WHO PQT/VCP Implementation Guidance – Product Manufacturing Details – ITNs

Introduction

The applicant must submit the current Product Manufacturing Details of each prequalified VCP to be reviewed as part of the WHO Prequalification Assessment of Vector Control Products and maintained on file by WHO as the baseline description of how a product is manufactured.

The Product Manufacturing Details is composed of four sections, each of which must be submitted as a separate document/file.

There is a critical distinction between the information provided as part of the Product Manufacturing Details, for inclusion in Module 3 of the dossier, and the Sites Master Files (SMF), for inclusion in Module 6. The Product Manufacturing Details describe the sites and processes which must be followed in order to produce the product as intended. The SMF and its description of the quality management system (QMS) describe the system by which a manufacturer ensures that the declared processes are followed.

IMPORTANT NOTE – In situations where potential issues regarding the quality of a product(s) arise, the Product Manufacturing Details on file with WHO will be regarded as the point of reference for conducting a root cause analysis to determine if changes in the manufacturing process may have led to the issues.

Summary Table

Document	**Content/Purpose**
Declaration of Manufacturing Sites (DMS)	• [LINK to DMS FORM] • Identify the associated manufacturing sites and their respective activities in the production of the product
Control of Starting Materials	• Acceptance specifications applied to raw materials and to intermediates manufactured at a different site by a third party or the applicant
Batch Delineation and Formula	• Description of the approach for delineation of batches and lots • Actual quantities used for the manufacture of typical commercial batch sizes (or for the minimum and maximum batch sizes) • Rationale for any differences between nominal quantity in Declaration of Product Formulation and batch formula
Description of Manufacturing Process (DMP)	• Process Code and Version Identifier o Unique identifier for the manufacturing process and version identifier which allows for identification of the process used for manufacturing of an individual net/batch • Flow chart • Detailed step-by-step description for each stage of manufacturing

	○ See section Considerations for DMP for Incorporated ITNs. ○ See section Considerations for DMP for Coated ITNs. • Targets and/or acceptable ranges for process parameters and raw material inputs • Storage conditions and maximum holding times for intermediates • Description of variations in the manufacturing process to support the production of various shapes and sizes of the fabric/constructed ITN • Description of the various constructions of the ITN • Identification of in-process tests and the applied acceptable limits • Identification of post-process tests and the applied acceptable limits • Storage conditions and maximum holding times for constructed ITNs

Declaration of Manufacturing Sites (DMS)

Specific instructions for completing the DMS are included in the available template.

Control of Starting Materials

For those raw materials or intermediates produced at different manufacturing sites by a third party or by the legal manufacturer, the acceptance criteria/specifications for use in production must be declared.

Batch Delineation and Formula

The DMP must include descriptions of the approaches for delineating **batches** and **lots** for the constructed ITNs as well as formulated intermediates, if appropriate. For example, constructed ITNs may be an aggregation of manufactured treated fabric batches allowing for delineation of the batch for roof panels versus side panels.

Description of Manufacturing Process (DMP)

This guidance has been developed to support reporting of the manufacturing process by the applicant and to describe the level of detail required to support the product assessment. Manufacturing processes for ITNs, including approaches and orders of operations, can vary from product to product as a result of the treatment type(s), fabric design(s) and construction of the final ITN(s). Therefore, a template has not been developed for the documentation of the Description of Manufacturing Process (DMP). However, a description of the sections which should be considered and expanded guidance on the information to include has been developed.

In general, the DMP documentation submitted by the applicant must include information for those steps of the process covering: receipt/quality checks of raw materials, production of intermediates, production of the constructed ITN, packaging, storage and release from site.

The submitted DMP must include a unique process code and version identifier. If changes are made to the DMP, the version must be revised. By so doing, the manufacturing process used for any individual net/batch can be identified easily by reference to the appropriate process code and version number.

The manufacturing process should be described in sufficient detail to support the assessment of the adequacy of the in-process and post-process controls and to facilitate the assessment of Post-PQ changes by PQT-VCP, including determining the level of evidence required to support changes to the manufacturing process. Where ranges and flexibility in a manufacturing process are required, the nature of the ranges/flexibility must be documented.

For the purposes of WHO prequalification assessment of ITNs, the beginning of the manufacturing process is identified as the quality verification of starting materials for use in the production of the ITN. The end of the manufacturing process is identified as the release from storage by the manufacturer to another party, after which the responsibility for control and handling of the ITN is no longer that of the manufacturer.

The DMP should be organized into sections which align with the documented flow chart (for example, preparation of the active ingredient (AI) masterbatch, extrusion of the filament, warping, knitting, heat setting, cutting and stitching, quality control (QC), packaging). The description must be clear, readable and understandable to a reader with a scientific background but no specific knowledge of the manufacturing process.

Where possible, the incorporation or attachment of images or videos of the process are encouraged to ensure that the DMP is clear.

Further Considerations

The following questions may be of assistance in writing DMP with the required level of detail.

These questions are only to provide guidance. The dossier should include a description of the manufacturing process, not a series of answers to questions.

Every manufacturing process is different. Some of the questions listed below may not be relevant to every process, and some manufacturing processes may include aspects not covered by the questions.)

<u>Questions to consider when preparing a DMP</u>

- Does this stage use a batch process or a continuous process?
- For batch processes, what quantity of the intermediate/finished product is manufactured per batch? (This may be a range rather than a single quantity.)
- For continuous processes, what quantity of the intermediate/finished product is manufactured per hour/day, what is the duration of a single manufacturing run (this may be a range), and how are runs divided into lots?
- What equipment is used in this stage of the manufacturing process? (Specify the model and capacity for machines such as mixers, extruders, knitting machines, stenters, etc.)
- What are the inputs into this stage of the process (raw materials and/or intermediates from previous stages), and what quantities are used per batch/hour/day? Notes:
    - Materials that are used in the process but are not part of the finished product, such as water used to prepare a coating suspension then removed during the drying step, should be included.
    - Any differences between the batch quantities and the quantities in the Declaration of Product Formulation (DPF), such as excesses added to compensate for losses during manufacture, must be described and justified.

- What is the full sequence of operations performed in this stage of the manufacturing process, from dispensing of the inputs to obtaining the intermediate/finished product? In describing the sequence of operations, consider the following:
    - What is the order, method and rate of addition of the inputs into the process? For continuous processes, what is the capacity of any hoppers, baths or other devices for holding raw materials, and how often are they refilled?
    - How and when are the inputs mixed? For example, prior to adding to a hopper, in the screw of an extruder prior to melting, in the screw of an extruder after melting, etc.
    - What conditions/operating parameters need to be controlled during each operation? (For example, feed-in rates, mixing speeds, times, temperatures, pressures, etc.) What are the targets and/or acceptable operating ranges for each parameter, and how often are they checked? (Note: Evidence to support the proposed acceptable operating ranges should be available if requested.)
    - If relevant, how is the end-point for this stage in the process determined? (This is especially relevant to processes such as mixing and/or granulation steps performed batch-wise rather than continuously.)
- What chemical/physical tests are performed, either during the manufacturing process or on the intermediate/finished product, to ensure the consistency and quality of the output from this stage of the process (e.g., denier of filaments/yarns and/or dimensions of netting fabrics, etc.)?
- If this stage of the manufacturing process produces an intermediate rather than the finished product, is the intermediate transferred immediately to the next stage or is it stored? If it is stored, what are the conditions of storage (including packaging, temperature, humidity, etc.) and what is the maximum storage period? (Note: Evidence to support proposed maximum storage periods should be available if requested.)
- Are any augmentations of the manufacturing process to accommodate for various sizes of a fabric and shapes/sizes of the constructed ITN adequality described?

Specific Considerations for Coated ITNs

TBD

Specific Considerations for Incorporated ITNs

TBD