



**World Health
Organization**

PHARMACEUTICAL DEVELOPMENT FOR MULTISOURCE (GENERIC) PHARMACEUTICAL PRODUCTS

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Schedule for the proposed adoption process of working document QAS/08.251:
Pharmaceutical development for multisource (generic) pharmaceutical products

History	Date
Preparation of a draft guideline which was endorsed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations	15-18 October 2007
Mailing of draft for comments	March 2008
Discussion of draft with collated comments by a WHO Expert Working Group	June 2008
Mailing of revised draft for comments	July 2008
Collation of comments received on revised draft	September 2008
Presentation of revised draft with collated comments to WHO Expert Committee on Specifications for Pharmaceutical Preparations	13-17 October 2008
Collation of all comments received, including those arriving after the above-mentioned Expert Committee	February 2009
Discussion at the WHO Expert Committee on Specifications for Pharmaceutical Preparations	12-16 October 2009
Discussion at the WHO consultation on paediatrics and generics guideline	29-30 April 2010
Mailing of revised draft for comments	June 2010
Collation of comments received	August 2010
Presentation of revised draft with collated comments to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010

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1. INTRODUCTION

The aim of pharmaceutical development is to design a quality product and the manufacturing process to deliver the product in a reproducible manner. The information and knowledge gained from pharmaceutical development studies provide scientific understanding to support the establishing of specifications and manufacturing controls.

This guideline focuses on the development of multisource pharmaceutical products which are bioequivalent to the relevant comparator (innovator) product. The multisource product should accordingly be pharmaceutically equivalent to the comparator product. In the case 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. For instance, in the case of considering a biowaiver for an immediate release solid oral dosage form containing a BCS Class 3 active pharmaceutical ingredient (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.”¹

The guideline offers a systematic methodology to industry for developing high-quality, multisource finished pharmaceutical products (FPPs). It also intends to provide a good understanding of the best practices in the development of the generic medicine and its manufacturing process to assessors and inspectors.

Manufacturers who have chosen a more systematic approach to product development would follow the development within the broader context of quality assurance principles, including quality risk management and pharmaceuticals quality systems.²

The manufacturing process development is the same for innovator and generic pharmaceutical industries.

1.1 General principles

The information and knowledge gained from pharmaceutical development studies and experience with the manufacture of primary batches provide scientific evidence to support the proposed critical quality attribute(s) (CQA(s)) of the FPP (quality control (QC), in-process control (IPC) acceptance limits), critical process parameter(s) (CPP(s)) and their manufacturing controls, which are essential inputs for quality risk management.

1.2 Scope

This guideline provides guidance on the contents of a pharmaceutical development plan for both the applicants for marketing authorizations and national medicines regulatory authorities (NMRAs). Pharmaceutical development issues also depend on the dosage form of the FPP.

¹ WHO Technical Report Series, No. 937, 2006, Annex 7: *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.*

² ICH Q9: *Quality risk management* and Q10: *Pharmaceutical quality system.*

Examples in the annexes are focused on solid pharmaceutical dosage forms; however, the general principles are applicable to all dosage forms, including injectables, modified release products and respiratory products.

2. GLOSSARY

critical process parameter (source: ICH Q8)

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) (source: ICH Q8)

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.

control strategy (source: ICH Q8)

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and 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 (ICH Q10).

finished pharmaceutical product (FPP)

The finished pharmaceutical product always represents a pharmaceutical product after final release (manufacturing control release, quality control release, packaging control release).

formal experimental design (source: ICH Q8)

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”.

multisource (generic) pharmaceutical products (source: WHO Technical Report Series, No. 837, Annex 7)

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

pharmaceutical development (new)

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.

pharmaceutical equivalence (source: WHO Technical Report Series, No. 837, Annex 7)

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 (source: WHO Technical Report Series, No. 953)

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 (source: WHO Technical Report Series, No. 953)

A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) 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. A primary batch of an API should be at least a pilot-scale batch. For an FPP, two of the three batches should be at least pilot-scale batches, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

process robustness (source: ICH Q8)

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

production batch (source: WHO Technical Report Series, No. 953)

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 (source: ICH Q8)

Degree to which a set of inherent properties of a product, system or process fulfils requirements.

3. PRE-DEVELOPMENT ACTIVITIES

3.1 Desk research

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

- WHO, European Medicines Agency (EMA) and United States Food and Drug Administration (US-FDA) web sites¹ which contain regulatory information, for example, the qualitative composition, mode of administration and the primary packing materials of the innovator and multisource (generic) FPPs; and
- compendial monographs, scientific literature references, patents, technical information typically found in the open part of the API master file, technical information on excipients and prior company knowledge.

