PHARMACEUTICAL DEVELOPMENT OF
MULTISOURCE (GENERIC) FINISHED PHARMACEUTICAL
PRODUCTS
– POINTS TO CONSIDER

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During the past few years we have moved more towards an electronic system for sending out our working documents for comment, for convenience and in order to speed up the process. If you do not already receive our documents electronically, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.
## Schedule for the proposed adoption process of working document QAS/08.251:

### Pharmaceutical development of multisource (generic) finished pharmaceutical products

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**Points to consider**

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<td>Preparation of a draft guideline which was endorsed by the WHO Expert</td>
<td>15-18 October 2007</td>
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<td>Mailing of draft for comments</td>
<td>March 2008</td>
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<td>Discussion of draft with collated comments by a WHO Expert Working</td>
<td>June 2008</td>
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<td>Group</td>
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<td>Mailing of revised draft for comments</td>
<td>July 2008</td>
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<tr>
<td>Collation of comments received on revised draft</td>
<td>September 2008</td>
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<tr>
<td>Presentation of revised draft with collated comments to WHO Expert</td>
<td>13-17 October 2008</td>
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<tr>
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<td>Collation of all comments received, including those arriving after the</td>
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<td>Discussion at the WHO Expert Committee on Specifications for</td>
<td>12-16 October 2009</td>
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<td>Pharmaceutical Preparations</td>
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<tr>
<td>Discussion at the WHO consultation on paediatrics and generics guideline</td>
<td>29-30 April 2010</td>
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<tr>
<td>Mailing of revised draft for comments</td>
<td>June 2010</td>
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<td>Collation of comments received</td>
<td>August 2010</td>
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<tr>
<td>Presentation of revised draft with collated comments to WHO Expert</td>
<td>18-22 October 2010</td>
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<tr>
<td>Committee on Specifications for Pharmaceutical Preparitions</td>
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<tr>
<td>Revised draft (Rev.2) transferred into CTD format</td>
<td>March 2011</td>
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<tr>
<td>Mailing of revised draft for comments to the participants of the</td>
<td>March 2011</td>
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<tr>
<td>informal consultation</td>
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<tr>
<td>Discussion of revised draft (Rev.2) at the WHO consultation on</td>
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<td>May 2011</td>
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<tr>
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<td>August 2011</td>
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<td>Presentation of revised draft with collated comments to WHO Expert</td>
<td>10-14 October 2011</td>
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1. INTRODUCTION

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

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

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

The guideline also intends to provide a good understanding of best practices in the development of multisource FPPs and their manufacturing processes 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 the use of quality risk management and pharmaceutical quality systems.1

This document is designed to be used in conjunction with other WHO guidelines and guidance documents, including the WHO Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part.

1.1 General principles

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

1.2 Scope

This guideline addresses the pharmaceutical development of multisource FPPs containing existing active pharmaceutical ingredients (APIs) of synthetic or semi-synthetic origin. For the purposes of this guideline, an existing API is one that has been previously authorized through a finished product by a stringent regulatory authority (SRA).2 APIs from biological, or biotechnological origin are covered by other guidelines.

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1 WHO draft on Quality risk management (WHO/10.376) and ICH Q9: Quality risk management and Q10: Pharmaceutical quality system.
2 Stringent regulatory authority (SRA): a regulatory authority which is:
   a member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org);
   or
   an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, and Health Canada (as may be updated from time to time); or
   a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).
This guideline provides guidance on the contents of a pharmaceutical development plan for multisource pharmaceutical products for both the applicants for marketing authorizations and national medicines regulatory authorities (NMRAs).

Pharmaceutical development issues depend on the API(s), the excipients, the dosage form, the manufacturing process and the container closure system. Examples in the appendices are focused on immediate release solid oral pharmaceutical dosage forms; however, the general principles are applicable to all types of dosage forms, including injectables, modified release products and respiratory products.

2. PRE-DEVELOPMENT ACTIVITIES

2.1 Desk research

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

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

An example of the type of information that may be publicly available and how it may be used in risk management (see below) is provided in Appendices 1 and 2.

