WHO Prequalification of Vector Control Products

Analytical bridging studies for determination of active ingredient content in data generation to support PQ decision making

PURPOSE

This document is intended to provide:

- clarification on the the requirements for the use of independently validated analytical methods for the determination of active ingredients/synergists in the generation of data to be submitted to PQ as part of a new product, change or reassessment application, and
- guidance on the conduct of analytical bridging studies to confirm similarity of methods and inclusion of the study in an application to PQT/VCP.

BACKGROUND

Data generated for submission to WHO as part of the PQ assessment must rely on independently validated analytical methods to determine active ingredient (and synergist, if present) identity and content/isomer ratio and relevant impurities content (when applicable) in the formulated vector control product (VCP). Established reference methods may be found in the published WHO specification and/or relevant manufacturing release specifications. The reference method is considered the enforcement analytical method for quality testing conducted by/on behalf of Member States, procurers, or other interested parties. When available, the established reference method should be used for data generation.

However, in generating supporting data during the development of product dossiers for regulatory submission, manufacturers may face situations, in which:

- available methods have not yet been independently validated through an appropriate body (e.g. CIPAC, AOAC, or equivalent),
- established methods need to be augmented and thereafter revalidated, or
- deviations from the reference method were implemented.

The inclusion of an analytical bridging study to support a prequalification assessment may be necessary anytime the method used for identification and quantification of the active ingredient(s)/synergist(s) in generating supporting data differs from the established reference method. Depending on the situation, an analytical bridging study may be required as either a premarket (e.g. prior to the finalization of a PQ decision) or a post-prequalification commitment.

Demonstrating the comparability of methods is critical to ensure that the differences would not interfere in the interpretation of baseline datasets, establishment of manufacturing release specifications and quality testing for product procurement and/or post-market surveillance.

The following examples are intended to guide manufacturers in identifying situations where an analytical bridging study may be necessary. If manufacturers have identified the potential need for an analytical bridging study, they are encouraged to request a meeting with PQT/VCP to present the situation.

- If independent validation of a new, or augmented, method occurs after generation of data using the method, manufacturers are required to declare any changes in the method during the validation process. Depending upon the extent of the changes, an analytical bridging study may be required.
- If deviations from a reference method are introduced, the applicant is expected to provide the complete details of the method used and include a rationale and justification for the deviations. (Example deviations - use of methanol instead of acetonitrile in the HPLC mobile phase, use of nitrogen instead of helium as gas chromatography carrier gas, different stationary phase in HPLC, different concentrations in calibration solutions, use of another internal standard, etc.) Depending on the extent of the deviation(s) and the potential to generate dissimilar results, an analytical bridging study may be required.

WHO Prequalification of Vector Control Products
Avenue Appia 20
1211 Geneva 27
Switzerland

For further information, contact:
pqvectorcontrol@who.int
https://extranet.who.int/pqweb/vector-control-products

Note: Manufacturers may, in their internal quality assurance and control, use an in-house analytical method. In such cases, manufacturers are expected to have available an appropriate bridging study on file to justify their use of the in-house method for their purposes. PQT/VCP may request the bridging study at any time to support assessments within the scope of the established procedures (e.g. complaint investigation) or for inspection purposes.

ADVICE

The analytical bridging study should demonstrate that an analytical method used for determination of the content of AI in the vector control product provides comparable results as the independently validated reference method, thereby ensuring reliability of the submitted data.

The analytical bridging study must include the analysis of the same set of samples using the two methods and include supporting statistical evaluation of the results.

Bridging study requirements:

Number of batches and replicates:

- A minimum of 3 batches must be analysed as per the two methods.
- Analyses must be conducted on 2 different days with independent sample weightings, and 2 independent calibrations.
- A minimum of 2 replicates per batch is expected on each day.

Method details and reports:

The manufacturer must include a clear declaration of the reference method to which the proposed method is being bridged, and a table showing the technical comparison between the methods presenting the parameters and their equivalence/significance.

For the proposed method, full method details and appropriate method validation data must be submitted. GLP compliant validation studies are preferred. If the study is not GLP compliant it should still be formatted in the GLP-style for easy identification of information.

The report must include:

- full details on the test items and the analytical standard(s)
- raw data on all weightings, dilutions and sample preparations
- statistical evaluation for the selectivity/specificity, linearity, repeatability, reproducibility, precision of the analytical method and sampling method, accuracy/recovery, limit of quantification and robustness
- statistical evaluation for the standard deviation (SD), standard deviation of the mean (SDm), relative standard deviation (RSD %), RSDr (mod. Horwitz) and Horrat calculations to demonstrate repeatability based on a comparison of the results.
- CoA(s) of the substances used in the study
- complete and **legible** chromatograms (solvent, blank, internal and calibration standard, AI, all batches test samples)
- the raw data of analytical results.