The example is illustrated in Annex 1.

¹ http://www.who.int/prequal/WHOPAR/pq_whopar.htm (downloaded on 29 December 2007);
<http://www.emea.europa.eu/htms/human/epar/a.htm> (downloaded on 29 December 2007);
<http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm> (downloaded on 29 December 2007).

3.2 Quality risk assessment

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

The open part of the APIMF/DMF may already reveal risks associated with API. For instance, the reagents (e.g. dimethyl sulphate) or solvents (in particular class 1) used in the process may each pose a risk factor themselves. Biotechnological APIs require supplementary assessment of issues non-existent with chemical APIs.

APIs that show BCS low solubility over the physiological pH range would require further investigation with respect to polymorphism, including pseudo-polymorphism, and particle size as possible risk factors. For instance *The International Pharmacopoeia* (Ph.Int.) clearly 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 pharmacopoeia may contain information on other risk factors, such as the following statement provided in the Ph.Int. monographs of Saquinavir mesilate and Nelfinavir mesilate under *Manufacture*: “The production method must be evaluated to determine the potential for formation of alkyl mesilates [genotoxic], which is particularly likely to occur if the reaction medium contains lower alcohols. Where necessary, the production method is validated to demonstrate that alkyl mesilates are not detectable in the final product.”

The prior knowledge of potential genotoxic impurities in an API is regarded as highly important. Another example is provided in Annex 1, where the publicly available assessment information reveals that tenofovir disoproxil fumarate (TDF) may contain 9-propenyladenine, a process-related impurity, which is mutagenic. The Ph.Int. monograph for TDF includes a limit for this impurity under *Manufacture*. The presence and control of this impurity should accordingly be verified in the open part of the API master file (APIMF)/drug master file (DMF) before selecting potential API manufacturer(s).

An initial risk assessment of critical quality attributes and critical process parameters based on an available public assessment report is provided in Annex 2.

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 literature¹, though all pharmacopoeial monographs could not clearly reveal the presence of this impurity. Recently a specific test was included in the European Pharmacopoeia (Ph.Eur.) for control of this impurity.

The least risky strategy for generic product development is to use the same qualitative and, where possible, quantitative formula as that of the comparator (innovator) FPP in order to minimize the risks related to compatibility, stability and bioequivalence.

It should be noted, to enable "biowaiver", that in some instances some of the excipients have to be similar to the comparator product, e.g. for sorbitol in liquids and mannitol in solid dosage forms.

¹ B. Prasad *et al.*, *Pharmacopoeial Forum*, 33, 326-333 (2007).

In the case of fixed-dose combination FPPs, the development strategy should take into account the formulae 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 may be used in the BE study (see also WHO *Guidelines for registration of fixed-dose combination medicinal products* (WHO Technical Report Series, No. 929, Annex 5)¹). Prior art may also demonstrate the incompatibility of APIs and FDC; for instance the Ph.Int. monograph for Rifampicin and isoniazid tablets includes a test to control the condensation product between these two APIs.

Accompanying reconstitution diluents² should also be included in the development strategy where appropriate.

The initial risk assessment of CQAs and CPPs of a generic company should be based on desk research and the applicant's own experience with the manufacture of the dosage form (an example is illustrated in Annex 2).

3.3 Additional considerations

The least risky strategy for generic product development is to use, where possible, the same qualitative and quantitative formula as that of the comparator (reference/innovator) FPP in order to minimize the risks related to compatibility, stability and bioequivalence.

It should be noted, to enable "biowaiver", that in some instances some of the excipients have to be similar to the comparator product, e.g. for sorbitol in liquids and mannitol in solid dosage forms.

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Accompanying reconstitution diluents² should also be included in the development strategy where appropriate.

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.

4. PRODUCT DEVELOPMENT

The following types of information should be provided to detail elements of the products' development process.

¹ WHO Technical Report Series, No. 929, 2005, Annex 5: *Guidelines for registration of fixed-dose combination medicinal products*.

² For a finished pharmaceutical product supplied with reconstitution diluents, information on the diluents should be provided in a separate part, as appropriate. Choice and development of co-packaged diluents should be included in 3.2.P.2.2.1 and 3.2.P.2.6.

4.1 Product-specific analytical methods

Noncompendial APIs and FPPs should be tested with methods developed by the manufacturer. Particular attention should be paid to the validation¹ of analytical test methods so that the laboratory and pilot-scale product and process development studies identify the acceptable ranges of CQAs and CPPs. In-house reference standards should be established² at the start of the development process and they should be established against compendial reference standards as soon as an officially recognized pharmacopoeia monograph has been published.

