

Annex 3

Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider

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1. Introduction

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies provide scientific understanding to support the establishment of specifications and manufacturing controls.

This document focuses on the development of multisource finished pharmaceutical products (FPPs) which are intended to be bioequivalent to the relevant comparator product. Multisource FPPs should¹ accordingly be therapeutically equivalent to the comparator product.

This document provides a structured approach for industry following the International Conference on Harmonisation (ICH) common technical document (CTD) format, for developing high-quality, multisource FPPs. The ICH-CTD structure for pharmaceutical development information allows for a logical, progressive description of the development process.

The document is also intended to provide assessors and inspectors with a good understanding of best practices in the development of multisource FPPs and their manufacturing processes.

Manufacturers who have chosen a more systematic approach to product development would follow the development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems.

This document is designed to be used in conjunction with other WHO guidelines and guidance documents (1).

1.1 General principles

The pharmaceutical development studies and the manufacture of primary batches are essential elements for the science and risk-based approach to establish the critical quality attributes (CQAs) of the FPP and the critical process parameters (CPPs) of the manufacturing process.

1.2 Scope

This document addresses the pharmaceutical development of multisource FPPs containing existing active pharmaceutical ingredients (APIs) of synthetic or semi-synthetic origin. For the purposes of this document an existing API is one that has been previously authorized through a finished product by a stringent regulatory authority (SRA) or, for the purposes of a national medicines regulatory authority

¹ For the purpose of this document the term “should” is generally to be interpreted as “is recommended” or “is usually required”.

(NMRA), that has been authorized by that NMRA or for which a monograph exists in the pharmacopoeia(s) recognized by that NMRA. APIs of biological or biotechnological origin are not covered here.

This document provides guidance on the contents of a pharmaceutical development plan for multisource pharmaceutical products for both the applicants for marketing authorizations and NMRAs.

Pharmaceutical development issues depend on the API(s), the excipients, the dosage form, the manufacturing process and the container-closure system.

2. Predevelopment activities

2.1 Desk research

Desk research includes all relevant documentation being collected and evaluated prior to initiation of any laboratory activities. This documentation may include information such as is found in:

- WHO, European Medicines Agency (EMA) and United States Food and Drug Administration (US-FDA) web sites that contain regulatory information, for example, the qualitative composition, mode of administration and the primary packing materials of the innovator and multisource FPPs;
- compendial monographs, scientific literature, patents, technical information typically found in the applicant's (open) part of the API master file (APIMF), technical information on excipients and prior company knowledge.

2.1.1 Quality risk management

An essential part of desk research entails the identification of possible risks prior to the development of a multisource product.

An important consideration when selecting the API manufacturer is the fact that the FPP manufacturer is responsible for the control of the API and as such must have a comprehensive understanding of the API. Analysis of the applicant's part of the APIMF (or drug master file) is, therefore, important.

Poor solubility in aqueous medium is an important quality risk factor for APIs administered in the solid state as there is a high risk that inter-batch variability in physical properties may translate into significant differences in the *in vivo* performance.

It is recommended that polymorphism, pseudo-polymorphism and the implications of variability in particle size be routinely considered. Variability in any of these key physical properties is likely to be of particular significance for APIs that have low solubility according to the biopharmaceutics classification

system (BCS). The requirement for routine control of polymorphic form and particle size should be considered in accordance with advice in Decision Trees 3 and 4 of ICH Q6A (2). When controls are necessary they should be established based on the results obtained for the API lot(s) used in the biostudies.

For example, *The International Pharmacopoeia* (Ph. Int.) (3) restricts the polymorphic form of mebendazole API to form C and furthermore states that the formulation, manufacturing process and product packaging of chewable mebendazole tablets are designed and controlled so as to minimize the conversion of the polymorphic form of mebendazole from C to A.

The initial risk assessment of potential CQAs and CPPs of a multisource product should be based on desk research and the applicant's own experience with the manufacture of the dosage form.

Literature, preferably peer-reviewed, may contain risk information essential for predevelopment. For example, the presence of meso-ethambutol hydrochloride in commercial ethambutol hydrochloride API material has been demonstrated in the literature (4), although some pharmacopoeial monographs do not clearly reveal the presence of this impurity. Recently a specific test was included in the *European Pharmacopoeia* (Ph. Eur.) (5) for control of this impurity.