2.1.1 Quality risk management

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

The applicant’s part of the API master file (APIMF)/drug master file (DMF) (if referenced) may reveal risks associated with the API. For instance, reagents (e.g. dimethyl sulfate) or solvents (in particular class 1) used in the process may each pose a risk.

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

It is recommended that polymorphism, pseudo-polymorphism and the implications of variability in particle size be routinely considered. Variability in any of these key physical properties is likely to be of particular significance for APIs that are of low solubility according to the biopharmaceutics classification system (BCS). The requirement for routine control of polymorphic form and particle size should be considered in accordance with advice in Decision Trees 3 and 4 of ICH Q6A. When controls are necessary they should be established based on the results obtained for the API lot(s) used in the biostudies.

For example The International Pharmacopoeia (Ph.Int.) 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 reference source 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.” Alternately, if present, these impurities should be limited to a suitable justified level (refer to the Guideline on the Limits of Genotoxic Impurities - EMEA/CHMP/QWP/251344/2006).

Prior knowledge of potential genotoxic impurities in an API is regarded as highly important. Another example is provided in Appendix 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 applicant’s part of the APIMF/DMF before selecting potential API manufacturer(s).

The initial risk assessment of potential CQAs and CPPs of a multisource product should be based on desk research and the applicant's own experience with the manufacture of the dosage form. An example is provided in Appendix 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 literature, though some pharmacopoeial monographs do not clearly reveal the presence of this impurity. Recently a specific test was included in the European Pharmacopoeia (PhEur.) for control of this impurity.

The least risky strategy for multisource product development is to use the same qualitative and, where possible, quantitative formula as that of the comparator FPP – in the absence of the possibility of patent infringement – in order to minimize the risks related to compatibility, stability and bioequivalence.

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

### 2.2 Additional considerations

#### 2.2.1 Selection and characterization of comparator FPP(s)

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 lists of comparator products. Note that for a dossier to be submitted to PQ, the comparator must be selected from its published lists. For guidance regarding PQ comparator products, reference should be made to the information available under Guidance on Bioequivalence Studies on the PQ web site.

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In the case of fixed-dose combination (FDC) FPPs, there will be instances when a combination of APIs is recommended for clinical use but an innovator fixed-dose combination (FDC) containing these APIs, whose approval was based on clinical trial data, will not be available as a comparator product. FDCs approved based on data such as bioequivalence data are not typically used as comparators, as the original safety and efficacy data is linked to the monocomponent products and not the FDC FPP. For FDC 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 bioequivalence (BE) study (see also WHO Guidelines for registration of fixed-dose combination medicinal products).

The comparator product batch may be selected by dissolution profile testing. Ideally, a batch which shows intermediate dissolution under the most discriminative condition (where the difference in dissolution between the fastest and slowest batches studied is the largest), should be selected as the reference product for pharmaceutical equivalence studies and bioequivalence studies.

### 2.2.2 Benchmarking for formulation experiments and stability studies

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

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

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

### 2.2.3 Formulation selection experiments

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

This may include determining the qualitative and quantitative composition of the comparator product. The qualitative information on the comparator product may be available in the public domain, e.g. in its summary of product characteristics (SmPC) or package leaflet. Screening different formulations to match the comparator dissolution profile is the best method to select the final formula for scale up (typical ranges of excipients are illustrated in Appendix 5) from laboratory to pilot batch.

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

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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 for their use should be provided in the product dossier (PD).