Officially recognized compendial specifications and methods should be verified, as applicable, to the synthesis route and formulation used by the generic manufacturer.

A preliminary dissolution method should also be developed, which can assist in formulation development. At later stages of product development a final dissolution method can act as a quality control tool to detect batch-to-batch product performance differences and to ensure retention of the bioavailability properties of the batch used in the bioequivalence or biowaiver dissolution study.

A discriminating dissolution method(s) should be developed, with limits set for each API in a fixed-dose FPP.

Regulatory authorities may also ask for data that demonstrate whether the dissolution method is sensitive to changes in manufacturing processes or changes in API particle size and polymorphism, for example, in the case of BCS class II and IV APIs.

4.2 Characterization of comparator finished pharmaceutical product(s)

4.2.1 Sourcing of comparator (reference) product

In many countries the NMRA provides a list of comparator products. Alternatively, references are also available from WHO (Prequalification of Medicines Programme (PQ), and International list of comparator products) :

- WHO Technical Report Series, No. 902, 2002, Annex 11
Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (update in process)
- WHO Prequalification of Medicines Programme Guidance Document, 28 September 2009
Recommended comparator products: antituberculosis medicines,
- WHO Prequalification of Medicines Programme Guidance Document, 22 June 2009
Recommended comparator products: antimalarial medicines
- WHO Prequalification of Medicines Programme Guidance Document, June 2009
Recommended comparator products: influenza-specific antiviral medicines

¹ http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf (downloaded on 29 December 2007).

² WHO Technical Report Series, No. 943, 2007, Annex 3: General guidelines for the establishment, maintenance and distribution of chemical reference substances. Revision.

- WHO Prequalification of Medicines Programme Guidance Document, September 2009
Recommended comparator products: medicines for HIV/AIDS and related diseases
- WHO Prequalification of Medicines Programme Guidance Document, June 2009
Recommended comparator products: reproductive health medicines

The comparator product batch may be selected by dissolution profile testing¹. 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.

4.2.2 *Bench marking for formulation experiments and stability studies*

The innovator 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 attributes of the dosage form should be analysed in the quality control (QC) laboratory (e.g. assay, related substances, dissolution rate, preservative concentrations) as well as physical properties (e.g. water content, total mass, mass variation, resistance to crushing, friability and disintegration of tablets).

The information obtained should be the basis for the development of the new multisource product.

4.3 **Formulation selection experiments**

Based on the outcome of the desk research and the national requirements for marketing authorization formulation experiments will be conducted to match the target profile of the innovator product.

This may include determining the qualitative and quantitative composition of the comparator product. Screening different formulations to match the innovator dissolution profile is the best method to select the final formula for scale up (typical ranges of excipients are illustrated in Annex 5) from laboratory to pilot batch.

Selected formulations may be stress-tested to challenge CQA(s) and to establish tentative acceptance limits for their control.

The use of overages in the manufacture of the pharmaceutical product, whether they appear in the final formulated product or not, should be justified.

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

¹ WHO Technical Report Series, No. 937, 2006, Annex 7: *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.*

4.4 Microbiological attributes

The microbiological attributes of the pharmaceutical product should be discussed regarding, for example:

- the rationale for performing or not performing microbial limits testing for non-sterile pharmaceutical products. The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial;
- for sterile products, the integrity of the container closure system as it relates to preventing microbial contamination.

Antimicrobial preservative effectiveness should be demonstrated during pharmaceutical development. The minimum concentration of preservative should be used that gives the required level of efficacy throughout the intended shelf-life of the product. Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented.

4.5 Compatibility studies

For API/API (in FDC products) or API/excipients interactions, compatibility stress studies should be performed to identify potential reaction products in the formula. Degradants likely to be formed during manufacturing and storage should be monitored during stability studies.

Information on the compatibility of reconstitution diluents and dosage devices to support claims on the label should be documented. Data from constitution or dilution studies that are performed as part of the formal stability studies to confirm product quality through shelf-life should be reported.

5. COMPONENTS OF FINISHED PHARMACEUTICAL PRODUCT

5.1 Active pharmaceutical ingredient(s)

The API in this part of the dossier is discussed as a component that can impact on the performance or the manufacturing capability of the FPP.

The manufacturer may investigate the use of an ester or salt of the API for development of a different dosage form accommodating, e.g. paediatric use.

Information on the intrinsic chemical and physicochemical properties of the molecule, e.g. solubility, partition coefficient (octanol/water), crystallinity, crystal habit and shape, polymorphism, melting range, pK_a and hygroscopicity, are needed for the development of the product to allow the FPP manufacturer to take full responsibility for the quality and quality control of the API and the FPP.

The specifications and retest period, derived from formal regulatory stability studies, should also be available to the FPP manufacturer.

Additionally the manufacturer will need information (either from the API manufacturer, or

determined 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, etc., which may affect dissolution rate and bioavailability, as well as density, bulk and tapped density, flowability, compressibility, etc., which may influence processibility. The above API properties should be supported by experimental data (or by information from peer-reviewed literature) and discussed regarding CQAs and CPPs.

Stress testing of the API should be designed to simulate as far as possible the conditions that may be encountered during the manufacturing process of the FPP (an example is illustrated in Annex 3).

5.2 Excipients

The characteristics of excipients that can influence the pharmaceutical product performance or manufacturing capability should 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 pharmaceutical product shelf-life should be demonstrated.

Many excipients such as povidone, microcrystalline cellulose and lactose are by nature multifunctional. The chemically same 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 supplier variations should be minimized by including additional user requirements to those specified in the pharmacopoeia, e.g. particle size distribution. .

5.3 Container closure system

Primary packing materials, particularly plastics, should comply with relevant pharmacopoeial and food contact regulations. Compatibility studies, for example to monitor leachables and extractables, should be carried out.

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 are conducted on samples packaged in the container closure system selected for marketing in order to confirm compatibility and product stability to support submissions for marketing authorization.

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

To facilitate the visual identification of counterfeit medicines (also by the public) the description should be in full and include the colour of the container closure system, e.g. 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 PVC film with a backing of aluminium foil coated with heat seal lacquer.

5.4 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 (DPIs), intranasal sprays and ready-made intravenous infusions.

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; and
- a secondary device associated with inhaled products such as MDIs and nebulisers is the spacer, particularly where paediatric administration is involved. This device enables dose delivery in situations where the patient cannot easily use the primary product to inhale the dose, acting as a temporary reservoir for the dose which can then be inhaled more easily by the patient. There will be some variability inherent with a spacer device but, nevertheless, an acceptable accuracy of dose delivery when using this device needs to be demonstrated.

In the case of infusion sets where a product formulation is added to an infusion vehicle in a 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; and
- specification control and secure sourcing of all giving set contact materials.

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 might also be a requirement. Examples include spoons, cups, syringes or droppers for oral delivery and droppers for nasal or aural delivery. In these cases the following data would be required to support a regulatory submission:

- where accuracy of dose is important, a demonstration of the registered dosing accuracy; and
- relevant compatibility data for product formulation and device material(s).

6. MANUFACTURING PROCESS DEVELOPMENT

6.1 General considerations

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;
- the sources of variability are minimized and controlled; and
- product quality attributes can be accurately and reliably predicted.

Process development studies should provide the basis for process improvement, process validation and any process control requirements. All critical process parameters should be identified, monitored or controlled to ensure that the product is of the desired quality. For those products intended to be sterile an appropriate method of sterilization for the pharmaceutical product and primary packaging material should be chosen and the choice justified.

6.2 Selection of process

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

6.3 Scale-up from laboratory to production scale

The progress from laboratory scale to pilot scale to production scale (proposed batch size) should be shown and explained in the dossier submitted for marketing authorization.

6.4 Finished pharmaceutical product specifications

FPP specifications are included at the time of submission of the dossier. A concept of continuous improvement recognizes that as more knowledge is obtained during the production, these specifications may be amended according to the requirements of the NMRA.

An example of setting the dissolution acceptance criteria from dissolution profiles is provided in Annex 6.

In the case of highly soluble and rapidly dissolving drug products (BCS classes 1 and 3), a single-point dissolution test limit of 80% in 30 minutes or less is sufficient as a routine quality control test for batch-to-batch uniformity. For slowly dissolving or poorly water-soluble APIs (BCS classes 4 and 2), a two-point dissolution range (a dissolution window), one at for instance 30 minutes and the other at a later point, e.g. 90 minutes to ensure 80% dissolution (in some cases it may even be lower than 80% if a plateau is reached), is recommended to characterize the quality of the product.

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

6.5 Manufacture of primary stability batches

The primary stability batches should be at least pilot-scale, though one of the three may be smaller (see Glossary), and should have the same composition and be packaged in the same container-closure system as proposed for marketing (presentation of data on the primary batches is illustrated in Annex 6).

6.5.1 Bioequivalence and dissolution studies

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

Summaries of all BE studies (passed and failed) on the final formulation should be discussed.

6.5.2 Stability studies

Two of the three stability batches should be at least pilot-scale¹ batches and the third one can be smaller, if justified (in the case of conventional dosage forms with APIs that are known to be stable, data from at least two primary batches should be provided)². Where possible batches of the FPP should be manufactured by using different batches of the API. Additional stability studies are required if more than one manufacturer of API is applied for.

