Product manufacturing details: spatial emanator products

1. Introduction

The applicant must submit the current product manufacturing details of each prequalified vector control product (VCP) to be reviewed as part of the WHO Prequalification Assessment of Vector Control Products. These are maintained on file by WHO as the baseline description of how a product is manufactured.

The product manufacturing details are 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 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.

2. Summary table

Document	Content and purpose
Declaration of manufacturing sites (DMS)	WHO PQT/VCP declaration of manufacturing sites – Template 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

Document	Content and purpose
Batch delineation and formula	Description of the approach for delineation of batches 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 the declaration of product formulation and the batch formula
Description of manufacturing process (DMP)	Process code and version identifier • Unique identifier for the manufacturing process and version identifier which allows for identification of the process used for manufacturing of a batch Flow chart Detailed step-by-step description for each stage of manufacturing Targets and/or acceptable ranges for process parameters and raw material inputs Storage conditions and maximum holding times for intermediates Identification of the product characteristics and processes which are Critical to Quality (CTQ) 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 finished products

2.1. Declaration of manufacturing sites (DMS)

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

2.2. 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.

2.3. Batch delineation and formula

The submission must include descriptions of the approaches for delineating **batches** for the finished spatial emanator product as well as formulated intermediates, if appropriate. Manufacturers should provide the description and reasoning for the batch system as part of the submission.

2.3.1. Establishment of batch identification systems and batch definitions

The responsibility for the establishment of a system for batch identification lies with the manufacturer. Batch identification systems promote traceability and facilitate simplification of the localization of manufacturing issues.

Batch identification systems are essential for communicating with external parties, for example, customers, third-party inspections and institutions.

A batch may contain more than one sub-batch used for internal manufacturing quality control. Typically, the quality in a batch is as homogenous as possible with regards to the raw materials and critical processes used in the production of that batch.

Internal batch quality control should be conducted in order to demonstrate the process for identifying out-of-specification products and the necessary remedial action that was undertaken. This information is not required to be submitted as part of Module 3 but should be available on request.

The size of a batch can vary, according to the needs of the manufacturer. Batches should be defined considering the production of intermediates, if applicable, within the manufacturing process to ensure traceability of the production of the finished products. The maximum batch size of finished products and inclusion of intermediate batches must be declared.

The batch number of each spatial emanator product should be captured on the product labelling. Batch numbers should be linked to purchase order numbers for traceability.

2.4. 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 products, including approaches and orders of operations, can vary from product to product. Therefore, a template has not been developed for the documentation of the DMP.

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 product, 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 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-prequalification changes, 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 the WHO prequalification assessment, the beginning of the manufacturing process is identified as the quality verification of starting materials for use in the production of the product. 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 product is no longer that of the manufacturer.

The DMP should be organized into sections which align with the documented flow chart. 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 preparing the 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 apply to every process, and some manufacturing processes may involve elements that are not addressed by these questions.

Questions to consider when preparing a DMP:

- 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 the stated sub-batches?
- What equipment is used in this stage of the manufacturing process? (Specify the model and capacity for equipment.)
- 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:
  - 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 equipment for holding raw materials, and how often are they refilled?
    - » How and when are the inputs mixed?
    - » What conditions/operating parameters need to be controlled during each operation? What are the targets and/or acceptable operating ranges for each parameter, and how often are they checked? (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?
- 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? (Evidence to support proposed maximum storage periods should be available, if requested.)

3. Related documents

- WHO PQT/VCP Declaration of manufacturing sites – Template
- WHO PQT/VCP Implementation guidance – Module 3. Data requirements table
- WHO PQT/VCP Implementation guidance – DPF for spatial emanators
- WHO PQT/VCP Implementation guidance – DPF for spatial emanators – Template
- WHO PQT/VCP Implementation guidance – Manufacturing release specifications
- WHO PQT/VCP Manufacturing release specifications – Template
- Implementation guidance – Guidance for development of SMFs