The least risky strategy for multisource product development is to use the same qualitative and, where possible, quantitative formula as that of the comparator FPP – so long as this does not lead to the possibility of patent infringement – in order to minimize the risks related to compatibility, stability and bioequivalence.

Accompanying reconstitution diluents should also be included in the development strategy where appropriate. This topic is discussed further in section 3.

2.2 Additional considerations

2.2.1 Selection and characterization of comparator finished pharmaceutical product(s)

In many countries the NMRA provides a list of comparator products. Alternatively, references are available from WHO (Prequalification of Medicines Programme), and in international lists of comparator products. Note that for a dossier to be submitted to the Prequalification of Medicines Programme the comparator must be selected from the published lists. Guidance regarding Prequalification of Medicines Programme comparator products is available under Guidance on bioequivalence studies on the Prequalification of Medicines Programme web site (apps.who.int/prequal/).

In the case of fixed-dose combination (FDC) FPPs, there will be instances when a combination of APIs is recommended for clinical use but an innovator FDC FPP containing these APIs, whose approval was based on clinical trial data, will not be available as a comparator product. FDCs approved based on data

such as bioequivalence data are not typically used as comparators, as the original safety and efficacy data are linked to the monocomponent products and not the FDC FPP. For FDC FPPs, the development strategy should take into account the formulas of the individual component comparator FPPs. If the innovator FDC exists this should be the target product for the FDC multisource product development – even if the individual comparator tablets could also be used in the bioequivalence study (see also WHO *Guidelines for registration of fixed-dose combination medicinal products* (6)).

The comparator product batch may be selected by dissolution profile testing (see WHO's *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (7)). Ideally a batch which shows intermediate dissolution under the most discriminative condition (where the difference in dissolution between the fastest and slowest batches studied is the largest) should be selected as the reference product for pharmaceutical equivalence studies and bioequivalence studies.

2.2.2 Benchmarking for formulation experiments and stability studies

The comparator sample should be thoroughly examined for parameters such as physical properties, shelf-life, including in-use stability information, storage instructions and details of the container-closure system in comparison to the outcome of the desk research and the requirements for marketing the new multisource product in the intended market.

All the relevant quality attributes of the dosage form should be analysed, e.g. assay, related substances, dissolution rate, pH, preservative concentrations, water content, total mass, mass variation, resistance to crushing, friability and disintegration of tablets.

The information obtained forms the basis for the development of the new multisource FPP.

2.2.3 Formulation selection experiments

Based on the outcome of the desk research and the national requirements for marketing authorization, formulation experiments will be conducted to develop the quality target product profile (QTPP) of the FPP.

Experiments may include determining the qualitative and quantitative composition of the comparator product. The qualitative information on the comparator product may be available in the public domain, e.g. in its summary of product characteristics (SmPC) or package leaflet. Screening different formulations to match the comparator dissolution profile is the best method to select the final formula for scale-up from laboratory to pilot batch.

Selected formulations may be stress-tested to challenge CQAs and to establish tentative acceptance limits for their control.

Any special design features of the pharmaceutical product (e.g. tablet score-line, overfill, or anti-counterfeiting measure) should be identified as such features affect the pharmaceutical product and a rationale for their use should be provided in the product dossier (PD).

2.2.4 Bioequivalence and dissolution studies

Bioequivalence and comparative dissolution studies should be conducted with samples from a batch of the FPP of at least pilot size. The dissolution conditions and acceptance criteria should be derived from the dissolution profiles obtained for the biobatch.

Where an *in vivo* bioequivalence study could be waived, similarity of the formulations may be required, in particular with respect to excipients that may have an influence on the extent and rate of absorption, e.g. sorbitol in liquid formulations or mannitol in solid dosage forms. For instance, when considering a biowaiver for an immediate-release solid oral dosage form containing a BCS class 3 API, the risk of reaching an inappropriate biowaiver decision needs to be critically evaluated, especially when the extent of absorption (f_{abs}) is less than 50%. As part of the risk assessment the excipients used will also need to be scrutinized carefully in terms of both qualitative and quantitative composition – the greater the deviation from the comparator composition, the greater the risk of an inappropriate biowaiver decision.

Inclusion of summaries of all bioequivalence studies (passed and failed) on the final formulation in the PD may be required.