6.6 Scale-up and validation

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

Based on monitoring closely the manufacturing process of 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.

Validation should be conducted on production scale batches. If validation data are not available by the time of submission, a process validation protocol should be provided in the application dossier.

¹ A pilot batch should be manufactured by a process fully representative of and simulating that to be applied to a full production scale batch. For oral solid dosage forms this size should be 10% of production scale or 100 000 units whichever is the larger.

² WHO Technical Report Series, No. 953, 2009, Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products.

ANNEX 1

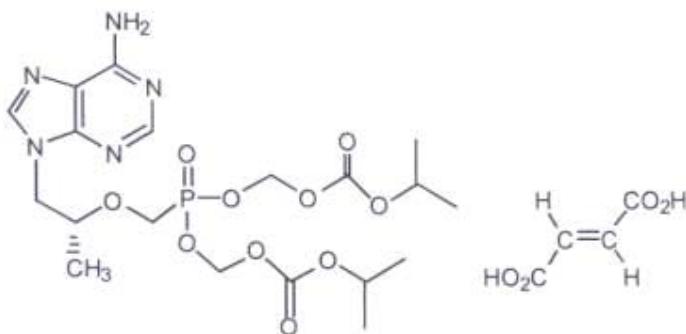
PUBLICLY AVAILABLE INFORMATION ON TENOFOVIR

General note: Example includes specific references to a regional authority regulation.

For general requirements we refer to the WHO Prequalification web site:

<http://www.who.int/prequal/>

Tenofovir disoproxil fumarate has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula¹:



Tenofovir disoproxil fumarate is a salt of an oral prodrug of tenofovir². Because tenofovir was not well absorbed from the intestine, the prodrug, tenofovir disoproxil, was developed to increase bioavailability.

The recommended dose is one 245 mg tablet daily taken orally with a meal.

Active pharmaceutical ingredient

Tenofovir disoproxil fumarate (*tenofovir DF*) is a diester prodrug used as a promoiety in order to increase lipophilicity and enhance the oral bioavailability of the parent compound.

The *physicochemical characteristics* of tenofovir DF with respect to salt selection, hygroscopicity, dissociation constant, partition coefficient, solubility, solution and solid state have been studied. Tenofovir disoproxil fumarate is manufactured as an anhydrous crystalline form using a linear synthesis. Following isolation the product is dried at not more than 45°C to a solvent content (LOD or GC) of not more than 0.5 %. The dry product is milled to break up any aggregates.

Tenofovir DF contains a single chiral centre at the C-11 position (C-2 of the propyl side-chain) and the defined method of synthesis routinely produces the R-enantiomer.

Two polymorphic forms have been identified by X-ray powder diffraction and DSC, a "high" melting polymorph (115-118°C) and a "low" melting polymorph (112-114°C). The melting enthalpies, intrinsic dissolution rates and solubility of these crystal forms are indistinguishable and, therefore, these solid-state differences are unlikely to result in clinical consequences.

¹ http://www.fda.gov/cder/foi/label/2002/21356slr001_Viread_lbl.pdf (downloaded on 26 December 2007).

² <http://www.emea.europa.eu/humandocs/PDFs/EPAR/viread/351001en6.pdf> (downloaded on 26 December 2007).

The proposed **specification** for the active substance includes relevant tests for: appearance; identity (IR & HPLC); assay by HPLC (97-101% tenofovir DF, non-chiral); enantiomeric purity by HPLC (not less than 98% of the R-isomer); 14 potential related impurities are described of which eight are controlled in the specification by HPLC; organic volatile impurities; and heavy metals. Physical tests include: clarity of solution; water content; DSC (main endotherm characterization); and particle size.

9-propenyladenine (9-PA) is a process-related impurity which is mutagenic. Although the amounts found in batches of the drug substance have been monitored and limited throughout development, a routine test and limits for this impurity should be included in the active substance specification.

Analytical validation data for all analytical methods are provided and take into account current guidelines. Details of the reference standards are provided.

Batch analyses data are presented for a total of 39 batches of tenofovir DF used in toxicological, clinical and stability studies, with precise impurity profile. However, some further clarification is required.

Tenofovir DF shows excellent physicochemical **stability** when stored at 5°C for up to 36 months (three lots, packaged in polyethylene bags, sealed and then placed into tightly-capped HDPE bottles), the primary route of chemical degradation being hydrolysis. There was no significant loss in purity or increase in total impurity and degradation product content after storage under accelerated storage conditions (same packaging, at 25°C/60%RH and 30°C/60%RH) for up to 6 months.