2.2.4 Bioequivalence and dissolution studies

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

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, e.g. sorbitol in liquid formulations or mannitol in solid dosage forms. For instance, in the case of considering a biowaiver for an immediate release solid oral dosage form containing a BCS Class 3 API, the risk of reaching an inappropriate biowaiver decision needs to be critically evaluated, especially when the extent of absorption (\(f_{\text{bio}}\)) 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.”\(^1\)

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

3. PHARMACEUTICAL DEVELOPMENT

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

The text of the M4Q (CTD-Q) guideline has been restated in this guideline in bold text, verbatim, with minor modifications to accommodate WHO terminology and to include certain text that would be appropriate for multisource pharmaceutical products, notably:

- “Drug substance” is replaced with “active pharmaceutical ingredient” or “API”;
- “Drug product” is replaced with “finished pharmaceutical product” or “FPP”;
- “application” is replaced with “product dossier” or “PD”;
- “combination product” is replaced with “fixed-dose combination” or “FDC”;
- “clinical batches” is replaced with “comparative bioavailability or biowaiver batches”.

Following the bold text of the M4Q (CTD-Q) guideline, additional guidance by WHO is provided in plain text to easily distinguish from the ICH text and is included to provide further clarity on WHO’s expectations and requirements. This approach is intended to facilitate the identification and origin of the text in the guideline (i.e. from ICH or WHO).

3.2.P.2 Pharmaceutical development

The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, formulation, manufacturing process,

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

Pharmaceutical development information usually includes, at a minimum:

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

These features are usually required to be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product (reference: ICH Q8). The information gained through the pre-development activities may already have disclosed some of these features and could form an integral part of pharmaceutical development.

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

Reference documents: ICH Q6A, Q8, Q9, Q10

3.2.P.2.1 Components of the FPP

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

3.2.P.2.1.1 Active pharmaceutical ingredient

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

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.
Information on the intrinsic physicochemical properties of the molecule, e.g. solubility, solid state properties, including polymorphism and habit, melting range, pKₐ, 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.

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 are usually required to be supported by experimental data (or by information from peer-reviewed literature) and discussed regarding CQAs and CPPs.

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

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

Stress testing of the API should be designed to include simulation, as far as possible, of the conditions that may be encountered during the manufacturing process of the FPP. An example is illustrated in Appendix 3.

### 3.2.P.2.1.2 Excipients

The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the FPP performance is usually required to be discussed relative to their respective functions.

When choosing excipients, those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations such as the FDA IIG list and the Handbook of Pharmaceutical Excipients. Use of excipients in concentrations outside of established ranges is discouraged and generally requires justification. In addition, available guidelines are usually required to be referenced which address particular excipients to be avoided, for example azo colourants as listed in EMA guideline CPMP/463/00 and Colorcon Regulatory Information Sheet on azo and non-azo colourants. Other guidelines such as the WHO Points to consider for the development of paediatric medicines may provide useful general guidance in this regard.

The characteristics and amounts of excipients that can influence the pharmaceutical product performance or manufacturing capability are usually required to 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 FPP shelf-life is usually

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required to be demonstrated.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

Many excipients such as povidone, microcrystalline cellulose, and lactose are by nature multifunctional. The chemically 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.

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

3.2.P.2.2 Finished pharmaceutical product

3.2.P.2.2.1 Formulation development

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

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

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

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or the product(s) may be eligible for a biowaiver. WHO reference documents (e.g., the WHO guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products, WHO Technical Report Series, No. 937, Annex 7) can be consulted.
Tablet scoring may be recommended or required in certain jurisdictions or, for example, when scoring is indicated in the WHO invitation for expression of interest (EOI), or is specified for an invited FPP in the listing of recommended comparator products, or when division into fractional doses may be necessary according to approved posology.

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

If splitting of a tablet is intended for a paediatric dose, a demonstration of content uniformity of tablet fragments may be required.

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

**In vitro dissolution or drug release**

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

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, medium) are usually required to be provided in the PD. Data are also usually required to be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters.

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

In the case of rapidly dissolving FPPs containing highly-soluble APIs (BCS classes 1 and 3), a single-point dissolution test limit of 80% in 30 minutes or less is considered sufficient as a routine quality control test for batch-to-batch uniformity. For slowly dissolving or poorly water-soluble APIs (BCS classes 2 and 4) in immediate-release products, a two-point dissolution range (a dissolution window), one at an early time-point 45 minutes (e.g. Q=60% in 45 minutes) and the other at a later point (e.g. Q=80% in 90 minutes) is recommended to characterize the quality of the product. Note that in some cases the latter point may be lower than 80% if a plateau is
Modified-release FPPs are usually required to have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vitro-in vivo correlation. Results demonstrating the effect of pH on the dissolution profile are usually required to be submitted if appropriate for the type of dosage form.