3. Pharmaceutical development

It is recommended to use an internationally harmonized structure when submitting a dossier for obtaining a marketing authorization. This section therefore follows the ICH-CTD structure according to ICH M4 (8).

The text of the M4Q (CTD-Q) guideline (9) is reproduced verbatim in this document in *italic* text, with minor modifications to accommodate WHO terminology and to include certain changes to the text that would be appropriate for multisource pharmaceutical products, notably:

- drug substance is replaced with active pharmaceutical ingredient or API;
- drug product is replaced with finished pharmaceutical product or FPP;
- application is replaced with product dossier or PD;

- combination product is replaced with fixed-dose combination or FDC;
- clinical batches is replaced with comparative bioavailability or biowaiver batches.

Following the *italic* text of the M4Q (CTD-Q) guideline (9), additional guidance by WHO is added in normal type to enable it to be easily distinguishable from the ICH text. This additional text is included to further clarify WHO's expectations and requirements. This approach is intended to facilitate the identification and origin of the text in the document (i.e. whether from ICH or WHO).

In section 3.2.P.2 below, reference may be made to CTD sections that are not discussed in this document. This is done to guide the manufacturer in completing the PD according to national or regional requirements.

3.2.P.2 *The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.*

Pharmaceutical development information usually includes, at a minimum:

- the definition of the QTPP as it relates to quality, safety and efficacy, considering, for example, the route of administration, dosage form, bioavailability, strength and stability;
- identification of the potential CQAs of the FPP so as to adequately control product characteristics that could have an impact on quality;
- discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount necessary to deliver the product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development, using the principles of risk management over the entire life-cycle of the product (ICH Q8 (10)). The information gained through the predevelopment activities may already have disclosed some of these features and could form an integral part of pharmaceutical development.

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference can be made to WHO Technical Report Series, No. 929, Annex 5, section 6.3.2 (6).

Reference documents for pharmaceutical development include ICH guidelines Q6A, Q8, Q9 and Q10 (2, 10–12).

3.1 Components of the finished pharmaceutical product

3.2.P.2.1 The components of the FPP are the ingredients listed under section 3.2.1.P.1 (Description and composition of the FPP in the PD). The components thus include the API(s) and all the excipients, as well as those excipients that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. water for granulation) and any others (e.g. nitrogen or silicone for stoppers).

3.1.1 Active pharmaceutical ingredient

3.2.P.2.1.1 *The compatibility of the API with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the FPP should be discussed. For FDCs, the compatibility of APIs with each other should be discussed.*

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

Information on the intrinsic physicochemical properties of the molecule, e.g. solubility, solid-state properties, including polymorphism and habit, melting range, pK_a and hygroscopicity, is needed for the development of the product to allow the manufacturer of the FPP to take full responsibility for the quality and quality control (QC) of the API and the FPP.

Additionally, the manufacturer will need information (either from the API manufacturer, or gathered by another party, or by itself) on potentially critical properties of the API, together with specifications, as applicable, e.g. solubility at 37 °C at relevant physiological pH values to permit BCS classification of the API, partition coefficient (octanol/water) at 37 °C and particle size distribution, which may affect dissolution rate and bioavailability, as well as density, bulk and tapped density, flowability, compressibility, and other factors which may influence processibility. The above-mentioned properties of the API should usually be supported by experimental data (or by information from peer-reviewed literature) and discussed with respect to CQAs and CPPs.

The specifications of the API manufacturer and the retest period or expiry date derived from formal regulatory stability studies should also be available to the manufacturer of the FPP.

Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (6). In addition to visual examination, chromatography results (assay, purity) are required to demonstrate API-API and API-excipient compatibility. In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. in the SmPC or product leaflet) that the excipients are present in the comparator product.

Stress testing of the API should be designed to include simulation, as far as possible, of the conditions that may be encountered during the manufacturing process of the FPP. An example is provided in Appendix 1.

3.1.2 Excipients

“3.2.P.2.1.2 The choice of excipients listed in 3.2.P.1, their concentration and their characteristics that can influence the FPP performance should be discussed relative to their respective functions.”