Tenofovir DF active substance is specified to be stored under refrigeration at 2-8°C. Tenofovir DF is to be stored in polyethylene bags, which are placed into tightly closed HDPE containers and the proposed retest period of 24 months is supported.

Finished pharmaceutical product

Viread is formulated as immediate-release, film-coated tablets containing 245 mg of tenofovir disoproxil (as fumarate), equivalent to 136 mg of tenofovir. The **excipients** are those commonly used in this type of product: pregelatinized starch (binder); croscarmellose sodium (disintegrant); lactose monohydrate (filler); microcrystalline cellulose (filler); magnesium stearate (lubricant); and a proprietary hypromellose-based film-coating (lactose monohydrate, glycerol triacetate, hypromellose, titanium dioxide [E171], indigo carmine lake [E132]).

The tablets are presented in **high density polyethylene (HDPE) bottles with aluminium foil induction seals** and polypropylene child-resistant caps. Each bottle contains 30 tablets and includes a canister of silica gel as a desiccant to reduce the headspace moisture and polyester fibre to prevent tablet chipping in transit.

The fumarate salt of the diester prodrug of tenofovir is chosen to increase intestinal permeability and to improve the bioavailability of the active substance. The choice for a tablet presentation and the rationale for both the proposed qualitative and quantitative composition of the formulation have been presented.

The **processing parameters**, including those for the film-coating, have been investigated and optimized. The **free moisture in the tablets is minimized** both during the manufacturing process and in the packaging.

The **HDPE** resin used for the primary packaging (**bottles**) is thick and was selected based **upon moisture vapour transmission data**, as the product must be protected from extended periods of exposure to high moisture conditions. The use of 1 gram of silica gel (in a canister) per bottle was established based upon stability data. Induction sealing of the bottle (with aluminium foil) also reduces the available moisture.

Film-coated tablets of different strengths have been used in clinical trials and the formulations for these have been presented.

The manufacturing processes have all been well described. Manufacture commences with a **conventional wet granulation process**, followed by a drying of the granules (to LOD \leq 3%) to reduce the intragranular moisture content. After compression, the bulk uncoated tablets are tested for hardness and friability. Finally the film coating (aqueous-based) is applied.

The industrial batch size has been stated to be up to 1000 kg. The frequency of in-process control testing remains to be fully clarified.

Nine lots of up to 230 kg in size have been manufactured and used for **validation studies** and although the process has been shown to be robust and to result in consistent product some points for clarification remain and some further validation data are also required.

The **product specification** contains the relevant tests and limits for a product of this type. Tests include appearance, identification of the active substance (HPLC and UV), assay (96-105% at release, 90-105% during shelf-life, by HPLC), and limits for 10 named related impurities/degradates. Unspecified impurities are limited to not more than 0.2% each. In addition there are also pharmacopoeial tests for content uniformity, dissolution, water content and microbial limits.

The proposed specification limits for total impurities and degradation products in both the release and shelf-life specifications are very high and remain to be tightened or further justified by reference to the original toxicological studies.

The analytical methods are described and suitably validated in accordance with current guidelines. Batch analyses results on 10 batches are provided.

Long-term and accelerated stability studies were conducted on nine batches of tenofovir DF tablets, 245 mg. The stability batches were produced at a scale that is greater than one-tenth of the intended commercial scale, were identical in the composition, used the same manufacturing process, and were packaged into the same container-closure system as the intended commercial product.

Long-term stability studies were conducted at 25°C/60%RH and 12-months data are available for two batches and 9-months data for three batches.

The results indicate an acceptable long-term stability. The tablets remained within the product specifications when stored for up to 12 months at 25°C/60%RH. A statistical analysis was performed to estimate the total impurity and degradation product content at the proposed expiration dating period of 24 months. However, the stability data provided do not yet support

the claimed limit of 8.0% for impurities/degradation products in the shelf-life specification.

No significant change in physicochemical stability was observed for tenofovir DF tablets stored for 6 months at 40°C/75%RH. The pharmaceutical product remained within the product specifications over the 6-month study duration. No significant change in physicochemical stability was observed for tenofovir DF tablets exposed to artificial daylight fluorescent lamps.

On the basis of the long-term and accelerated stability data and the statistical analyses, the proposed shelf-life, i.e. 24 months with no specific storage condition, is acceptable. However, clarification of some of the stability data and some additional data are required.

All the excipients in the product comply with current pharmacopoeial specifications and monographs and are widely used for the manufacture of solid oral dosage forms.

