prior to the distribution of the ITN and initiation of use, including during transport. Assuming that ITNs are transported and stored in appropriate conditions, i.e. in accordance with the manufacturer's recommendations that were evaluated as part of the prequalification assessment, products are expected to perform as indicated.

Storage and transport of ITNs outside of the recommended storage/handling conditions may impact the performance of ITNs. In cases where the recommended storage conditions cannot be maintained, a risk mitigation plan should be developed by the responsible party(ies), and storage conditions should be monitored to inform any augmentation in distribution plans, or changes in expectations for product performance/residual efficacy. Additionally, implementing organizations may wish to test ITNs that have been stored in improper or uncontrolled conditions before distribution, to ensure that the products remain compliant with the declared specification and/or to inform mitigating strategies.

In accordance with the implementation of an ISO 9001-based QMS, manufacturers are expected to retain samples from batch production, to be used as a point of reference in identifying how products may have changed in response to storage and transport conditions.



4.5.2 In-use life stage of ITNs

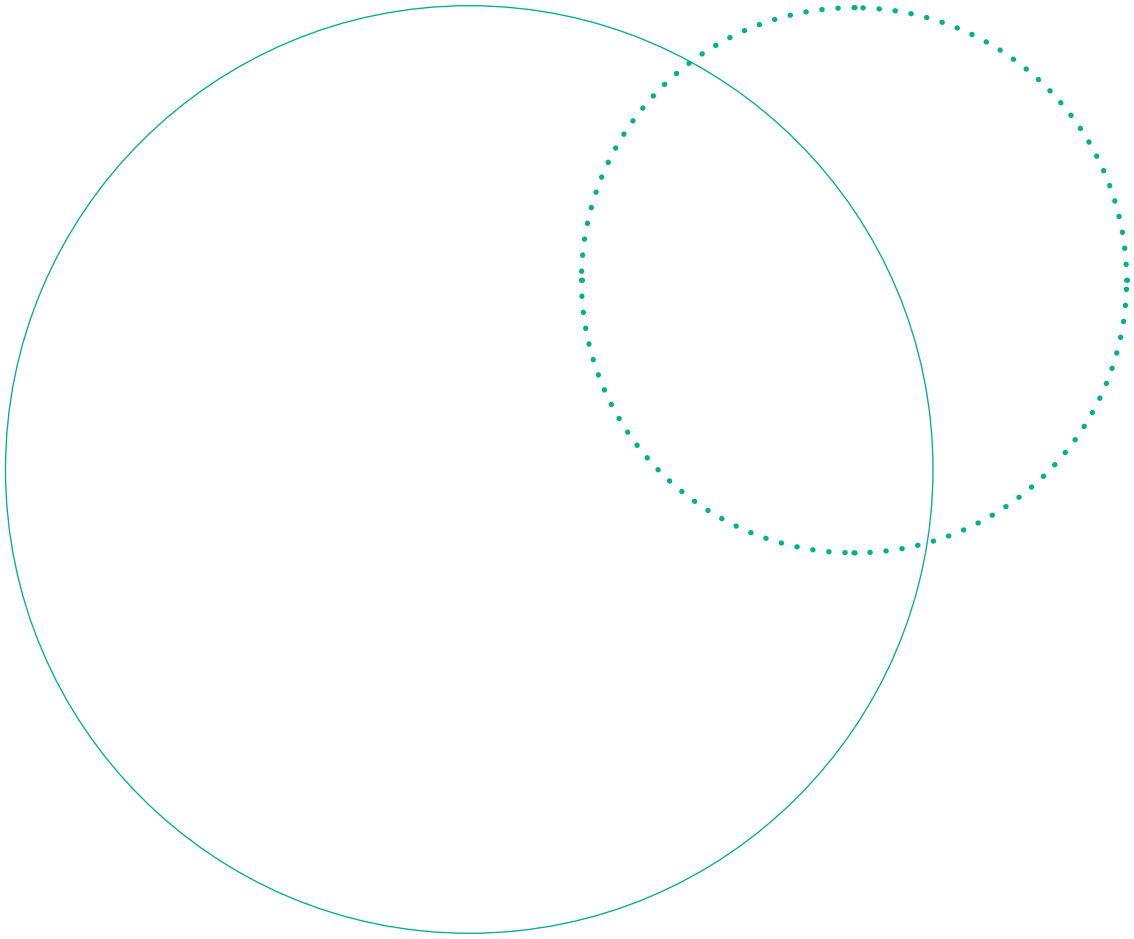
ITNs are typically used indoors. Users, and households, may have ITNs for individual sleepers or for multiple sleepers. The number of ITNs per household varies. ITNs may be hung in the afternoon/evening then taken down and stored during the day or left hanging continuously.

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, although other factors, such as evaporative loss and abrasion, also deplete the AI. The frequency and methods for washing ITNs are highly variable.

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, which is the ability of the treated yarn/fabric and constructed ITN to resist wear and deterioration from continual use.

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

While in operational use, the performance of an ITN, including its physical durability, continuous release of AI, and duration of entomological efficacy can be influenced by the manner in which it is used.



