Physical Chemical Data Characterization Requirements for Spatial Emanators

Common deficiencies in **physical/chemical characterization studies:**

- Not enough batches
- Not enough replicates
- Raw data not provided

1. Purpose

This implementation guidance is intended to provide guidance on the data to be generated and the study reports to be included in Module 3 (e.g. 5 batch physical chemical characterization and how to report the study results) for the purposes of establishing a point of reference for the physical and chemical properties of the product, informing manufacturing release specification attributes and values, and demonstrating the appropriateness of the sample handling and preparation procedures used in the studies included in Module 5.

2. Background

The data and study reports to be included in Module 3 for spatial emanators are required to fulfill the following purposes:

- **Physical chemical characterization of the product, which provides the baseline data for setting of manufacturing release specifications**:
    - The values and tolerances for all the properties in the manufacturing release specifications are dependent upon the results and inter/intra batch variability obtained in the 5-batch physical chemical characterization study and storage stability studies. Manufacturers should ensure that properties' values and tolerances (i.e. mean AI and synergist content) are reflective of the values and tolerances according to the values and inter- and intra-batch variability identified in the physical chemical characterisation studies, storage stability studies, and variability identified in the manufacturing process.

      IMPORTANT NOTE – The manufacturing release specifications are distinct from the complete product specifications, which include full characterization of the product based on the defined dossier and data requirements. In most cases, all product specifications (attributes tested in the 5-batch physical chemical characterization study) are necessary nor appropriate for quality control related product testing activities.

The Manufacturing release specifications template is used to clearly convey the product manufacturing release specifications. A Manufacturing release specifications Template is required for each product.

- **Linkage between Module 3 and Module 5**:
  - The same batches of the product used in the physical/chemical studies should be used for Module 5 studies. A baseline quality check is recommended before starting any study to ensure that the quality of the product is as expected, especially when products have been shipped to different facilities for testing. The physical chemical characterization data obtained in Module 3 (which includes parameters that have the potential to affect biological activity of the product) provides insights into guiding the selection of conditions to be used in efficacy studies.

3. Scope

This implementation guidance describes the Module 3 data requirements for spatial emanator products. Formulation types covered by this implementation guidance include i.e. vapor-releasing products.

Note: Data requirements for spatial emanator products with formulation types outside this scope may differ from those described in this implementation guidance. PQT/VCP should be contacted for advice prior to commencing the physical/chemical characterization studies.

4. Definitions and Characteristics

Spatial emanators are products designed to emit one or more active ingredients (AIs) into the air through passive or active mechanisms. For more detail on the definition and characteristics of spatial emanators, see section *3. Characteristics of spatial emanator products* in the document *Interim guidance for the prequalification assessment of spatial emanator products*.

For passive emanation products, the formulation type would most commonly be a vapor-releasing product formulation which may include, solid or viscous liquid formulations held on solid supports or held or adsorbed into other materials, which emit AIs through evaporation without a source of heat or air movement. They consist of one or more AIs with or without a solvent or other inactive formulants, such as stabilizers. For active emanation products, the proposed product could be a vapor releasing product formulation type or other liquid or solid form.

The source materials of the AIs used in formulating spatial emanator products must comply with the requirements of relevant WHO specifications.

5. Physical/Chemical Characterization of the Product

Module 3 should include one or more reports describing studies performed to characterize physical and chemical properties of the product, as packaged, relevant to its quality and performance.

5.1. Selection and number of batches

Full physical/chemical characterisation data should be provided for a minimum of five pilot- or commercial-scale batches of the product. (A pilot-scale batch is considered as not less than one tenth of the proposed maximum commercial batch size.)

All batches of the product used in semi-field and/or field studies should also be included in the physical/chemical characterization studies and should be characterised fully.

If fewer than five batches were used in the semi-field and/or field studies, or if five or more batches were used but some were below pilot scale, additional batches should be included in the physical/chemical characterization studies to ensure that the requirement for a minimum of five pilot- or commercial-scale batches is met.

5.2. Tests to be performed

Due to the potential variety of spatial emanator products and their design, some of the tests below may not be relevant for all products and formulations, and some tests not listed may be appropriate in specific cases. Read the notes carefully and contact PQT/VCP if there is any uncertainty over the tests to be included in a physical/chemical characterization study.

Table 1. Parameters to be tested for physical/chemical characterization

DR code	Test	Method/Reference
1	Appearance	
2	AI/synergist	CIPAC, AOAC or equivalent (Note 7)
2.1	Identification (Note 1)	CIPAC, AOAC or equivalent (Note 7)
2.2	Mean total content (Note 1)	CIPAC, AOAC or equivalent (Note 7)
2.3	Isomer ratio (Note 2)	CIPAC, AOAC or equivalent (Note 7)
2.5	Release rate test (Note 3)	IG – Emanation rate study
2.6	Verification of the target dose, homogeneity of the formulated product and consistency of production (Note 4)	CIPAC, AOAC or equivalent (Note 7)
3	Impurities	CIPAC, AOAC or equivalent (Note 7)
3.1	By-products (Note 2)	CIPAC, AOAC or equivalent (Note 7)
3.2	Water (Note 5)	
4	Inactive formulants (Note 6)	
5	Treated surface area	Note 8

Notes:

1. Tests for identification and mean total content should be performed for each AI or synergist included in the formulation.
2. Where the WHO specification for an AI or synergist in the formulation includes a test for isomer ratio or for content of an impurity potentially formed as a by-product of manufacture and storage, these tests should also be included in the physical/chemical characterization of the product.
3. An emanation rate study is a separate requirement (please refer to IG – Emanation rate study).
4. Chemical analysis of total AI conducted in a manner to capture heterogeneity of the formulated product. Includes identification of the enforcement analytical method.
5. Water content is unlikely to be relevant for this type of products. If there are any circumstances where the test could conceivably be relevant, then this test should be included.
6. Inactive formulants content is unlikely to be relevant. If there are any circumstances where the test could conceivably be relevant (e.g. if the inactive formulant improves the volatility of the AI) then this test should be included.
7. Internationally validated methods (for example, CIPAC or equivalent) must be used for the identification, quantification, isomer ratio of AI from product samples, or for content of an impurity potentially formed as a by-product of manufacture and storage.
   In cases where a new or amended extraction or preparation method is required, an independently validated method should be developed and submitted to support the assessment of AI quantification of samples. New or augmented methods must then be internationally validated for use as the reference method for manufacturing release specifications and other forms of product testing.
8. The treated surface area of the product in general can be determined by measuring the length and width of the treated substrate (a figure should be provided for reference). Measurements should be taken from one edge of the substrate to another, including any part of the substrate, using a calibrated measurement tool, such as a ruler or caliper. The equations used to determine the total treated surface area of the product should be provided.

5.3. Reporting of results

The results to be reported for the physical chemical characterization study are, for each tested parameter:

• arithmetic mean results and range;

• percentage Relative Standard Deviation (RSD).

The inter- and intra-batch variability are analysed using RSD to measure the precision. RSD should be expressed as percentage. It is obtained by multiplying the standard deviation (SD) by 100 and dividing by

product average (%RSD = SD *100/Mean). A table showing the summary results (production batch, number of samples, global arithmetic mean result, range, %RSD), should be included in the body of the report and individual sample results in an appendix of the report.

In general, for the variety of spatial emanator products, a replicate (or sample) is a unit product. For this type of product, testing should be completed using the full product and sub-samples should not be taken as representative of the whole product (unless the product concept and design dictate that sub-sampling is necessary). Please refer to IG – Declaration of product sampling.

6. Storage Stability Studies

Real-time and accelerated storage stability studies are required. Please refer to IG – Storage Stability Study for specific guidance.

The identified properties of relevance to the product should be considered for their relevance within both accelerated and real time storage stability studies.

7. Related documents

- WHO PQT/VCP Implementation guidance – Template Manufacturing release specifications
- WHO PQT/VCP Implementation guidance – IG – Declaration of product sampling
- WHO PQT/VCP Implementation guidance – IG – Emanation Rate Study
- WHO PQT/VCP Implementation guidance – IG – Storage Stability Study
- WHO PQT/VCP Implementation guidance – Module 3 Data Requirements Table
- WHO PQT/VCP Advice to manufacturers series – WHO specifications vs Product Manufacturing Release Specifications
- WHO PQT/VCP Advice to manufacturers series – Number of batches required for testing of physical/chemical properties