For extended-release FPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or ±12.5% of the targeted value.

Dissolution results are usually required to be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

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

**3.2.P.2.2.2 Overages**

Any overages in the formulation(s) described in 3.2.P.1 are usually required to be justified. Justification of an overage to compensate for loss during manufacture are usually required to be provided in the PD, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

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

**3.2.P.2.2.3 Physicochemical and biological properties**

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

**3.2.P.2.3 Manufacturing process development**

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

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

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

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

Efforts should be primarily directed towards reducing variability in process and product quality.
In order to achieve this:

- all critical sources of variability should be identified and explained;
- the sources of variability should be minimized and controlled; and
- CQAs should be accurately and reliably predicted.

Process development studies should provide the basis for process improvement, process
validation and any process control requirements. All CPPs are usually required to 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. Where relevant,
justification for the selection of aseptic processing or other sterilization methods over terminal
sterilization is usually required to be provided in the PD.

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

The scientific rationale for the selection, optimization and scale-up of the manufacturing process
described in 3.2.P.3.3 is usually required to be explained, in particular the critical aspects (e.g.
rate of addition of granulating fluid, massing time, granulation end-point). A discussion of the
CPPs, controls and robustness with respect to the QTPP and CQA of the product is usually
required to be included (ref: ICH Q8).

Based on closely monitoring 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 for production batches.

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

3.2.P.2.4 Container closure system

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

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

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

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

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

Primary packing materials, particularly plastics, are usually required to comply with relevant pharmacopoeial and food contact regulations.

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

<table>
<thead>
<tr>
<th>Description of any additional treatments*</th>
<th>Solid oral products</th>
<th>Oral liquid and topical products</th>
<th>Sterile products (including ophthalmics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
<td>X (sterilization and depyrogenation of the components)</td>
<td></td>
</tr>
<tr>
<td>Extraction studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Interaction studies (Migration/sorption)</td>
<td>X</td>
<td>X</td>
<td>X (usually loss)</td>
</tr>
<tr>
<td>Moisture permeability (uptake)</td>
<td>X (usually loss)</td>
<td>X</td>
<td>X (usually loss)</td>
</tr>
<tr>
<td>Light transmission (uptake)</td>
<td>X**</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*e.g. coating of tubes, siliconization of rubber stoppers, sulfur treatment of ampoules/vials

X = information is usually required to be submitted

--- = information does not need to be submitted
The suitability of the container-closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g. premixes, bulk FPP) should also be discussed.

**Not required if product has been shown to be photostable**

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. In these cases the data necessary to support a regulatory submission would include:

- physical and chemical stability data for the product formulation-device combination in its primary pack in order to support the claimed shelf-life and storage conditions;
- relevant data on extractables and leachables;
- for multidose products, demonstration of accurate dose delivery over the shelf-life of the product under the registered storage conditions;
- for multidose products with a dose-counting mechanism, stability data to demonstrate reliable performance of that mechanism over the shelf-life of the product under the registered storage conditions;
- specification control and secure sourcing of all device components; and
- relevant information on any secondary device associated with the FPP, such as a spacer device sometimes associated with inhaled products such as MDIs and nebulisers. This device enables dose delivery in situations where the patient cannot easily use the primary product to inhale the dose, particularly where paediatric administration is involved, 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.

Alternatively, the codeveloped device may be intended to facilitate measurement of the prescribed dose prior to administration; this is particularly important for paediatric products where flexibility of dose may also be a requirement. Examples include spoons, cups, syringes or droppers for oral delivery and droppers for nasal or aural delivery. A device is required to be included with the container-closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package provides for multiple doses.

