FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGISTRATION OF ALLOPATHIC DRUGS-QUALITY PART

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Guidelines on submission of documentation for a finished pharmaceutical product for marketing authorization: quality part

1. Introduction

1.1 Background

This guideline provides recommendations for applicants preparing application for a Registration of allopathic drugs for submission to the FDA. The document is based on the World Health Organization (WHO) Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products and the International Conference on Harmonisation (ICH) Common Technical Document (CTD) requirements for Registration of Pharmaceuticals for Human Use.

Through the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization for the Quality module of the registration documents with the issuance of the *Common technical document (CTD) – quality (ICH M4Q)* guideline (1). This format, recommended in the M4Q guideline for the quality information of registration applications, has become widely accepted by regulatory authorities both within and beyond the ICH regions.

The current document provides recommendations on the quality information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to FDA to support applications.

Alternative approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. It is also important to note that the FDA may request information or material, or define conditions not specifically described in this guidance, in order to adequately assess the quality of a pharmaceutical product.

Applicants are requested to carefully read this guideline, fill in application form, prepare dossier and submit two electronic copies (in a Portable Document Format (PDF), on a CD-Rom) and **should include MS-Word**

document for Module 2, cross-referenced to the dossier by clearly indicating the title and section number of all the supporting documents.

1.2 Objectives

This revised guideline presents a common format for the preparation of an application that will be submitted to the Food and Drugs Authority (FDA). Its update to the existing one and provides further better clarity for applicants in submitting product dossiers to the FDA.

This revised guideline has been improved to assist in the following;

- Preparation of documentation for pharmaceutical products by providing clear guidance on the format.
- Fully adopt the modular format of the *Common Technical Document* (CTD) as developed by International Conference on Harmonization (ICH) as well as World Health Organization (WHO) Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products
- Provide guidance on the technical and other general data requirements.
- Reduce the time lines to compile applications for registration of medicines
- Give more details on the requirements for active pharmaceutical ingredients (API) as well as finished pharmaceutical product (FPP).
- Promote effective and efficient processes for the development of these applications and the subsequent evaluation processes by the FDA.

Through the ICH process, considerable harmonization has been achieved on the organization of registration documents with the issuance of the CTD.
This harmonised format has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

1.3 Scope

This revised guideline is developed in pursuance of Section 118 of the Public Health Act, 2012, Act 851 (2), these guidelines are hereby made to provide guidance to applicants on the organization of information to be presented in registration applications for allopathic drugs. Applicants are encouraged to familiarize themselves with this document and the above law before completing the application form for registration of allopathic drugs.

1.4 General principles

To facilitate the preparation of the PD, these guidelines are organized in accordance with the structure of the ICH *Common technical document – quality (M4Q)* guideline (1).

The text of the M4Q (CTD-Q) guideline (*2*) has been restated verbatim in these guidelines in **bold text,** with minor modifications to accommodate FDA 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 biobatch or ‘‘biowaiver batches”.

Additional guidance by FDA, following the **bold** text reproduced from the M4Q (CTD-Q) guideline (*2*), is printed in plain text to make it easily distinguishable from the ICH text and is included to provide further clarity on WHO's expectations for the content of PDs. This approach is intended to facilitate the identification and origin of the text in these guidelines (i.e. from ICH or from FDA).

The content of these guidelines should be read in conjunction with relevant information described in other existing FDA, WHO or ICH reference documents and guidelines. The quality of existing APIs and corresponding multisource products should not be inferior to new APIs and innovator (comparator) FPPs. Therefore, the principles of the ICH guidelines that are referenced throughout this document and in other FDA guidelines may equally apply to existing APIs and multisource products.

Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in these guidelines (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable to the proposed API or FPP. In these situations, either a summary and the full reference to the scientific literature should be provided, or the non-applicability of the requested information should be clearly indicated with an accompanying explanatory note.

1.5 Guidance on format

There may be a number of instances where repetition of sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are recommendations for the presentation of the information in the Quality module for different scenarios that may be encountered:

- The Open part (non-proprietary information) of each APIMF should always be included *in its entirety* in the PD, as an annex to 3.2.S.
- For an FPP containing more than one API, one complete “3.2.S” section should be provided for one API, *followed by* another complete “3.2.S” section for each of the other APIs.
- For an API from multiple manufacturers, one complete “3.2.S” section should be provided for the API from one manufacturer, *followed by* another complete “3.2.S” section for the API from each of the other API manufacturers.
- For an FPP with multiple strengths (e.g. 10, 50, 100 mg) one complete “3.2.P” section should be provided with the information for the different strengths provided *within* the subsections. One complete copy of the PD should be provided for each FPP strength.
- For an FPP with multiple container-closure systems (e.g. bottles and unit dose blisters) one complete “3.2.P” section should be provided with the information for the different presentations provided *within* the subsections.
- For multiple FPPs (e.g. tablets and a parenteral product) a separate dossier is required for each FPP.
- For an FPP supplied with reconstitution diluent(s) one complete “3.2.P” section should be provided for the FPP, *followed by* the information on the diluent(s) in a separate part “3.2.P”, as appropriate.
- For a co-blistered FPP one complete “3.2.P” section should be provided for each product.