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations such as the US-FDA IIG (13) list and the *Handbook of pharmaceutical excipients* (14). Use of excipients at concentrations outside the established ranges is discouraged and generally requires justification. In addition, available guidelines which address particular excipients to be avoided should usually be consulted, for example, azo colourants as listed in EMA guideline CPMP/463/00 (15). Other guidelines such as WHO's *Development of paediatric medicines: points to consider in pharmaceutical development* (16) may provide useful general guidance in this regard.

The characteristics and amounts of excipients that can influence the performance of the pharmaceutical product or its manufacturing capability should usually be discussed relative to the respective function. The ability of functional excipients, e.g. pH-adjusting agents, buffers, stabilizers (such as antioxidants and chelating agents), preservatives and dissolution modifiers (such as surface active agents), to perform throughout the intended shelf-life of the FPP should usually be demonstrated.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

Many excipients such as povidone, microcrystalline cellulose and lactose are by nature multifunctional. The chemically identical excipients may have different grades (physical properties) with different functional characteristics; therefore, conformance to pharmacopoeial specifications does not always

provide sufficient confidence that an excipient will perform according to its intended purpose.

When an excipient is critical for manufacturing capability of the FPP, batch or batch variations should be minimized by including user requirements additional to those specified in the pharmacopoeia, e.g. particle size distribution.

Ranges or alternatives for excipients are normally not accepted unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine API with lactose) should be included to justify the choice of excipients. Specific details should usually be provided in the PD where necessary (e.g. on use of potato or corn starch).

3.2 Finished pharmaceutical product

"3.2.P.2.2"

3.2.1 Formulation development

3.2.P.2.2.1 *A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed when appropriate.*

When preparing the PD for submission, the data requirements of the NMRA regarding formulation development may depend on whether the multisource product has been newly developed by the applicant or manufacturer or whether it is an established multisource product.

The WHO Prequalification of Medicines Programme defines an established multisource product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established multisource product, all sections of P.2.2.1 of the dossier should usually be completed with the exception of P.2.2.1 (a). In addition, a product quality review should usually be provided in the PD as outlined in Appendix 2 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1).

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g.

WHO guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products (7) can be consulted.

Tablet scoring may be recommended or required in certain jurisdictions or, for example, when scoring is indicated in the WHO invitation for expression of interest, or is specified for an invited FPP in the listing of recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should usually include a description of the test method, individual values, mean and relative standard deviation of the results. Uniformity testing (i.e. content uniformity or mass variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an example the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisectioned tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions only needs to be demonstrated once and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. SmPC, labelling or package leaflet) should reflect the presence of a score line.

If a paediatric dose is to be obtained by splitting a tablet, a demonstration of content uniformity of tablet fragments may be required.

For modified-release tablets designed to be divided into equal halves, demonstration of dissolution profile similarity of the tablet halves against the whole tablet may be required.

Where relevant, labelling should state that the score line is only intended to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses. In this case a demonstration of uniformity is unlikely to be required.

In vitro dissolution or drug release

A discussion should usually be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed and medium) are usually required in the PD. Data should also usually demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/

or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1).

In the case of rapidly dissolving FPPs containing highly soluble APIs (BCS classes 1 and 3), a single-point dissolution test limit of 80% in 30 minutes or less is considered sufficient as a routine QC test for batch-to-batch uniformity. For slowly dissolving or poorly water-soluble APIs (BCS classes 2 and 4) in immediate-release products, a two-point dissolution range (a dissolution window), one at an early time-point (e.g. Q = 60% in 45 minutes) and the other at a later point (e.g. Q = 80% in 90 minutes), is recommended to characterize the quality of the product. Note that in some cases the later point may be lower than 80% if a plateau is reached.

Modified-release FPPs should have a meaningful *in vitro* release rate (dissolution) test that is used for routine QC. Preferably, this test should possess *in vitro*–*in vivo* correlation. Results demonstrating the effect of pH on the dissolution profile are usually required, if appropriate for the type of dosage form.

For extended-release FPPs the testing conditions should be set to cover the entire period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally the acceptance range at each intermediate test point should not exceed 25% or $\pm 12.5\%$ of the targeted value. Dissolution results are usually required for several lots including those used for pharmacokinetic and bioavailability or biowaiver studies.

The dissolution acceptance limit(s) should also be incorporated into the stability programmes.