5. Indicators of ITN 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 an ITN's ability to perform the following functions:

- provide continuous and controlled release of the AI(s) to maintain the intended effects of the product on target 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. Bioassays can be either laboratory or semi-field tests. Laboratory bioassays do not directly provide information about the potential **efficacy** of the product but are integral in investigating how a treated fabric behaves in response to washing and/or ageing. The use of bioassays is further discussed and defined in sections 8.3 and 8.5.

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 ITNs, 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);
- **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 7.5.

Physical durability is the ability of the treated yarn/fabric and constructed ITN to resist wear and deterioration from continual use. The aggregation of four key characteristics (bursting strength, resistance to hole formation, abrasion test, snag strength) have been shown to predict the **physical durability** of ITNs in operational use conditions. The inclusion of these physical tests as data requirements, and discussion on the incorporation of these in the product assessment, are discussed in section 7.3.

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.

6. 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 (2)*.

Manufacturers interested in the prequalification of an ITN are invited to contact 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 are conducted as per the criteria below.

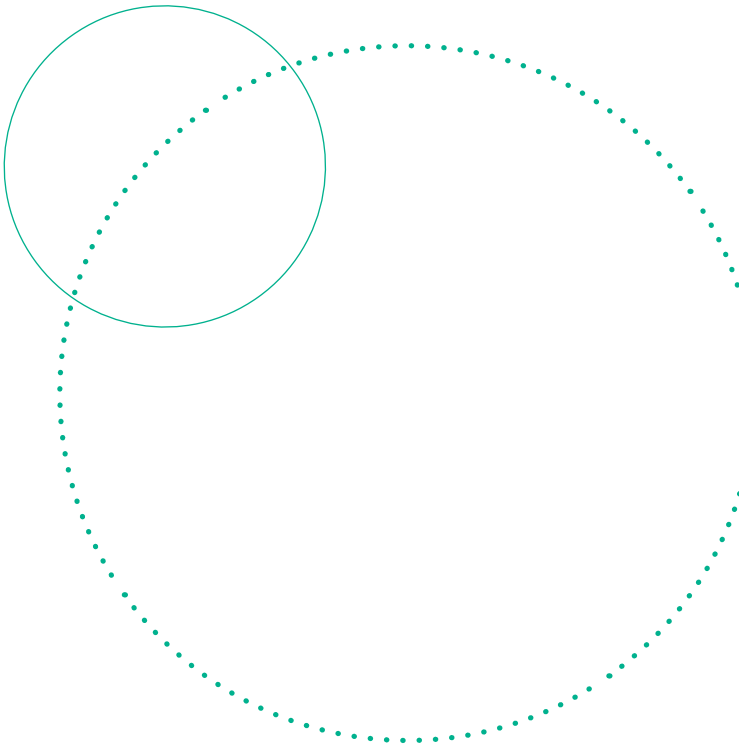
- **Quality:** Assess product formulation, manufacturing process, and physical/chemical characteristics of the yarn(s), fabric(s), and constructed ITN(s), including entomological characterisation of the ITN fabric using bioassays.
- **Safety:** Assess the hazard, exposure and risk, based on the formulation and intended use of the proposed product.
- **Efficacy:** Assess information substantiating the impact of the product on the target vector(s) in 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 ITNs is overseen by the WHO PQT Inspections Team.

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, 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 if the product is still supported by the available product dossier, or if a new product application must be submitted.



7. 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.