In accordance with the Ph.Int. general chapter *Liquid Preparations for Oral Use*:

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

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

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

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

3.2.P.2.5 Microbiological attributes

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

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

As outlined in the WHO guidelines on Stability testing of active pharmaceutical ingredients and finished pharmaceutical products,¹ a single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 Compatibility

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

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

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

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

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

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

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

4. GLOSSARY

**active pharmaceutical ingredient**
A substance or compound intended to be used in the manufacture of a finished pharmaceutical product as therapeutically active compound (ingredient).

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

**control strategy** (source: ICH Q8)
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredient and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

**critical process parameter (CPP)** (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.
A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

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

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

Products are pharmaceutical equivalents if they contain the same amount of the same actives 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 manufacturing process and some other variables can lead to differences in product performance.
pharmaceutical product (source: Marketing Authorization of Pharmaceutical Products with
Special Reference to Multisource (Generic) Products: A Manual for Drug Regulatory Authorities
– Regulatory Support Series No. 005, 1998)
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.

A batch of an API or FPP 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.

A batch of an API or 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.

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.

A batch of an API or FPP manufactured at production scale by using production equipment in a
production facility as specified in the application.

quality (source: ICH Q8)
The suitability of either an API or a pharmaceutical product for its intended use. This term
includes such attributes as the identity, strength and purity (ICH Q6A).

quality target product profile (QTPP) (source: ICH Q8)
A prospective summary of the quality characteristics of a finished pharmaceutical product that
ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of
the finished pharmaceutical product.

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

5. REFERENCES

[Note from the Secretariat:
The references will be added here when the document has been finalized.]
APPENDIX 1

PUBLICLY AVAILABLE INFORMATION ON TENOFOVIR

General note: Example includes specific references to a regional authority regulation.¹

For general requirements refer to the WHO Prequalification web site

Tenofovir disoproxil fumarate has a molecular formula of \( C_{19}H_{30}N_{5}O_{10}P \cdot C_{4}H_{4}O_{4} \) and a molecular weight of 635.52. It has the following structural formula:

![Tenofovir Disoproxil Fumarate Structural Formula](image)

Tenofovir disoproxil fumarate is a salt of an oral prodrug of tenofovir. 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 (245 mg tenofovir disoproxil (as fumarate)) daily taken orally with a meal.

Active pharmaceutical ingredient

Tenofovir disoproxil fumarate (tenofovir DF) is a diester prodrug of the purine-based nucleotide analogue, tenofovir. Tenofovir DF is obtained by introduction of labile esters on the phosphonate group of tenofovir. This (isopropoxycarbonyloxy)methoxy ester is utilized 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.

The proposed **specification** for the API 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 API have been monitored and limited throughout development, a routine test and limits for this impurity should be included in the API 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 six months.

Tenofovir DF API 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 has 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 API (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 nine 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 six months at 40 °C/75%RH. The pharmaceutical product remained within the product specifications over the six-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

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).
APPENDIX 2

INITIAL RISK ASSESSMENT OF CRITICAL QUALITY ATTRIBUTES AND CRITICAL PROCESS PARAMETERS

Using Appendix 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 CQA.
- 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 ºC 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 ºC/60%RH and 30 ºC/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 ≤ 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 ºC/60%RH and 12 months data are available for two batches and nine 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 multisource company based on experience with the manufacture of film-coated tablets.

<table>
<thead>
<tr>
<th>Quality attributes</th>
<th>Unit operations</th>
<th>Weighing</th>
<th>Granulation</th>
<th>Drying</th>
<th>Blending</th>
<th>Compression</th>
<th>Coating</th>
<th>Packing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Identity test</td>
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<td><strong>NIR</strong></td>
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<tr>
<td>Uniformity of mass</td>
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<td></td>
<td></td>
<td></td>
<td><strong>Red</strong></td>
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<td></td>
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<tr>
<td>Uniformity of content</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Disintegration</td>
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<td></td>
<td></td>
<td></td>
<td><strong>Red</strong></td>
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<td></td>
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<tr>
<td>Dissolution</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Red</strong></td>
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<tr>
<td>Resistance to crushing</td>
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<tr>
<td>Friability</td>
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<td></td>
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<tr>
<td>Water content</td>
<td></td>
<td></td>
<td><strong>Red</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degradants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbial limits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 pharmaceutical products.
APPENDIX 3
EXAMPLES OF PRESENTING ACTIVE PHARMACEUTICAL INGREDIENT QUALITY ATTRIBUTES