Information has been provided to demonstrate that the CPMP is satisfied that the materials, lactose monohydrate, magnesium stearate (vegetable source) and the proprietary film coating (Opadry II Y-30-10671-A) are in compliance with the latest EU guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products¹.

Satisfactory control ***specifications and certificates are provided for the packaging materials***. The bottles and closures are controlled according to the general pharmacopoeial requirements for plastic containers and closures.

¹ WHO guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products (www.who.int/bloodproducts/tse).

ANNEX 2

INITIAL RISK ASSESSMENT OF CRITICAL QUALITY ATTRIBUTES AND CRITICAL PROCESS PARAMETERS

Using Annex 1 as the source of information the following risk statements can be made:

Active pharmaceutical ingredient (Tenofovir DF):

- The publicly available QC and stability information does not suggest racemization during storage.
- Polymorphism is unlikely to be a critical quality attribute.
- Potentially critical physical attributes include clarity of solution, water content and particle size.
- 9-propenyladenine (9-PA) is a process-related impurity, which is mutagenic.
- Tenofovir DF shows excellent physicochemical stability when *stored at 5°C* for up to 36 months. (Note: unusual storage conditions which deserve special attention.)
- The primary route of chemical *degradation is hydrolysis*.
- There was no significant loss in purity or increase in total impurity and degradation product content after storage under accelerated storage conditions (same packaging, at 25°C/60%RH and 30°C/60%RH) for up to 6 months. (Note: the packing materials protect the API from environmental humidity.)

Finished pharmaceutical product

- The FPP is formulated as immediate-release film-coated tablets containing 245 mg of tenofovir disoproxil (as fumarate), equivalent to 136 mg of tenofovir.
- The excipients are those commonly used in this type of product.
- The tablets are presented in high density polyethylene (HDPE) bottles with aluminium foil induction seals and polypropylene child-resistant caps. Each bottle contains 30 tablets and includes a canister of silica gel as a desiccant.
- The free moisture in the tablets is minimized both during the manufacturing process and in the packaging.
- The HDPE resin used for the primary packaging (bottles) is thick and was selected based upon moisture vapour transmission data, as the product must be protected from extended periods of exposure to high-moisture conditions.
- Manufacture commences with a conventional wet granulation process, followed by a drying step to dry the granules (to LOD \leq 3%) to reduce the intragranular moisture content.
- Finally the film coating (aqueous-based) is applied.
- The product specification contains the relevant tests and limits for a product of this type. The proposed specification limits for total impurities and degradation products in both the release and shelf-life specifications are very high and remain to be tightened or further justified by reference to the original toxicological studies.
- Long-term stability studies were conducted at 25°C/60%RH and 12-months data are available for two batches and 9-months data for three batches. The results indicate an acceptable long-term stability. The stability data provided, however, do not yet support the claimed limit of 8.0% for impurities/degradation products in the shelf-life specification.

The following table* exemplifies the initial risk assessment of critical quality attributes of a generic company based on experience with the manufacture of film-coated tablets.

Quality attributes	Unit operations						
	Weighing	Granulation	Drying	Blending	Compression	Coating	Packing
Appearance	Yellow	Green	Green	Green	Green	Yellow	Green
Identity test	NIR	Green	Green	Green	Green	Green	Green
Uniformity of mass	Green	Green	Green	Green	Red	Green	Green
Uniformity of content	Red	Red	Green	Red	Yellow	Green	Green
Disintegration	Green	Green	Green	Green	Yellow	Yellow	Green
Dissolution	Green	Yellow	Green	Green	Yellow	Green	Green
Resistance to crushing	Green	Yellow	Yellow	Green	Yellow	Green	Green
Friability	Green	Yellow	Yellow	Green	Green	Green	Green
Water content	Green	Yellow	Red	Green	Yellow	Green	Yellow
Degradants	Green	Yellow	Yellow	Green	Green	Green	Green
Assay	Red	Green	Green	Yellow	Yellow	Green	Green
Microbial limits	Yellow	Green	Yellow	Green	Green	Green	Yellow
Control strategy		Monitoring strategy			Prior knowledge		

* This table is based on ICH Q9 Quality risk management, Annex II – Potential applications: “Risk Management approach to focus on critical attributes” and has been modified to comply with multisource (generic) pharmaceutical products.