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

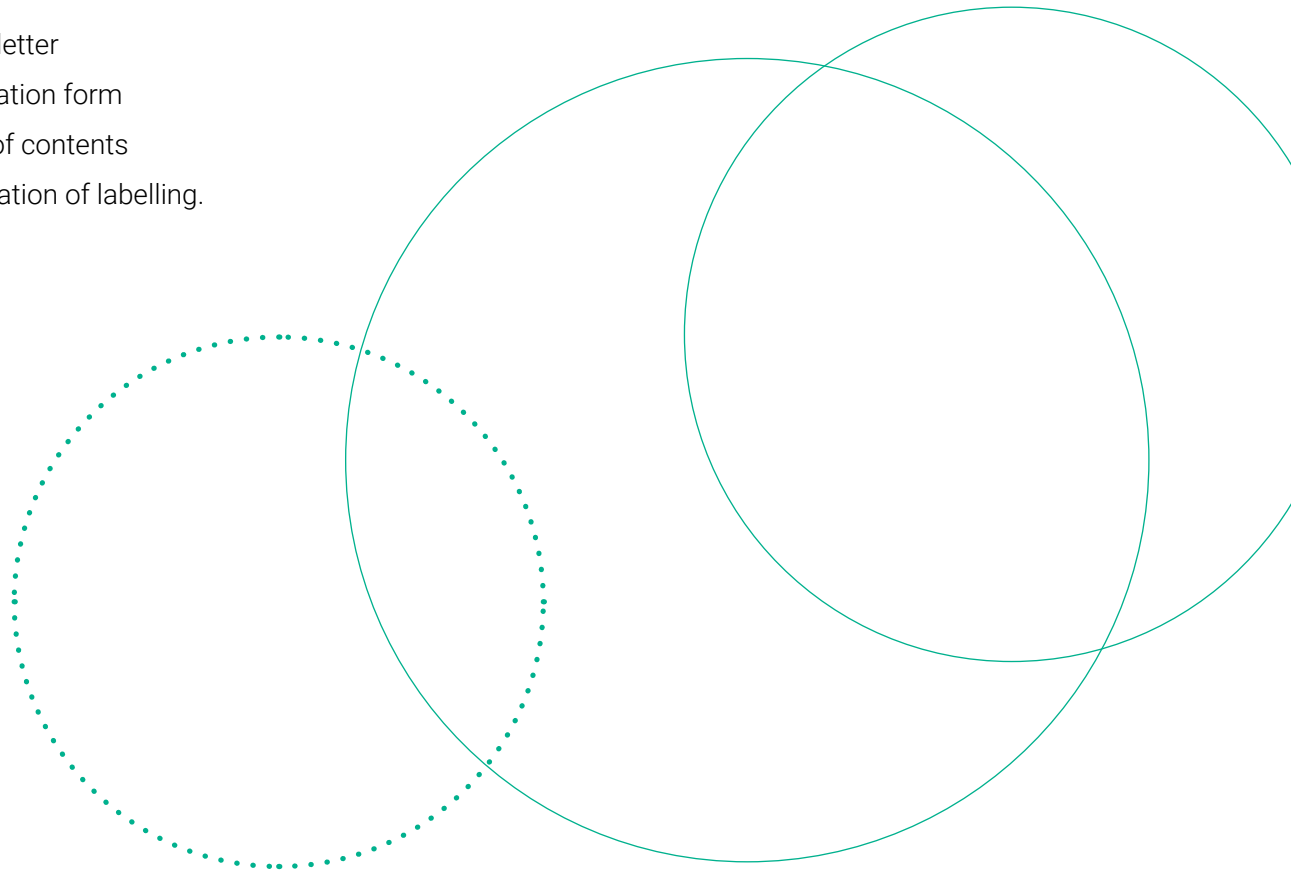
7.1 Module 1: Administrative information and labelling

Statement of intent

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



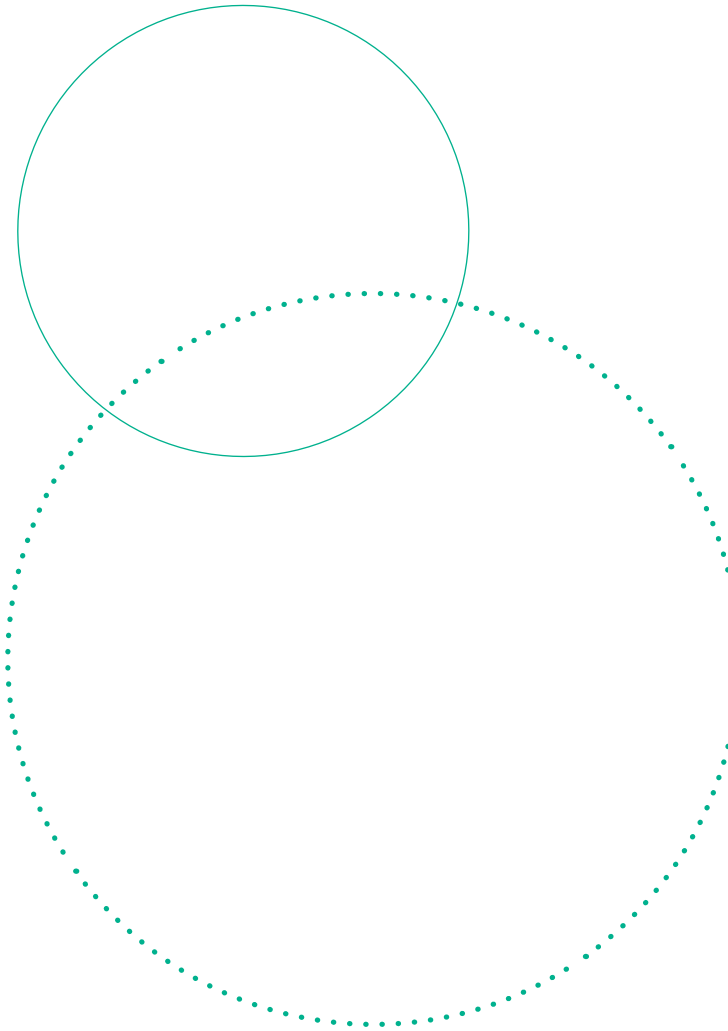
7.2 Module 2: Discipline summaries

Statement of intent

- The intent of Module 2 for ITNs is for manufacturers to provide WHO with information and summarized 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

- Product development: Information regarding product development, for example, the rationale for choosing specific ingredients in the formulation; their concentration informed by assessments of quality, safety and efficacy; their compatibility with the AI(s) and polymers; optimization of the formulation and manufacturing process, etc.
- Samples: 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.
- Quality: Summary of data submitted in support of the product quality and interpretive analysis.
- Safety: Summary of risk conclusions in support of the product safety, and identification of any recommended/required mitigative approaches for reducing potential risks.
- Efficacy: Summary of data submitted in support of the product efficacy and interpretive analysis across the available studies.