[Note from the Secretariat:
Comments are being sought as to whether this information would be useful here, or should rather be given as practical advice, e.g. on the web site of the Prequalification Programme.]

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:

Method (compendial):

<table>
<thead>
<tr>
<th>Particle size of API used in relevant laboratory and pilot-scale batches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured data (µm)</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>D 10</td>
</tr>
<tr>
<td>D 50</td>
</tr>
<tr>
<td>D 90</td>
</tr>
<tr>
<td>Add</td>
</tr>
</tbody>
</table>

Method (compendial):

<table>
<thead>
<tr>
<th>Apparent density of API used in relevant laboratory and pilot-scale batches</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;API batch No.&gt;</td>
</tr>
<tr>
<td>&lt;FPP batch No.&gt; (design)</td>
</tr>
<tr>
<td>&lt;FPP batch No.&gt; (final laboratory)</td>
</tr>
<tr>
<td>&lt;FPP batch No.&gt; (stability)</td>
</tr>
<tr>
<td>&lt;FPP batch No.&gt; (bioequivalence)</td>
</tr>
<tr>
<td>Bulk</td>
</tr>
<tr>
<td>Tapped</td>
</tr>
</tbody>
</table>
Method (compendial):

<table>
<thead>
<tr>
<th>Stress</th>
<th>Treatment</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Initial values of the API</td>
<td>Assay:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insert as many rows as necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insert as many rows as necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total unspecified:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total impurities:</td>
</tr>
<tr>
<td>Temperature</td>
<td>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</td>
<td>Assay:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total unspecified:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total impurities:</td>
</tr>
<tr>
<td>Humidity</td>
<td>A thin layer of the API is kept at 40 °C /100% RH for four (4) weeks in a Petri dish (open system) with sampling once a fortnight</td>
<td>Assay:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total unspecified:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total impurities:</td>
</tr>
<tr>
<td>Oxidation</td>
<td>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</td>
<td>Assay:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D1:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total unspecified:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total impurities:</td>
</tr>
</tbody>
</table>

S1, S2, etc., are synthesis impurities (as in API specifications).
D1, D2, etc., are degradation products.
APPENDIX 4

INFORMATION ON DEVELOPMENT BATCHES

[Note from the Secretariat:
Comments are being sought as to whether this information would be useful here, or should rather be given as practical advice, e.g. on the web site of the Prequalification Programme.]

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

<table>
<thead>
<tr>
<th>Composition of formulation development experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredients</td>
</tr>
<tr>
<td>API 1</td>
</tr>
<tr>
<td>API 2</td>
</tr>
<tr>
<td>API 3</td>
</tr>
<tr>
<td>Excipient 1</td>
</tr>
<tr>
<td>Excipient 2</td>
</tr>
<tr>
<td>Excipient 3</td>
</tr>
<tr>
<td>Excipient 4</td>
</tr>
<tr>
<td>Excipient 5</td>
</tr>
<tr>
<td>Dissolution, % at pH …</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>% API dissolved</th>
<th>% API dissolved</th>
<th>% API dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>pH 1.2 buffer</td>
<td>pH 4.5 buffer</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td>20</td>
<td>65</td>
<td>42</td>
</tr>
<tr>
<td>30</td>
<td>76</td>
<td>48</td>
</tr>
<tr>
<td>45</td>
<td>88</td>
<td>49</td>
</tr>
<tr>
<td>60</td>
<td>92</td>
<td>49</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>50</td>
</tr>
</tbody>
</table>

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: