



DRAFT

**PHARMACEUTICAL DEVELOPMENT FOR
MULTISOURCE (GENERIC) PHARMACEUTICAL
PRODUCTS**

This draft is based on the concept paper QSM/EC/07.29 “Guideline for pharmaceutical development for generics” presented to the 42nd meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva, 15-19 October 2007, and on the draft report from that meeting. The Expert Committee agreed to prepare this working document, which has been drafted by Dr. János Pogány, Hungary, for circulation among WHO Member States, the pharmaceutical industry, WHO experts, specialists and nongovernmental organizations in accordance with WHO's procedure for establishing standards in quality assurance.

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**Schedule for the proposed adoption process of working document QAS/08.251:
Draft 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

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1. INTRODUCTION

Differences between the innovator and multisource (generic) finished pharmaceutical products (FPPs) justify the need for a WHO guideline on pharmaceutical product development:

Innovator FPP	Multisource FPP
Pharmaceutical product target profile (PPTP) forms the basis of design for the development of a new FPP. PPTP includes selection of: <ul style="list-style-type: none"> ➤ Dosage form and route of administration. ➤ Dosage form strength(s). ➤ Therapeutic moiety release and pharmacokinetic characteristics as appropriate to the pharmaceutical product dosage form being developed. 	PPTP is the innovator product.
Composition and manufacturing method of the FPP should be experimentally developed.	Qualitative composition of innovator FPP is known from public information sources and the manufacturing method is basically determined by the composition and the dosage form of the innovator FPP.
Container and closure system (and delivery device, as applicable) should be developed.	Qualitative characteristics of primary packing materials are known.
Shelf-life and storage conditions should be derived from stability studies.	Target information on shelf-life and storage conditions are known.
The PTPP begins as a prospective summary and it is amended or updated through clinical and development experience.	The PTPP is identified through iterative laboratory experiments.
PPTP will be achieved through clinical studies to ensure the required quality focused on safety and efficacy.	PPTP will be achieved through demonstrating pharmaceutical equivalence and bioequivalence with the innovator FPP.
Active pharmaceutical ingredient (API) and FPP are developed typically by the same company. API specifications include user requirements in addition to the pharmacopoeial acceptance criteria.	The multisource FPP manufacturer buys the API from the international market and should develop API specifications (user requirements) additional to those in the official compendia.
Fixed-dose combinations (FDCs) are rare among prescription drugs.	FDCs occur frequently in the WHO List of Essential Medicines and they have special features for pharmaceutical development.

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

1.1 Objectives

Essential similarity of a generic FPP with the corresponding innovator FPP is described in terms of pharmaceutical equivalence and bioequivalence. A generic FPP is considered pharmaceutically equivalent to the innovator product if its formula is qualitatively the same

and quantitatively essentially similar to the comparator formula and it is manufactured with a controlled, robust process.

The guideline offers a systematic methodology to industry for developing high quality generic FPPs, which are consistently pharmaceutically equivalent to the innovator (comparator/reference) FPPs. The guideline also intends to provide a good understanding of the generic medicine and its manufacturing process for assessors and inspectors.

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

1.2 Scope

Section 3.2.P.2 Pharmaceutical Development in the Common Technical Document is first produced for the original marketing application. This guideline provides guidance on the contents of the Pharmaceutical Development section both for the applicants for marketing authorizations and drug regulatory authorities (DRAs) that do not use the International Conference on Harmonisation (ICH) Q8 guideline.

Pharmaceutical development issues also depend on the dosage form of the FPP. Examples in the Annexes are focused on solid pharmaceutical forms and will be removed from the final version of the guideline.

2. DEVELOPMENT STRATEGY

2.1 Desk research

The WHO, European Medicines Agency (EMA) and United States Food and Drug Administration (US-FDA) websites¹ provide regulatory information on the qualitative composition and the primary packing materials of the innovator and multisource (generic) FPPs (an example is illustrated in Annex 1).

2.2 Initial quality risk assessment

The following table illustrates the API risk factors, which should be taken into account both by the pharmaceutical industries and by the regulatory authorities:

Market availability	Manufacturing method	Source of quality standard
First-time generic API	Chemical synthesis	In-house R&D + API master file (APIMF) + WHO and ICH guidelines + regulatory information from EMA and US-FDA
	Biosynthesis	
	Extraction from natural sources	
Multisource API	Chemical synthesis	Pharmacopoeias + OP of APIMF + in-house R&D + WHO guidelines
	Biosynthesis	
	Extraction from natural sources	

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).

The quality risks associated with first-time generic APIs are higher (pink cells) than those of multisource APIs, which have already been available in international trade for several years. The method of API manufacture is a further risk factor because biotechnological APIs require supplementary assessment of issues non-existent with chemical APIs.

The following table illustrates a risk classification of finished pharmaceutical products most frequently encountered in the WHO List of Essential Medicines:

Market availability	Pharmaceutical form	Source of quality standard
First-time generic FPP	Conventional dosage form	In-house R&D + APIMF + WHO and ICH guidelines + regulatory information from EMEA and US-FDA
	FDC in conventional dosage form	
	FDC in special dosage form	
	Sterile dosage form	
Multisource FPP	Conventional dosage form	Pharmacopoeias + OP of APIMF + in-house R&D + WHO guidelines
	Fixed-dose combination	
	FDC in special dosage form	
	Sterile dosage form	

As regards pharmaceutical development of FPPs, there are also high-risk pharmaceutical forms (pink cells) among the multisource FPPs while fixed-dose combinations (pale yellow cells) should also meet requirements additional to those of single-component products.

The best strategy for generic product development is to use the same qualitative and quantitative formula as that of the comparator (reference/innovator) FPP in order to minimize the risks related to compatibility, manufacturability, stability and bioequivalence. The generic development strategy should aim, as a minimum, at the same qualitative formula and a close quantitative matching of excipients of the comparator FPP.

In the case of fixed-dose combination FPPs, the development strategy should take into account the formulae of the individual component comparator FPPs.

Accompanying reconstitution diluents¹ should also be included in the development strategy.

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

3. PRODUCT DEVELOPMENT

3.1 Product-specific analytical methods

Noncompendial APIs and FPPs should be tested with methods developed by the applicant. Particular attention should be paid to the validation² of analytical test methods so that the laboratory and pilot-scale product and process development experiments identify the acceptable ranges of CQAs and CPPs. In-house reference standards should be established at the start of the development process and they should be qualified against compendial reference standards as soon as a pharmacopoeia monograph has been published.

¹ 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 copackaged diluents should be included in 3.2.P.2.2.1 and 3.2.P.2.6.

² http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf (downloaded on 29 December 2007).

A dissolution method should also be developed and validated at an early stage, which can act as a surrogate for bioequivalence only if it can detect changes (discriminate) between different formulations. To determine if a dissolution method can discriminate formulation changes, the method must be challenged. The most common way to challenge the discriminatory power of the method is to test formulations with differences in excipients and their concentrations. A discriminating dissolution method 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.

3.2 Characterization of comparator finished pharmaceutical product(s)

3.2.1 Sourcing of comparator product

The comparator/reference product should be selected by dissolution profile tests using 12 units or more for three batches of the innovator FPP by the paddle method at 50 rpm. The batch, which shows intermediate dissolution under the most discriminative condition (where the difference in dissolution between the fastest and slowest batches is the largest), should be selected as the reference product for pharmaceutical equivalence studies and bioequivalence studies.

3.2.2 Bench marking for formulation experiments and stability studies

The innovator sample should be scrutinized for batch numbers, shelf-life including in-use stability information, storage instructions and details of the container and closure system in comparison to what is described in the regulatory literature sources.

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

3.2.3 Primary packing materials

The potentially critical attributes of the container and closure system of the comparator FPP should be determined (e.g. wall thickness, moisture permeability and light transmission of the packaging materials, dimensions and tolerances of the closure components) and the results of studies should be converted into specifications.

Special studies include, e.g. testing the capacity of the desiccant to control moisture in the headspace of the container, or determination of the precision and accuracy of a dosing device.

4. COMPONENTS OF FINISHED PHARMACEUTICAL PRODUCT

4.1 Active pharmaceutical ingredient

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

When an APIMF procedure¹ is used, information on the intrinsic chemical and physicochemical properties of the molecule, e.g. solubility at 25°C, partition coefficient (octanol/water), crystallinity, crystal habit and shape, polymorphism, melting range, pK_a and hygroscopicity, is received from the API manufacturer, which allows the FPP manufacturer to take full responsibility for the quality and quality control of the API and the FPP.