ANNEX 3

EXAMPLES OF PRESENTING ACTIVE PHARMACEUTICAL INGREDIENT QUALITY ATTRIBUTES

Physicochemical characteristics of the API (not described under 3.2.S.1.3 General properties) that can influence manufacturing capability and the performance of the FPP should be tabulated and discussed, for example:

Quantitative aqueous pH solubility profile (at 37°C)		
pH (of the buffer)	Solubility (mg/mL)	Descriptive term (as defined in <i>The International Pharmacopoeia</i> (Ph.Int.))
1.2		
4.5		
6.8		

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					
<i>Add</i>	<i>rows, as needed</i>	<i>Change</i>	<i>data range, as</i>	<i>relevant</i>	

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	Treatment	Observations
None	Initial values of the API	Assay:
		S1:
		<i>Insert as many rows as necessary</i>
		D1:
		<i>Insert as many rows as necessary</i>
		Total unspecified:
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	Assay:
		S1:
		D1:
		Total unspecified:
		Total impurities:
		Humidity
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 eight (8) hours	
		S1:
		D1:
		Total unspecified:
		Total impurities:

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

D1, D2, etc., are degradation products.

ANNEX 4
INFORMATION ON DEVELOPMENT BATCHES

Screening laboratory batches with different proportions of excipients to match innovator dissolution.

Composition of formulation development experiments								
Ingredients	Lab01		Lab02		Lab03		Lab04	
	g	%	G	%	g	%	G	%
API 1								
API 2								
API 3								
Excipient 1								
Excipient 2								
Excipient 3								
Excipient 4								
Excipient 5								
Dissolution, % at pH ...								

Comparator product – bench mark (Hypothetical example - Ph.Int., paddle, 75rpm, 900ml)

	% API dissolved	% API dissolved	% API dissolved
Time (min)	pH 1.2 buffer	pH 4.5 buffer	pH 6.8 buffer
5	27	15	22
10	42	25	27
15	55	36	35
20	65	42	42
30	76	48	49
45	88	49	57
60	92	49	65
90	100	50	76

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:

ANNEX 5
CRITICAL INFORMATION ON PRIMARY BATCHES

Batch number(s) of the FPPs used in			
Bioequivalence			
Dissolution profile studies			
Stability studies (primary batches)			
< packaging configuration I >			
< packaging configuration II >			
<i>(Add/delete as many rows as necessary)</i>			
Stability studies (production batches)			
< packaging configuration I >			
< packaging configuration II >			
<i>(Add/delete as many rows as necessary)</i>			
Validation studies (production batches)			
<p>The attached manufacturing records and certificates of analysis on the above batches should include the manufacturing site, the batch size, and any significant equipment differences (e.g. difference in design, operating principle, size, etc.) between the primary and the production batches.</p>			

Draft for comments

Composition of bioequivalence, primary stability and production FPP batches								
Ingredients	Unit		Bioequivalence <batch number>		Primary stability <batch number>		Production <batch number>	
	mg	%	kg	%	kg	%	kg	%
Core tablet/capsule contents (<i>Please delete/change which does not apply</i>)								
API 1								
API 2								
API 3								
<i>Please add/delete as many rows as necessary</i>								
Excipient 1								
Excipient 2								
Excipient 3								
Excipient 4								
<i>Please add/delete as many rows as necessary</i>								
Purified water								
Subtotal 1								
Film coat/capsule shell (<i>Please delete/change which does not apply</i>)								
Proprietary film-coating mixture*								
Purified water								
<i>Please add/delete as many rows as necessary</i>								
Subtotal 2								
Grand total								
Equivalence of compositions or justified differences			The compositions of the bioequivalence, stability and validation batches are the same and differences are justified. (<i>Please delete/change which does not apply</i>)					
* All components (.....) of the proprietary mixture are described in the Ph.Int.								

ANNEX 6

SETTING DISSOLUTION ACCEPTANCE CRITERIA FROM DISSOLUTION PROFILES

The dissolution profiles for two brands of Isoniazid/ethambutol hydrochloride 150mg/400mg tablets are shown in the graphs below. The experimental conditions were as follows:

Apparatus	Paddle, 75 rpm
Dissolution medium	pH 6.8 phosphate buffer, 500 ml
Degassed?	No
Temperature	37°C ± 0.5°C
Sampling points	10, 15, 20, 30, 45, and 60 minutes

Product A, with disintegration time of 7 minutes in water, is very rapidly dissolving with respect to both APIs (≥ 85% dissolution within 15 minutes). An acceptance criterion of 80% at 20 minutes would be appropriate for this product to ensure batch-to-batch consistency.

Product B has a disintegration time of 11 minutes in water, and does not show very rapidly dissolving properties. Instead it is rapidly dissolving for both APIs, with ≥ 85% dissolution within 30 minutes. In this case the appropriate acceptance criterion would be 80% at 30 minutes for both APIs.

The acceptance criterion in the Ph.Int. for Isoniazid and ethambutol hydrochloride tablets is 80% at 30 minutes, using the same conditions as given above.