7.3 Module 3: Quality dossier

Statement of intent

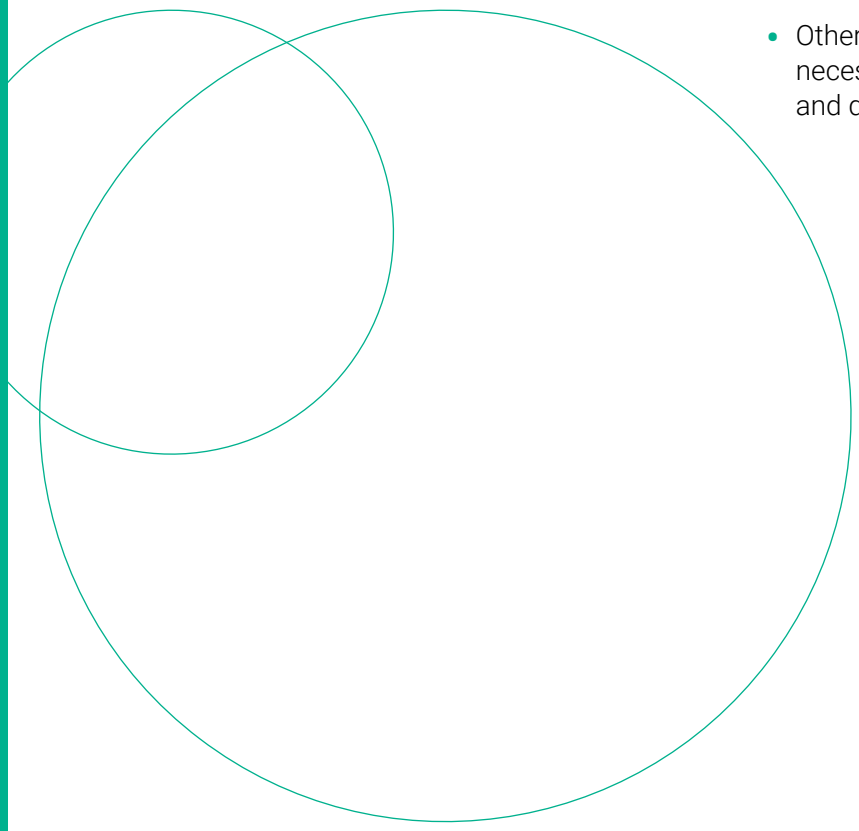
- The intent of Module 3 for ITNs is for manufacturers to provide WHO with information and data which demonstrate:
  - the composition of the ITN;
  - the manufacturing details of the ITN and the consistency of the production process;
  - stability of the ITN formulation, including AI(s), and continuity 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, 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.
- In lieu of analytical chemistry methods to quantify the surface concentration and characterize the form of AI(s) on an ITN, bioassays provide valuable information for characterizing the chemical behaviour of the fabrics used in the construction of an ITN. In the context of the weight of evidence approach, the use of bioassay-generated data to characterize chemical behaviour typically has higher uncertainty due to the reliance on interpreting induced responses in living test systems exposed to an unknown dose of AI. Therefore, generating robust results requires the management of multiple factors, which can contribute to uncertainty. This is further discussed in section 7.5.
- 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;
    - 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 and across studies.
  - The organism (test system):
    - species/strain characteristics;
    - health and consistency of lab-reared colonies;
    - test system preparation;
    - test system behaviour/responses (e.g. circadian rhythm).

The prequalification assessment has evolved from a framework for decisions relying solely on laboratory bioassay results meeting preselected thresholds, to the incorporation of expanded lines of evidence. The results of laboratory bioassays provide an indication of the bioavailability of the AI of the tested product samples, rather than predictions of efficacy. Laboratory bioassays provide critical information which helps to interpret 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

- The complete product composition and purpose of all formulants in intermediate formulations and finished fabrics.
- The complete product manufacturing details including:
  - declaration of manufacturing sites
  - control of starting materials
  - batch delineation and formula
  - description of manufacturing process.
    - Note: A key difference between the manufacturing details in Module 3 and the information required in site master files (SMF) 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 QMS, as presented in the SMF, is the system by which a manufacturer ensures that the declared process is followed.
- 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.
- The physical characteristics of the integral components (e.g. yarn), fabric(s), and constructed ITN:
  - characterization of the integral components includes identification of the polymer, number of filaments, denier, etc.;
  - characterization of the fabric includes various physical tests, e.g. bursting strength, snag strength, abrasion, resistance to hole formation.
- The chemical characteristics of the treated fabric(s), and their integral components:
  - verification of the target dose, homogeneity of the treated fabric, and consistency of production;
  - wash resistance index: this study provides information on how the fabric responds from 0–4 washes. This establishes a point of reference which can be measured as part of product testing for quality control purposes. The resulting value, indexed from the four washes, is not necessarily representative of the loss of AI to washing over the life of the product.
- Storage stability: physical/chemical data generated on product samples having been subjected to accelerated and real-time storage.