Where there are scientific grounds that the defined release characteristics of oral pharmaceutical products may be adversely affected by the presence of alcohol, e.g. for modified-release products containing opiates, 5%, 10% and 20% ethanol should be added to the dissolution medium proposed for routine testing in order to demonstrate that no dose dumping will occur through intake with alcoholic beverages.

3.2.2 Overages

3.2.P.2.2.2 *Any overages in the formulation(s) described in 3.2.P.1 should be justified.*

Justification of an overage to compensate for loss during manufacture

should usually be provided in the PD, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2.3 Physicochemical and biological properties

3.2.P.2.2.3 *Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and/or immunological activity, should be addressed.*

3.3 Manufacturing process development

3.2.P.2.3 *The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.*

For products that meet the criteria of an established multisource product, in order to fulfil the requirements of section P.2.3, section P.2.3 (b) of the dossier should be completed and a product quality review should usually be submitted as outlined in Appendix 2 of the WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (1). The guidance below applies to all other products, for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided in the PD. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence quality and performance of the FPP should usually be explained (e.g. wet granulation using high-shear granulator). The results of an API stress study may be included in the rationale. Any developmental work undertaken on protecting the FPP from deterioration (e.g. protection from light or moisture) should also be included.

The manufacturing process of the multisource FPP should be appropriate for the product that is in development. It does not need to be the same as that of the comparator FPP.

Efforts should be primarily directed towards reducing variability in process and product quality. In order to achieve this, all critical sources of variability should be identified and explained and the sources of variability should be minimized and controlled.

Process development studies should provide the basis for process improvement, process validation and any process control requirements. All CPPs should usually be identified, monitored or controlled to ensure that the product is of the desired quality.

For sterile products an appropriate method of sterilization for the pharmaceutical product and primary packaging material should be chosen. Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided in the PD.

Differences between the manufacturing process(es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should usually be explained, in particular the CPPs (e.g. rate of addition of granulating fluid, massing time, and granulation end-point). A discussion of the CPPs, controls and process robustness with respect to the QTPP and CQA of the product should usually be included (10).

Based on close monitoring of the manufacturing process in the pilot batches, provisional acceptance ranges should be proposed for the CQAs of intermediates and CPPs that impact on downstream processing. Interim acceptance criteria may be approved until enough knowledge is available to finalize CQAs of intermediates and CPPs for production batches.

The manufacturing process used for pilot batches should be the same as the one proposed to be applied to production batches and should provide product of the same quality and meeting the same specifications as that intended for marketing.

3.4 Container-closure system

3.2.P.2.4 The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g. choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

The properties of the container-closure systems should be defined by the characteristics of the FPP and the conditions prevailing in the intended market (e.g. climatic zone IVb).

Stability testing of primary batches of the FPP is conducted on samples packaged in the container-closure system selected for marketing in order to confirm compatibility and product stability to support PDs for marketing authorization.

When the container-closure system is a critical factor for FPP stability, batch or supplier variations need to be minimized through tight specifications and extended sampling plans for QC testing.

To facilitate the visual identification of spuriously or falsely-labelled, falsified or counterfeit (SFFC) medicines (including by the public) the description needs to be completely detailed in the product information. Details may include information on the container-closure system, such as “round, white opaque, high-density polyethylene (HDPE) bottles fitted with white opaque, polypropylene continuous thread closures with induction sealing liner”, or “a blister package comprising clear transparent polyvinyl chloride (PVC) film with a backing of aluminium foil coated with heat-seal lacquer”.

Primary packing materials, particularly plastics, should comply with relevant pharmacopoeial and food contact regulations.

Testing requirements to verify the suitability of the container-closure system contact material(s) depend on the dosage form and route of administration and possibly, the manufacturing process. The pharmacopoeias provide standards that are required for packaging materials; examples include the following:

- glass containers (17, 18);
- plastic containers (19, 20);
- rubber/elastomeric closures (21, 22).

Table 1 outlines the general recommendations for the various dosage forms for once-only studies to establish the suitability of the container-closure system contact materials.

Table 1
Studies to establish the suitability of the container-closure system contact materials

	Solid oral products	Oral liquid and topical products	Sterile products (including ophthalmic preparations)
Description of any additional treatments ^a	×	×	× (sterilization and depyrogenation of the components)
Extraction studies	–	×	×
Interaction studies (migration/sorption)	–	×	×
Moisture permeability	× (uptake)	× (usually loss)	× (usually loss)
Light transmission	× ^b	×	×

× Information should usually be submitted.