LIST OF ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndromme
API: Active Pharmaceutical Ingredient
AUC: Area under the plasma concentration time curve
BAN: British Approved Name
BIOTECH: Biotechnological Products
BP: British Pharmacopoeia
BSE: Bovine Spongiform Encephalopathy
CAS: Chemical Abstract Service
CEP: European Certificate of Suitability
Cmax: Maximum plasma concentration
CoA: Certificate of Analysis
CPP: Certificate of Pharmaceutical Product
DMF: Drug Master File
EC: European Commission
EU: European Union
FDA: Food and Drugs Authority
FDC: Fixed Dose Combination
FPP: Finished Pharmaceutical Product
GMP: Good Manufacturing Practice
HIV: Human Immune-deficiency Virus
ICH: International Council on Harmonization
INN: International Non-proprietary Name
JAN: Japanese Accepted Name
JP: Japanese Pharmacopoeia
LOD: Loss on Drying

NCE: New Chemical Entities
NMT: Not More Than
Ph.Eur: European Pharmacopoeia
Ph.Int : International Pharmacopoeia
PIL: Patient Information Leaflet

Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines.

Active Pharmaceutical Ingredient (API): A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

API starting material: A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

Allopathic drug: Any product or substance other than a medical device, which is to be administered to one or more human beings or animals on its own, or as an ingredient in the preparation of a substance, for a medicinal purpose.

Medicinal purpose: means treating or preventing a disease, diagnosing or ascertaining the presence and extent of a physiological function, contraception, inducing anaesthesia, altering normal physiologic function permanently or temporarily in any way in humans.

Applicant: The product owner or licence holder. Representatives of licence holders may not hold themselves as applicants unless they own the product.

BCS highly soluble: An API for which the highest dose recommended or highest dose strength available on the market as an oral solid dosage form is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37ºC.

Bio-equivalence: Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or alternatives and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

Composition: Composition in relation to a medicinal product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained.

Commitment batches: Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Comparator product: A pharmaceutical product with which the generic 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.

Container labelling: Means all information that appears on any part of a container, including that on any outer packaging such as a carton.

Container: Means a bottle, jar, box, packet, sachet or other receptacle which contains or is to contain in it, not being a capsule or other article in which the product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another receptacle, includes the former but does not include the latter receptacle.

Drug, medicine or pharmaceutical product: means a substance or mixture of substances prepared, sold or represented for use in -
(a) Diagnosis, treatment, mitigation or prevention of disease, disorders or abnormal physical state or the symptoms of it in man or animal
(b) Restoring, correcting or modifying organic functions in man or animal.

Drug Master File: A drug master file (DMF) is a master file that provides a full set of data on an API.

Established multisource (generic) product: A multisource product 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.

Excipient: Any component of a finished dosage form which has no therapeutic value.

Existing API: An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by FDA, but requires the filing of a dossier. This would include, for example, new PDs and variations to multisource products.

Finished Pharmaceutical Product (FPP): A product that has undergone all stages of production, including packaging in its final container and labelling.

Formulation: Means the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

FDA officially recognised list of publications -
Those pharmacopoeias recognized in the FDA Schedule 7 of the Public Health Act of 2012 (ACT 851) (i.e. British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int.), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP)).

Generic (multisource) product(s): Means products that are pharmaceutical equivalents or alternatives to innovator or reference products and which are intended to be therapeutically equivalent and can therefore be used interchangeably with the innovator or reference product. It is a pharmaceutical product usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company.

Interchangeability: An interchangeable pharmaceutical product is one that is therapeutically equivalent to an innovator (reference) product.

Label: Means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stencilled, marked, embossed or impressed on or attached to a container of any drug.

Manufacture (manufacturing): Means all operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.

Manufacturer: Means a person or firm that is engaged in the manufacture of product(s).

New chemical entity: A chemically-synthesized Active Pharmaceutical Ingredient (API) that has not previously been registered as an ingredient of any pharmaceutical product in any country.

Pharmaceutical alternatives: Two or more medicinal products are said to be pharmaceutical alternatives if they contain the same active ingredients, but which may differ in salt, esters, dosage forms, strength and/ or route of administration.

Pharmaceutical equivalents: Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standard; and if they are intended to be administered by the same route.

Pilot-scale batch: 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
Primary batch: 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 re-test period or shelf-life.

Release specifications: Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

Starting material: Means any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Shelf life specifications: Means the combination of physical, chemical, biological and microbiological test requirements that an active ingredient must meet up to its retest date or a drug product must meet during its shelf life.

Therapeutic equivalence: Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Variation: Means a change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

All sections and fields in the five (5) modules that would be applicable should be completed.
It is understood that certain sections and fields may not apply and should be indicated as such by reporting "not applicable" in the appropriate area with an accompanying explanatory note.
Should you have any questions regarding this guideline, please contact the Food and Drugs Authority.

LANGUAGE

All applications and supporting documents shall be in English and legible. Where material is not originally in English, a copy in the original language and a full translation should be submitted, the accuracy of the translation is the responsibility of the applicant.

Authentication of the translation has to be done at the nearest Ghana Embassy or by the National Drug Regulatory Authority of the country from where the document originates.

Reports submitted only in a language other than English will not be accepted.

DATA PRESENTATION

All data should be submitted in soft copies (2 electronic copies required) in the ***CTD format***. All pages shall be numbered sequentially with the format page numbered as ***page x of y*** and have a table of contents indicating the sections and page numbers in the relevant sections of the application form. Before submitting the completed form, check that you have provided all requested information. Acronyms and abbreviations should be defined the first time they are used in each part.

OFFICIAL REFERENCES AND TEXTS

References should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE).

When direct reference is made to specifications, quality control procedures and test methods in official compendia (FDA officially recognised list of publications), text books or standard publications, reprints or authenticated copies of relevant pages shall be enclosed. References to pharmacopoeias should be as per the current editions. References should be provided for all in-house processes.

There shall be no cross reference of particulars or documentation between one product and another.

SUBMISSION OF APPLICATION

1. An application for the registration of a drug, either locally manufactured or imported, shall be made in writing via a cover letter.

2. The cover letter submitted with the dossier should include a clear statement by the applicant indicating that the information submitted is true and correct.

3. If the applicant is a foreign company, it shall appoint a local agent through whom an application shall be submitted.

4. The local agent shall be a registered pharmaceutical wholesale company or an accredited manufacturer's representative in Ghana.

The application should be submitted through the authorized local agent by the regulatory contact person to the following address:

The Chief Executive Officer
Food and Drugs Authority
P. O. Box CT 2783
Cantonment-Accra

For purposes of submission to FDA, applications are classified into three categories as follows:

New applications for registration
This is an application for registration of a medicinal product that is intended to be placed on the Ghanaian market for the first time.

A new application may only be made by the applicant and he/she shall be the person who signs the declaration portion of FDA application form as per module 1.

A separate application is required for each product. Products that differ in active ingredient(s), strength, dosage forms, proprietary names though containing the same ingredients, are considered to be different products and hence require separate applications.

However, products containing the same active ingredients and the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes require only one application.

A new application for registration shall include submission of:

1. Two electronic copies in a text selectable Portable Document Format (PDF), on a CD Rom and should include MS-Word document for Module 2- see Annex I

2. Samples of the FPP as per FDA sample schedule.

3. Reference standards and impurity standards along with COAs used in the manufacture of FPPs classified as new drugs, new chemical entities and non-pharmacopeial FPPs as well as APIs with response factors should be submitted. The re-test period of the reference standards should have at least 6months re-test period at the time of submission.-

4. Non-refundable application fee for registration of medicines (Refer to FDA fee schedule).

5. Non-refundable GMP inspection fee for facilities not yet inspected by the FDA (Refer to FDA fee schedule).

Applications for Renewal of Registration

Applications for renewal of registration shall be made at least 3 months before the expiry of existing registration by submitting the following:

1. Dully filled application form for renewal of registration.

2. Periodic Safety Update Reports (PSUR)

3. Samples of the product as per the FDA sample schedule

4. Non refundable application fee for registration of medicines (refer to FDA fee schedule).

5. Certificate of analysis of the FPP, long-term stability studies and valid certificate of pharmaceutical product (CoPP)

5. Any other requirements that the FDA may determine from time to time.

Application for Variation of a registered medicinal product
All applications for variation to a registered product shall be made according to requirements stipulated in the FDA Application Guideline for Variation of Registered Medicinal Products.

PAYMENT OF FEES
Every application shall be accompanied by appropriate fees at the time of submission. Any application that is not accompanied by appropriate fees will not be accepted.
If an application for renewal is not made within three years following the expiration of the registration validity, it shall be considered as a new application for registration.