Specifications and retest period derived from formal regulatory stability studies are also included in the open part of the APIMF.

¹ Guideline on active pharmaceutical ingredient master file (APIMF) procedure
http://www.who.int/prequal/info_applicants/Guidelines/APIMF_Guide.pdf (downloaded on 29 December 2007).

The specifications of the API manufacturer should be completed with potentially critical properties of the API, together with acceptance criteria, as applicable, e.g. solubility at 37°C to permit BCS classification of the API, partition coefficient (octanol/water) at 37°C and at relevant physiological pH values, 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).

4.2 Excipients

The characteristics of excipients that can influence the pharmaceutical product performance or manufacturability 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 manufacturability of the FPP, batch or supplier variations should be minimized through including user requirements in the pharmacopoeial specifications.

4.3 Container and closure system

Primary packing material selection and pack options are recommended under 3.2.3 Primary packing materials for the comparator FPP. Primary packing materials, particularly plastics, should comply with relevant pharmacopoeial and food contact regulations.

Market specific needs (e.g. Climatic Zone IVb) and patient handling needs (hygienic and pilfer-proof blister cards) should be taken into account.

Stability testing of primary batches should be conducted in the selected markets packs, to confirm compatibility and product stability and to support submissions for marketing authorization.

When the container and 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.

4.4 Formulation experiments

Once the qualitative composition of the comparator FPP has been identified the individual excipients should be quantified. Screening laboratory batches with different proportions of excipients to match innovator dissolution profile is the best method to select the final formula for scale up (typical ranges of excipients are illustrated in Annex 5).

The final formula should be stress-tested (e.g. as illustrated in Annex 3) to identify CQA(s) and to establish tentative acceptance limits for their control.

Any 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 as it affects the pharmaceutical product) should be identified and a rationale provided for their use.

4.5 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.

4.6 Compatibility studies

One-time stress studies should be performed to identify potential reaction products between the API and the individual excipients in the formula. Degradants likely to be present during manufacturing and storage should be monitored during stability studies.

For fixed-dose combination products (FDCs), the compatibility of APIs with each other should be demonstrated.

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.

4.7 Finished pharmaceutical product specifications

Sufficient data may not available to finalize product specification at the time of submitting the dossier for marketing authorization. In such cases, an interim specification¹ should be set for a limited time frame. An interim acceptance criterion for a specific test involves setting provisional limits on a quality attribute of the API (e.g. particle size and bulk densities), an intermediate (e.g. granule properties, tablet hardness and friability), or the FPP (e.g. degradate limits for active metabolites of the API).

For highly soluble and rapidly dissolving drug products (BCS classes 1 and 3), a single-point dissolution test limit of NLT 85% (Q = 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 drugs (BCS class 2), a two-point dissolution range (a dissolution window), one at 15 minutes and the other at a later point (30, 45, or 60 minutes) to ensure 85% dissolution, is recommended to characterize the quality of the product.

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

¹ The need for interim specifications should be justified. A post-approval commitment from the applicant should define the number of batches or the time frame to finalize interim specifications.

5. MANUFACTURING PROCESS DEVELOPMENT

5.1 General considerations

Efforts should be primarily directed towards reducing variability in process and product quality. A process is well understood when:

- all critical sources of variability have been identified and explained;
- variability is managed by the process;
- 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.

5.2 Selection of process

The manufacturing process of the generic FPP should be the same as that of the reference FPP, which is frequently identified in publicly available sources of information. In the majority of cases, the manufacturing process can also be established from the qualitative composition of the comparator FPP.

5.3 Summary of progress from laboratory to pilot plant

The progress from preformulation (size: 1x) → formulation (10x) → pilot manufacture (100x but not less than 100 000 capsules or tablets) → production scale (approved batch size) manufacture should be shown in the dossier submitted for prequalification to be logical, reasoned and continuous.

5.4 Manufacture of primary batches

The primary batches should be at least pilot-scale 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).

5.4.1 Bioequivalence and dissolution studies

Bioequivalence and dissolution studies should be conducted with samples from the same primary batch of the FPP.

The dissolution profile of the generic FPP should be similar to the dissolution profile of the comparator FPP.

5.4.2 Stability studies

Two of the three stability batches should be at least pilot scale¹ batches and the third one can be smaller, if justified. Where possible batches of the FPP should be manufactured by using different batches of the API.

5.4.3 Prospective validation

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

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.

Based on monitoring closely the manufacturing process of primary 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.

Manufacturing control strategy is proposed for the mitigation of quality risks

GLOSSARY

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).

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.

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.

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”.

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.

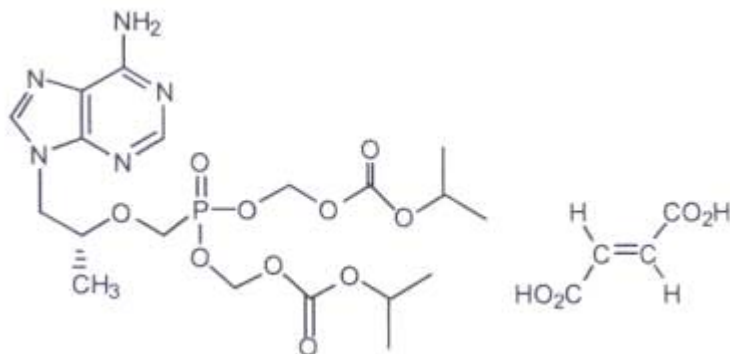
Process robustness (Source: ICH Q8)

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

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 pro moiety 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.

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 8 are controlled in the specification by HPLC; organic volatile impurities;

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).

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 the 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 & 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 9 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 Products.¹

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

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.

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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 manufacturability and the performance of the FPP should be tabulated and discussed.

Quantitative aqueous pH solubility profile (at 37°C)		
pH (of the buffer)	Solubility (mg/mL)	Descriptive term (as defined in the Ph. Int.)
1.2		
4.5		
6.8		
8.0		

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 ≤ 0.1					
D ≤ 0.5					
D ≤ 0.9					
<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:
		Total impurities:
Temperature	A thin layer of the API is wetted with water and 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	A thin layer of the API is wetted with water and kept at 40°C /100% RH 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 eight (8) hours	Assay:
		S1:
		D1:
		Total unspecified:
		Total impurities:

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

D1, D2, etc., are degradants

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)

Time (min)	% API dissolved		% API dissolved
	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. USUAL RANGES OF EXCIPIENTS IN TABLETS AND CAPSULES

Nonproprietary Name (INN if available)	Functional Category	Concentration range (w/w %)
Microcrystalline Cellulose	Capsule binder/diluent	20-90
	Tablet disintegrant	5-15
	Tablet binder/diluent	20-90
Colloidal silicon dioxide	Glidant	0.1-0.5
Croscarmellose sodium	Capsule disintegrant	10-25
	Tablet disintegrant	0.5-5
Crospovidone	Tablet disintegrant	2-5
Hydroxypropyl cellulose	Tablet binder	2-6
	Tablet film coating	5
Lactose	Tablet and capsule diluent	High
Magnesium stearate	Lubricant	0.25-5
Methylparaben + propylparaben	Antimicrobial preservative	0.18 + 0.02
Povidone	Tablet binder	0.5-5
Pregelatinized starch	Capsule diluent	5-75
	Tablet binder	5-20
	Tablet disintegrant	5-10
Sodium lauryl sulfate	Solubilizer and wetting agent	1-2
Sodium starch glycollate	Tablet and capsule disintegrant	2-8
Starch	Tablet binder	2.5-12.5
	Tablet and capsule disintegrant	3-15
	Glidant	2.5-12.5
Stearic acid	Tablet and capsule lubricant	1-3
Talc	Glidant	1-5

ANNEX 6. 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>			
<Add/delete as many rows as necessary>			
Stability studies (production batches)			
< packaging configuration I>			
< packaging configuration II>			
(Add/delete as many rows as necessary)			
Validation studies (primary batches)			
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> <p>* Batch number in the pharmaceutical quality information form (PQIF) is the same as the batch number in the bioequivalence trial information form (BTIF).</p>			

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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.								