– Information does not need to be submitted.

^a E.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules or vials.

^b Not required if product has been shown to be photostable.

The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate or in-process products (e.g. premixes, bulk FPP) should also be discussed.

Devices

There are certain situations in which pharmaceutical dosage forms are developed in association with specific devices. The device might be critical to enabling delivery of the medicine or it might be included in order to facilitate administration.

Where the device is critical to drug delivery and fully integrated with the product formulation, this product formulation–device combination should be considered as the primary product for the purposes of regulatory submission. Examples of such products include metered dose inhalers (MDIs), dry powder inhalers, intranasal sprays and ready-made intravenous infusions. For these products the data necessary to support a regulatory submission would include:

- physical and chemical stability data for the product formulation–device combination in its primary pack in order to support the claimed shelf-life and storage conditions;
- relevant data on extractables and leachables;
- for multidose products, demonstration of accurate dose delivery over the shelf-life of the product under the registered storage conditions;
- for multidose products with a dose-counting mechanism, stability data to demonstrate reliable performance of that mechanism over the shelf-life of the product under the registered storage conditions;
- specification control and secure sourcing of all device components;
- relevant information on any secondary device associated with the FPP, such as a spacer device sometimes associated with inhaled products such as MDIs and nebulizers. This device enables dose delivery in situations where the patient cannot easily use the primary product to inhale the dose, particularly where administration to children is involved. The device acts as a temporary reservoir for the dose which can then be inhaled more easily by the patient. There will be some variability inherent to a spacer device but, nevertheless, an acceptable accuracy of dose delivery when using this device needs to be demonstrated.

Alternatively, the co-developed device may be intended to facilitate measurement of the prescribed dose prior to administration; this is particularly important for paediatric products where flexibility of dose may also be a requirement. Examples include spoons, cups, syringes or droppers for oral

delivery and droppers for nasal or aural delivery. A device is required to be included with the container-closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), whenever the package provides for multiple doses.

In accordance with the Ph. Int. (3) general chapter *Liquid preparations for oral use*:

“Each dose from a multidose container is administered by means of a device suitable for measuring the prescribed volume. The device is usually a spoon or a cup for volumes of 5 ml or multiples thereof, or an oral syringe for other volumes or, for oral drops, a suitable dropper.”

In these cases the following data would be required to support a regulatory submission:

- for a device accompanying a multidose container, the results of a study demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose;
- specifications for the device materials, including specific identification testing of the material which will be in contact with the FPP.

When the intention is to submit a PD in CTD format a sample of the device should usually be provided with Module 1 of the PD.

3.5 Microbiological attributes

3.2.P.2.5 *Where appropriate the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products the integrity of the container-closure system to prevent microbial contamination should be addressed.*

Where an antimicrobial preservative is included in the formulation the amount used needs to be justified by submission of results of studies of the product formulated with different concentrations of the preservative(s) to demonstrate the lowest necessary but still effective concentration. The effectiveness of the agent needs to be justified and verified by appropriate studies (e.g. national, regional or international pharmacopoeial general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent has to be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

As outlined in the WHO guidelines on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (23), a single

primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) for the duration of the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.6 Compatibility

3.2.P.2.6 *The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.*

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for reconstitution), which are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

Where sterile, reconstituted products are to be further diluted, compatibility will have to be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers.

In the case of infusion sets where a product formulation is added to an infusion vehicle in an intravenous administration set (giving set) immediately prior to administration, the following data would be required:

- physical and chemical stability data for the prepared infusion to support the claimed in-use shelf-life and storage conditions;
- compatibility data to support the claimed in-use shelf-life and storage conditions;
- specification control and secure sourcing of all giving set contact materials.

Studies are usually required to cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other FPPs, compatibility should be demonstrated with respect to the principal FPP as well as the co-administered FPP (i.e. in addition to the other, aforementioned parameters for the mixture, the assay and degradation levels of each co-administered FPP should be reported).

In some cases when a pharmaceutical product is developed for global marketing there may also be a need to consider alternative diluents or liquids for dispersion and/or in-use reconstitution for a product, and compatibility with these diluents or liquids may be required to be established.

4. Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

active pharmaceutical ingredient

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

comparator product

The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. The selection of the comparator product is usually made at the national level by the medicines regulatory authority. (For the WHO Prequalification of Medicines Programme, the selection of the comparator product is based on the information presented under Guidance on bioequivalence studies available on the Prequalification web site.)

control strategy

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredient and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

critical process parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and, therefore, should be monitored or controlled to ensure the process produces the desired quality.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more active pharmaceutical ingredients.

formal experimental design

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

generic product

See *multisource (generic) pharmaceutical products*.

life-cycle

All phases in the life of a product from the initial development through marketing until the product’s discontinuation.

multisource (generic) pharmaceutical products

Multisource pharmaceutical products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

pharmaceutical alternatives

Products are pharmaceutical alternative(s) if they contain the same molar amount of the same active pharmaceutical moiety(s) but differ in dosage form (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters). Pharmaceutical alternatives deliver the same active moiety by the same route of administration but are otherwise not pharmaceutically equivalent. They may or may not be bioequivalent or therapeutically equivalent to the comparator product.

pharmaceutical equivalence

Products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet comparable standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process and some other variables can lead to differences in product performance.

pharmaceutical product

Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

pilot-scale batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

primary batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life, as the case may be.

process robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

production batch

A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

quality

The suitability of either an active pharmaceutical ingredient or a pharmaceutical product for its intended use. This term includes such attributes as the identity, strength and purity.

quality target product profile (QTPP)

A prospective summary of the quality characteristics of a finished pharmaceutical product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the finished pharmaceutical product.

stringent regulatory authority (SRA)

For the purpose of this document, a stringent regulatory authority (SRA) is the medicines regulatory authority in a country which is:

- (a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (European Union, Japan and the United States of America); or (b) an ICH Observer, being the European Free Trade Association as represented by SwissMedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time);
- only in relation to good manufacturing practices inspections: a medicines regulatory authority that is a member of the Pharmaceutical Inspection Co-operation Scheme as specified at <http://www.picscheme.org>.

therapeutic equivalence

Two pharmaceutical products are considered to be therapeutically equivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same when administered to patients by the same route under the conditions specified in the labelling. This can be demonstrated by appropriate bioequivalence studies, such as pharmacokinetic, pharmacodynamic, clinical or in vitro studies.

References

1. WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 4 (WHO Technical Report Series, No. 970).
2. Q6A: *Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf.
3. *The International Pharmacopoeia, 4th ed., Vol. 1. General notices; monographs for pharmaceutical substances (A–O) and Vol. 2: Monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents*. Geneva, World Health Organization, 2006, also available in CD-ROM format and online.
The International Pharmacopoeia, 4th ed., First supplement. Geneva, World Health Organization, 2008 (<http://apps.who.int/phint/en/p/docf/>).
The International Pharmacopoeia, 4th ed., Second supplement, 2011, available on CD-ROM.
4. Prasad B. et al. A new validated differential scanning calorimetric procedure for monitoring the less active R,S isomer of ethambutol dihydrochloride in bulk drug samples and anti-tuberculosis formulations. *Pharmaceutical Forum*, 2007, 33: 326-333.
5. *European pharmacopoeia, 7th ed*. Strasbourg, European Directorate for the Quality of Medicines, 2010.
6. Guidelines for registration of fixed-dose combination medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 5 (WHO Technical Report Series, No. 929).
7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 7 (WHO Technical Report Series, No. 937).
8. M4: *ICH Harmonised Tripartite Guideline – Organisation of the common technical document for the registration of pharmaceuticals for human use*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2004 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3_organisation.pdf).
9. M4Q: *ICH Harmonised Tripartite Guideline – The common technical document for the registration of pharmaceuticals for human use: quality*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2000.
10. Q8: *Pharmaceutical development*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf).
11. Q9: *Quality risk management*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2005 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf).