AN OUTLINE OF THE EVALUATION PROCESS

Receiving of new applications
An application consists of documentation in hard copies and electronic copy (a summary of the dossier contents), samples and fees. An application may only be received by FDA upon payment of the application fees.

Evaluation process
The evaluation of applications is done on a first in first out (FIFO) basis unless the product meets the expedited review process as set out in this guideline.

An application may be expedited if the product is for:

a. Public health programmes. These include HIV/AIDS, Malaria, Tuberculosis, reproductive health, Neglected tropical diseases eg Buruli Ulcer, products on the Expanded Programme of Immunization, and any other disease condition that may be determined by the FDA from time to time.

b. Paediatric formulation.

c. Ministry of Health tender purposes only.

d. Post approval variation.

e. Renewal of registration.

The evaluation report produced by the evaluator is peer-reviewed by a second evaluator. The FDA reserves the right to request any additional information to establish the quality, safety and efficacy of medicines.

During evaluation, additional data and/or samples may be requested through a deferral letter. Once a query has been issued to the applicant, the evaluation process stops until the FDA receives a written response to the query.

Further processing of the application may only be made if responses to queries issued in the same deferral letter contains all outstanding information requested in one submission.

Failure to comply with this condition or if the queries have been reissued for a third time and the applicant provides unsatisfactory responses, the application will be **rejected**.

In the event the responses to the queries are not submitted **within six (6) months or a specified time in the respective application deferral letter** from the date they were issued, it will be considered that the applicant has **withdrawn the application**. Thereafter, registration of the product may only be considered upon submission of a new application.

Verification of compliance to current Good Manufacturing Practices (cGMP)
If the new application is from a new manufacturing site, FDA will conduct inspection of the facility or use other means to verify whether the facility complies with cGMP Regulations and/or guideline before a product is registered. No product shall be registered unless the facility complies with cGMP.
The report of the cGMP inspection will form part of the registration process.

Review of application by Product Registration Committee.
Label review, dossier evaluation, laboratory analysis and GMP status reports will be presented before the Drug Registration Committee for review and making final decisions for granting or rejecting registration of the product. In the event, that there are safety, quality or efficacy issues to be resolved as per the decision of the Committee, the application may be deferred pending resolution of the issues. Should the applicant fail to provide the required data within twelve months, it will be considered that the applicant has withdrawn the application. Thereafter, registration of the product may only be considered upon submission of a new application.

The FDA will register the product in the event that data on safety, quality and efficacy is deemed satisfactory by the Product Registration Committee in accordance with Section 118 of the Public Health Act, 2012, Act 851. A certificate of registration shall be issued as per Section 118, subsection 7(c) of the Public Health Act, 2012, Act 851. The registration shall be valid for a period of three (3) years. In the event that the FDA suspends or cancels the registration validity, the FDA will give reasons in writing.

TIMELINES

The following timelines will be implemented by the FDA in processing applications for registration of products.

Processing of Fast track applications – applications under this category shall have a decision made within three (3) months.

Processing of locally manufactured applications- applications under this category shall have a decision made within three (3) months

Processing of new applications (imported medicines)
A decision on a new application will be made within 6months of receipt of the application. The applicant will be required to provide any requested additional data within 6 months. In case additional time is required, a formal request must be submitted to the FDA.

2 Quality summaries

Module 1.4.2: Quality information summary (QIS)

The QIS template should be completed to provide a condensed summary of the key quality informationfor the PD and constitutes part of the submission package. The QIS provides an accurate record of technical data in the PD at the time of registration. The QIS is a condensed version of the QOS-PD and represents the final agreed-upon key information on the API and FPP from the PD assessment (including, but not limited to, identification of the manufacturer(s), site addresses, API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying the requisite information from the corresponding portions of the QOS-PD filed with the PD. It is acknowledged that the numbering of the sections in the QIS may not be entirely sequential. Those sections not considered necessary for inclusion in the QIS have been removed

(e.g. 2.3.S.5 Reference standards or materials) and the remaining sections have retained their original numbering to maintain consistency with the original PD.

The QIS will serve as an official reference document in the course of good manufacturing practices (GMP) inspections, variation assessments and re-registration assessments as performed by FDA.

Module 2.3: Quality overall summary – product dossiers (QOS-PD)

The Quality overall summary (QOS) is a summary that follows the scope and the outline of the Body of data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the Quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

The FDA*Quality overall summary – product dossiers (QOS-PD)* template should be completed for multisource pharmaceutical products containing APIs of synthetic or semi-synthetic origin (see 1.3 Scope for further clarification) and their corresponding FPPs.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths). These tables are included as illustrative examples of how to summarize information. Other approaches can be used to summarize the information if they fulfill the same purpose.