- Chemical release properties of the treated fabric (transition of AI from reservoir to bioavailable presentation) by means of:
  - regeneration study for the determination and selection of appropriate wash intervals for artificial ageing:
    - analytical chemistry: raw data, summarized data, graphical visualization, and analysis of the amount of AI lost from fabric per wash in relation to various wash intervals.
    - bioassays: raw data, summarized 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. The endpoint used to determine the selected wash interval must be scientifically justified and used consistently throughout data generation.
  - wash resistance studies for the determination of AI loss:
    - analytical wash resistance curve: raw data, summarized data, graphical visualization, and analysis of the amount of AI lost in relation to a series of washes of the fabric(s);
    - bioassay wash resistance curve: raw data, summarized 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. The endpoint used to evaluate wash resistance must be scientifically justified and used consistently throughout data generation.
  - 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. [Not a current dossier requirement, for discussion as a pilot project].
- Manufacturing release specifications, including methods and notes.
- Other related information as determined necessary, based on the characteristics and design of the product.



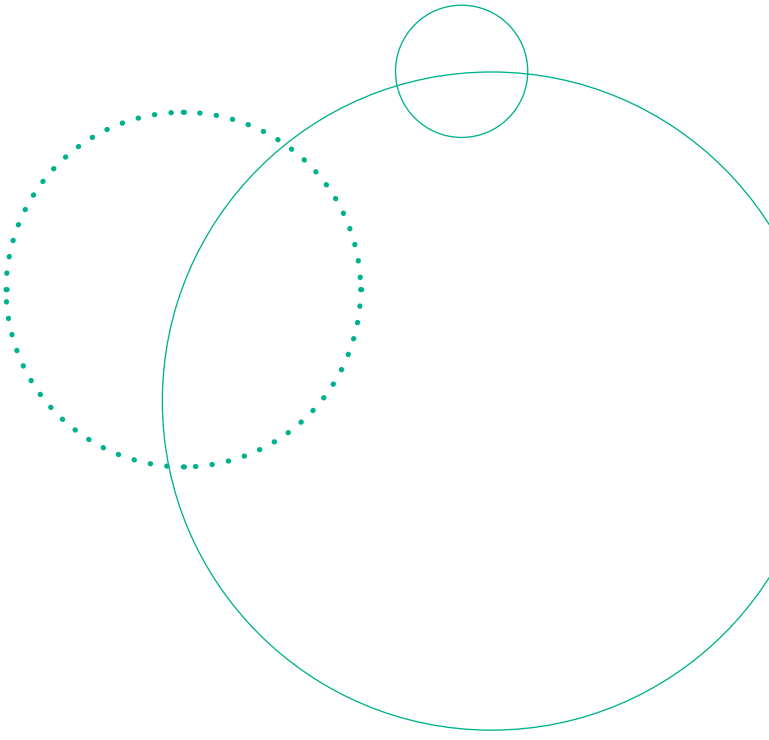
7.4 Module 4: Safety dossier

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 the available toxicological information of the AI has been reviewed by NRAs 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 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.
- Acute toxicology 6-pack: the standard acute 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 6-pack may not be necessary nor appropriate. Applicants should consider the requirements for countries in which they intend to register the product, and the use of waiver requests based on known acute toxicological properties of the AI and formulants.



7.5 Module 5: Efficacy dossier

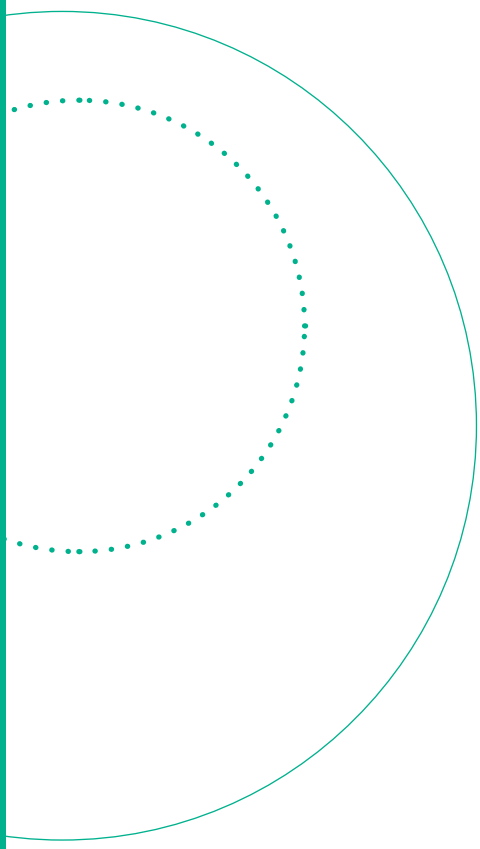
Statement of intent

- 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 impact of the constructed ITN on free-flying target vectors before and after artificial and operational ageing;
  - the biological and chemical consistency of the constructed ITN throughout the intended useful life, meaning the quantifiable induced biological response on the target vector in laboratory bioassays demonstrating the continuous, controlled release of AI of the ITN.
- 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:
  - assured quality of ITNs/samples;
  - appropriate sampling and preparation of whole ITNs and cut samples for use in studies;
  - 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);
  - robustness of the study design and implementation to support the appropriate statistical analyses of the generated data;
  - variability and heterogeneity in wild vector population composition, abundance, structures, resistance profiles, and behavioural characteristics in open system study designs, e.g. experimental hut study;
  - colony health and the consistency of lab-reared vectors for use in closed system

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.
- Semi-field efficacy studies:
  - must be designed to allow for normal interaction of the target vectors, constructed ITN and bait animal (usually a human volunteer), and to collect data on the endpoints relevant to the intended impact of the ITN;
  - may be conducted in open or closed systems. Open systems are considered to generate data that is closest to what may occur when an ITN is deployed in the community, however closed systems allow generation of data using target vectors carrying specific characteristics of interest. Closed systems may predict the results of open systems;
  - the endpoint selected for use in semi-field trials must be the same endpoint as selected for use in bioassays and be used consistently throughout the dossier;
  - the batches of all product samples used in the semi-field studies must be fully characterized as described in Module 3;

- sub-studies within a semi-field efficacy study:
  - experimental hut or ambient chamber study using unwashed and artificially aged nets;
  - supplementary bioassays using unwashed and artificially aged nets;
  - chemical characterization of unwashed and artificially aged nets;
  - adverse event reporting as defined and required by the regional/national/local governing authority.
- 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.



- Long-term community studies:
  - must be designed to allow for usage under routine conditions for three years, with interim time points such that the effectiveness of the ITN can be monitored throughout the study period. Longer trials may be conducted;
  - sub-studies within long-term community studies:
    - attrition and fabric integrity:
      - adverse events at baseline
      - usage of distributed nets at baseline
      - survivorship (attrition rate)
        - physical presence of the ITN in the household
      - physical integrity of ITNs
        - proportion of ITNs with holes
        - hole area
        - hole index
      - physical characterization
        - bursting strength
        - snag strength
        - abrasion
        - resistance to hole formation.
    - chemical and entomological fabric characterization:
      - bioassay assessment
      - determination of total AI content
      - 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].
    - entomological efficacy.
- 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).

7.6 Module 6: Inspection dossier

Statement of intent

- The intent of Module 6 for ITNs 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.

7.7 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 NRAs.

Product specific post-market commitments and data requirement are determined based on the assessment of available information in relation to a new product application or change application.

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

Further information on the modules and specific dossier requirements, including implementation guidance documents, are available on the PQT/VCP website.

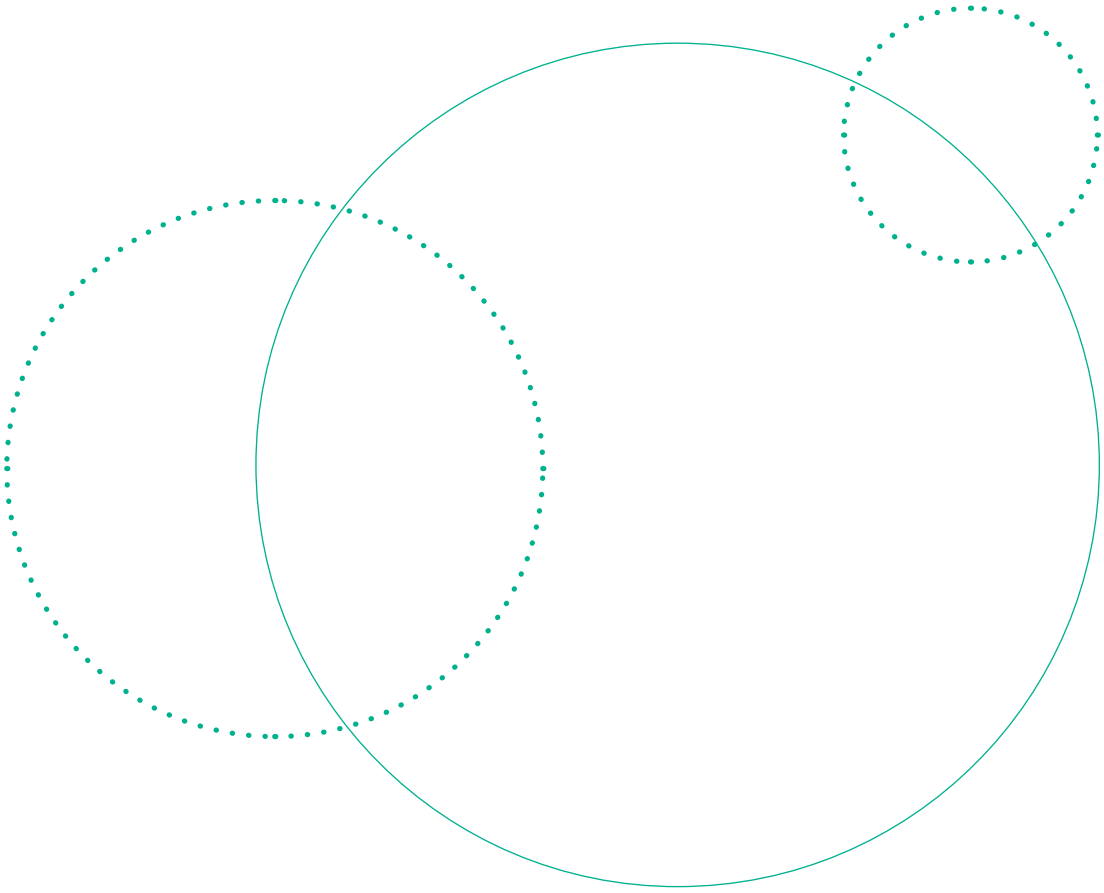
7.8 Importance of relying on the same production batches for generation of data for inclusion in both Modules 3 and 5

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.

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, which may preclude a positive decision for prequalification.

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.



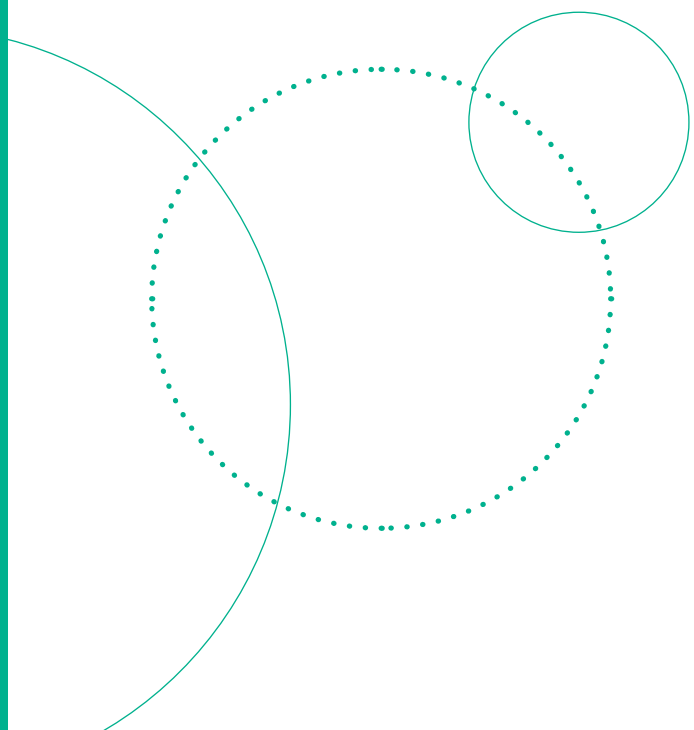
8. Fulfilling requirements for all prequalification application types for VCPs, including ITNs

Applicants are encouraged to investigate the requirements of 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 Global Malaria Programme and Department for Control of 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, 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 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.



8.1 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 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.

8.2 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.

8.3 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 vector control products 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 Generic Risk Assessments for ITNs, and toxicological data to support the safe use of the vector control product, e.g. 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 is 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/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 PQ's 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 pre-submission 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.

8.4 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.

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

9. Decision-making

9.1 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**.

9.2 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 supports the use of a weight of evidence approach to data evaluation and decision-making.

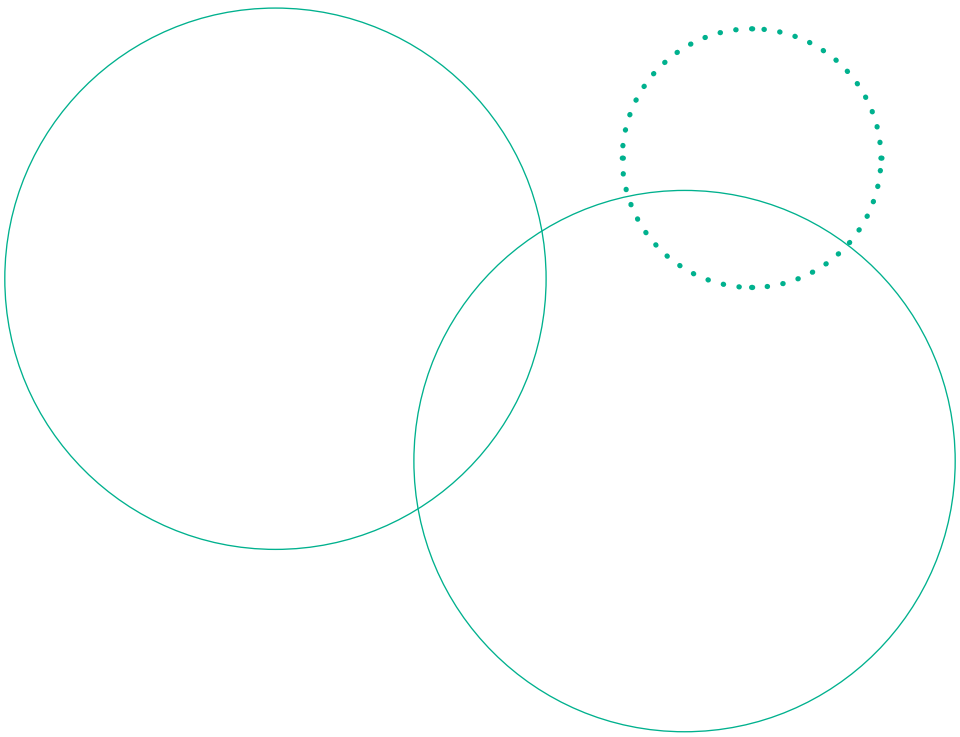
9.3 Weight of evidence

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.

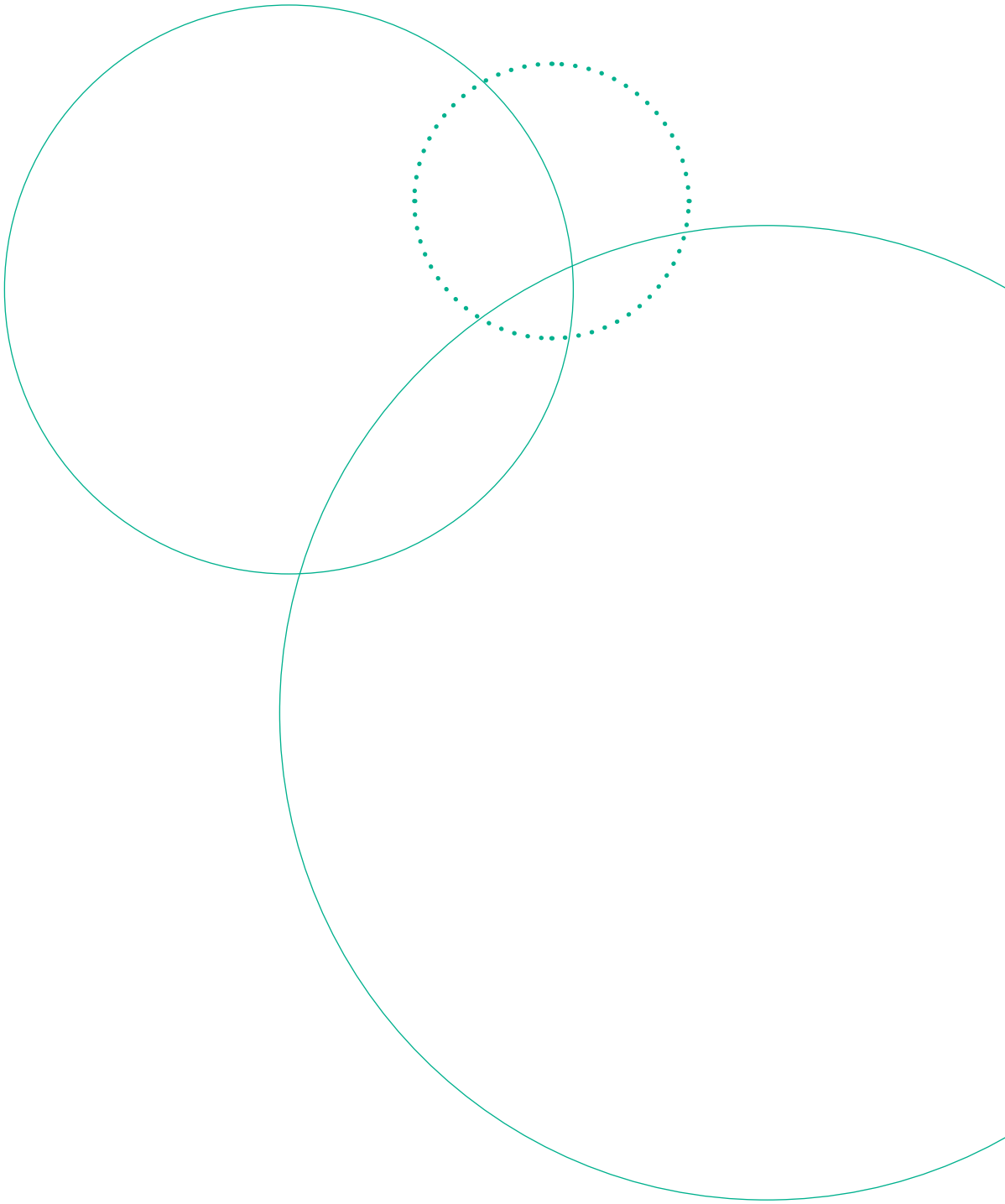
In assessing the information submitted within a product dossier, the scientific validity and appropriateness of the information in relation to the proposed product is determined in order to ensure that reliable lines of evidence are used in the decision-making process.

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.



10. Claiming equivalence to an already prequalified product

Considering the impact that differences in formulations and manufacturing processes, including equipment settings, can have on the physical and chemical characteristics and performance of an ITN, applications claiming equivalence to a currently prequalified product (PQ301) will no longer be accepted by PQT/VCP for ITNs. In order to assess new ITN products, a full product dossier is required.



11. References

1. Guidelines for laboratory and field-testing of long-lasting insecticidal nets. Geneva: World Health Organization & WHO Pesticide Evaluation Scheme; 2013 (https://iris.who.int/handle/10665/80270).
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World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

Email: pqvectorcontrol@who.int
Website: extranet.who.int/prequal/vector-control-products
pqvectorcontrol@who.int

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