12. Q10: *Pharmaceutical quality system*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2008 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf).
13. *Inactive ingredient guide*. US Food and Drug Administration (<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>).
14. Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of pharmaceutical excipients, 6th ed*. London, Pharmaceutical Press, 2009.
15. Excipients in the label and package leaflet of medicinal products for human use. Committee for Proprietary Medicinal Products, 2003 (CPMP/463/00Final).
16. Development of paediatric medicines: points to consider in pharmaceutical development. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-sixth report*. Geneva, World Health Organization, 2012, Annex 5 (WHO Technical Report Series, No. 970).
17. Containers – glass. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
18. Glass containers for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 303–307
19. Plastic containers and closures for pharmaceutical use. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 308–309.
20. Containers – plastic. In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007.
21. Elastomeric closures for injections, In: *United States Pharmacopeia*, 2nd suppl. Rockville, MD, 2007: 144–145.
22. Rubber closures for containers. In: *European Pharmacopoeia*. Strasbourg, European Directorate for the Quality of Medicines, 2010: 316–317.

Appendix 1

Examples of presenting quality attributes of active pharmaceutical ingredients

Physicochemical characteristics of the active pharmaceutical ingredient (API) that can influence manufacturing capability and the performance of the finished pharmaceutical product (FPP) should be tabulated and discussed, for example, as in the following tables.

pH (of the buffer)	Solubility (mg/ml)
1.2	
4.5	
6.8	
pKa of API	

Method (compendial):

Particle size of API used in relevant laboratory and pilot-scale batches					
Measured data (µm)	Batch number (and use)				Proposed acceptance range (µm)
	<API batch no.> <FPP batch no.> (design)	<API batch no.> <FPP batch no.> (final laboratory)	<API batch no.> <FPP batch no.> (stability)	<API batch no.> <FPP batch no.> (bioequivalence)	
D 10					
D 50					
D 90					

Add rows as needed. Change data range as relevant

Method (compendial):

Apparent density of API used in relevant laboratory and pilot-scale batches					
	<API batch no.> <FPP batch no.> (design)	<API batch no.> <FPP batch no.> (final laboratory)	<API batch no.> <FPP batch no.> (stability)	<API batch no.> <FPP batch no.> (bioequivalence)	Proposed acceptance range (g/ml)
Bulk					
Tapped					

Method (compendial):

Stress Condition	Treatment	Observations
None	Initial values of the API	Assay:
		S1:
		<i>Insert as many rows as necessary</i>
		D1:
Temperature	A thin layer of the API is kept at 80 °C for 4 weeks in a Petri dish (open system) with sampling once a week	<i>Insert as many rows as necessary</i>
		Total unspecified:
		Total impurities:
		Assay:
		S1:
		D1:
		Total unspecified:
		Total impurities:

continues

Stress Condition	Treatment	Observations
Humidity	A thin layer of the API is kept at 40 °C /100% relative humidity for 4 weeks in a Petri dish (open system) with sampling once a fortnight	Assay: S1: D1: Total unspecified: Total impurities:
Oxidation	Oxygen is bubbled slowly through the oxygen-saturated aqueous solution/suspension (under constant mixing) of the API for 24 hours with sampling every 8 hours	Assay: S1: D1: Total unspecified: Total impurities:

S1, S2, etc., are synthesis impurities (as in API specifications).

D1, D2, etc., are degradation products.

Appendix 2

Information on development batches

Table 1
Screening laboratory batches with different proportions of excipients to match comparator dissolution

Composition of formulation development experiments								
Ingredients	Lab01		Lab02		Lab03		Lab04	
	Grams	%	Grams	%	Grams	%	Grams	%
active pharmaceutical ingredient (API) 1								
API 2								
API 3								
Excipient 1								
Excipient 2								
Excipient 3								
Excipient 4								
Excipient 5								
Dissolution, % at pH ...								

Table 2

Example table for developmental multipoint dissolution profiles (hypothetical example – Ph. Int., paddle, 75 rpm, 900 ml)

	Percentage API dissolved	Percentage API dissolved	Percentage API dissolved
Time (min)	pH 1.2 buffer	pH 4.5 buffer	pH 6.8 buffer
5			
10			
15			
20			
30			
45			
60			
90			

Repeat the table as needed, for example, for comparator product and development batch chosen for scale-up.

When comparing dissolution profiles of products, for example, comparator and test products or different strengths of the same product, the dissolution conditions and sampling intervals must be the same.

Graphical presentation and summary evaluation of the results of comparative dissolution studies of the test (samples taken from the bioequivalence batch no. ...) and comparator products: