

Points to Consider for Inspections of Biowaiver Data

Principle

WHO inspects sites that have performed comparative dissolution studies submitted in product dossiers by applicants in support of requests for biowaivers (i.e. waivers of the necessity to perform clinical bioequivalence studies).

Background

For a number of years, WHO has carried out inspections of finished pharmaceutical product manufacturing (FPP) sites, active pharmaceutical ingredient (API) manufacturing sites, quality control laboratories, and sites used to conduct bioequivalence studies. Given the high importance of dissolution data that is used to support requests for biowaivers, WHO has decided to further focus on dissolution testing during site inspections.

Scope

This document sets out points that may be considered for review, verification and inspection. The list is not exhaustive list, but reflects elements that may be considered for inclusion during the inspections of sites which have performed comparative dissolution studies for Biopharmaceutics Classification System (BCS)-based and additional strength biowaivers.

Points that will be considered during the inspection of sites performing comparative dissolution studies in support of biowaivers

The requirements outlined in WHO guidelines (see references below) and in the International Pharmacopoeia monograph for dissolution testing and other pertinent pharmacopoeias will be applied, in addition to other requirements that are specific to on-site inspections.

All laboratories that perform comparative dissolution profile (CDP) should follow the good manufacturing, good laboratory and good documentation practices.

These requirements include but are not limited to the following:

Standard operating procedures (SOPs)

SOPs should address mechanical calibration, performance verification, cleaning and maintenance (in accordance with the apparatus manufacturer's instructions) of each type of dissolution apparatus used. These should include an SOP that provides exact instructions on: how to prepare the media (including degassing of the media); when/how to prepare for the dissolution test; the way in which tablets or capsules should be introduced in vessels or baskets; the way in which samples should be withdrawn and filtered; and sampling times with time variance.

Qualification of the equipment/instruments

Acceptable qualification protocols and reports should be available for laboratory equipment and instruments and should include installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). IQ should include documentation on compliance with Pharmacopoeial requirements; verification that all pertinent SOPs are approved and in place; and documentation that the equipment is enrolled in a preventive maintenance programme. OQ should include elements such as a rotational speed study and temperature mapping of the bath. For further details on qualification of equipment and instruments, see the general texts on Good Manufacturing Practices and Validation (reference: Dissolution Toolkit Procedures for Mechanical Calibration and Performance Verification Test, Apparatus 1 and Apparatus 2).

Mechanical calibration of the equipment

Mechanical calibration of the instrument should be performed at required intervals. The following calibration tests are generally recommended:

- shaft wobble
- paddle and basket shaft verticality
- basket wobble
- vessel centring
- vessel verticality
- basket and paddle depth
- rotational speed.

For additional information, see also notes in the pharmacopoeia (e.g. USP<711>).

A performance verification test is further required, using the valid prednisone tablet standards.

Note: Tools used during calibration and or testing (such as height gauges, wobble meters, timers and/or tachometers) should be traceable to recognized national standards (such as the National Institute of Standards and Technology) or international standards.

Suitability of instruments before use

Laboratories should ensure that instruments are suitable for use prior to carrying out dissolution testing. Specific tests to be performed before each and every test may include examination of the baskets, paddles, vessels, temperature, vibration, speed, wobble, centring, horizontality, etc.

Protocols used for conducting the comparative dissolution studies

Before the actual dissolution testing is performed, a protocol should be prepared describing how the testing will be conducted. This should at a minimum refer to the purpose or objective of the study; lot numbers and expiry dates of test and reference product; country of purchase; a clear description of the method used for the dissolution component of the method (time points that will be measured, with an inclusion of early timepoints such as 5 and/or 10 minutes); a clear statement regarding the conditions where f_2 values do not need to be calculated, the calculation formula and methodology that will be used to calculate f_2 values; and information on the analytical procedure (i.e., quantitation component) that will be followed (a reference can be made to the analytical procedure, which can be included as an attachment), on the equipment used and settings of the apparatus (e.g., stirring speed, media volume, temperature, etc.). The protocol should include the conditions required for comparative dissolution testing related to biowaivers (Reference 1).

Note: Requirements outlined in WHO Guidelines (see References below) should be followed for each of the above-mentioned points.

Reports

The results of the testing should be appropriately documented. Source data should be maintained and results should be reported in the recommended format. The report should be in accordance with WHO Prequalification requirements and with the dossier.

Note: Please consult the references at the end of this document for the data to be included in reports.

If, an Excel sheet is used to calculate, e.g. for the comparative dissolution profile, the same it should be qualified and periodically verified.

Test procedures

Test procedures can be divided into two individual components: (1) the dissolution procedure itself; and (2) the method used to quantitate the amount of API that is dissolved at each time point and for each sample:

- Dissolution component: The documentation should normally cover aspects relating to de-aeration (or not) of the dissolution media; the use of appropriate sinkers; and the manner of filtration of dissolution samples. All deviations should be recorded. The dissolution method should be clearly described including the type of apparatus used, agitation speeds, number of units tested, method of sample collection, sampling times, sampling, etc., and should be in line with WHO requirements (Reference 1).
- Quantitation component: The documentation should normally cover a description of the analytical procedure (including its design).

Method validation and verification

Documentation should be available reflecting the analytical method validation. Records should be traceable to source data, and acceptance criteria should be defined and meet the limits recommended. Normally the following parameters should be included in the method validation:

- Precision.
- Specificity (there should be no interference from tablet excipients, other active ingredients or degradants).
- Accuracy/recovery (95–105% acceptable according to USP <1092>).
- Repeatability (RSD of NMT 2%).
- Intermediate precision (NMT 10% at time points with less than 85% dissolved and NMT 5% at time points above 85%, according to USP <1092>).
- Linearity and range of about 50–120% of the labelled dose ($R^2 \geq 0.98$).
- Robustness as demonstrated by solution stability (covering the period of sample storage, which is especially important for HPLC testing), medium composition, pH, volume, agitation rate, temperature, adsorption of the drug on the filters).
- Use of sinkers should be considered, especially for dosage forms which otherwise float.
- Manual or automatic withdrawal may be performed, if manual withdrawal is performed, dedicated syringes for each vessels should be used to avoid carryover and to respect the time point.
- In case of automatic withdrawal, attention should be paid on the sampling probe.
- The choice of the filter should be justified especially considering adsorption and extractability.
- Test solutions should be filtered immediately upon sampling.

Note: The analytical method validation is normally undertaken for the test product, and forms part of the dossier requirements.

If compendial method is used by the applicant, verification should suffice.

References

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series, No. 1003, Annex 6, 2017.
2. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. WHO Technical Report Series, No. 1025) Annex 12, 2020.
3. Guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. WHO Technical Report Series, No. 1019, Annex 3, 2019.
4. WHO prequalification guidance document. *General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications*.
6. WHO prequalification *Biowaiver application form: Biopharmaceutics Classification System (BCS)*.
7. WHO prequalification *Biowaiver application form: additional strengths*.
8. Methods of Analysis: 5. Pharmaceutical technical procedures: 5.5 Dissolution test for solid oral dosage forms. *International Pharmacopoeia*, World Health Organization, ninth edition, 2019.
9. <1092> The dissolution procedure: development and validation. *United States Pharmacopeia*.
10. <711> Dissolution. *United States Pharmacopeia*.
11. Guidance on dissolution testing. *British Pharmacopoeia*.
12. Dissolution test for tablets and capsules (dissolution test for solid dosage forms). *British Pharmacopoeia*.
13. Dissolution test for solid dosage forms. *European Pharmacopoeia*.
14. Recommendations on dissolution testing. *European Pharmacopoeia*.