Module 3: Quality

3.1 Table of contents of Module 3

A Table of contents for the filed product dossier should be provided.

3.2 Body of data

3.2.S **Drug substance (or active pharmaceutical ingredient, API)** There are four options for submitting the API information to FDA:

- Option 1: confirmation of API prequalification document;
- Option 2: Certificate of Suitability of the *European Pharmacopoeia* (Ph.Eur.) (CEP); or
- Option 3: active pharmaceutical ingredient master file (APIMF) procedure; or
- Option 4: full details in the PD.

The applicant should clearly indicate at the beginning of the API section (in the PD and in the QOS-PD) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant or FPP manufacturer should include the following according to the options used.

■***Option 1:*** **Confirmation of API prequalification document.**

A complete copy of the Confirmation of API prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.
The applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.
- *3.2.S.2*– if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.
- *3.2.S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.
- *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.
- *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.
- *3.2.S.4.4 Batch analysis* – results from two batches of at least pilotscale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3*.2.S.5 *Reference standards or materials* – information on the FPP manufacturer's reference standards.
- *3.2.S.7 Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

■***Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP)***

A complete copy of the CEP (including any annexes) should be provided in Module 1. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the FDA.
In addition, a written commitment should be included that the applicant will inform FDA in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD.

Also a written commitmentto inform FDA in the event that the CEP is revised, that revisions to the CEP will be handled as per FDA variation guidelines.

The written commitment should accompany the copy of the CEP in Module 1.

Together with the CEP, the applicant should supply the following information in the dossier, with data summarized in the QOS-PD.

- *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant properties of the API that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs according to the guidance in this section.
- *3.2.S.3.1 Elucidation of structure and other characteristics*– studies to identify polymorphs (except where the CEP specifies a polymorphic form) and particle size distribution, where applicable, according to the guidance in this section.

- *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- *3.2.S.4.4 Batch analysis*– results from two batches of at least pilotscale, demonstrating compliance with the FPP manufacturer's API specifications.
- *3.2.S.5Reference standards or materials* – information on the FPP manufacturer's reference standards.
- *3.2.S.6 Container-closure system*– specifications including descriptions and identification of primary packaging components except where the CEP specifies a container-closure system and the applicant declares the intent to use the same container-closure system.
- *3.2.S.7 Stability*– except where the CEP specifies a retest period that is the same as or longer than that proposed by the applicant, and storage conditions are the same or at a higher temperature and humidity than those proposed by the applicant.

  In the case of sterile APIs, data on the process for sterilization of the API including validation data should be included in the PD.

■***Option 3: Active pharmaceutical ingredient master file (APIMF)*** **procedure**

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the API may be submitted as DMF an APIMF by the API manufacturer as outlined in FDA's *Guidelines on active pharmaceutical ingredient master file procedure* (*4*)

In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the PD as an annex to 3.2.S. In addition, the applicant or FPP manufacturer should complete the following sections in the PD and QOS-PD in full according to the guidance provided unless otherwise indicated in the respective sections:

General information S.1.1–S.1.3
Manufacture S.2
Manufacturer(s) S.2.1
Description of manufacturing process and process controls S.2.2
Controls of critical steps and intermediates S.2.4 *Elucidation of structure and other characteristics S.3.1*
Impurities S.3.2
Control of the API S.4.1–S.4.5
Reference standards or materials S.5
Container-closure system S.6
Stability S.7.1–S.7.3

It is the responsibility of the applicant to ensure that the complete APIMF (i.e. both the applicant's Open part and the API manufacturer's Restricted part) is supplied to FDA directly by the API manufacturer and that the applicant has access to the relevant information in the APIMF concerning the current manufacture of the API.
A copy of the letter of access should be provided in the PD Module 1.

APIMF holders can use the guidance provided for the option "Full details in the PD" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs.

■***Option 4:*** **Full details in the PD**

Information on the *3.2.S Active pharmaceutical ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the PD as outlined in the subsequent sections of these guidelines. The QOS-PD should be completed according to section 3.1 of these guidelines.

3.2.S.1 General information (name, manufacturer)

3.2.S.1.1 *Nomenclature (name, manufacturer)*

Information on the nomenclature of the API should be provided. For example:

- **(recommended) International Nonproprietary Name (INN);**
- **compendial name, if relevant;**
- **chemical name(s);**
- **company or laboratory code;**
- **other nonproprietary name(s) (e.g. national name, United States Adopted Name (USAN), British Approved Name (BAN));**
- **Chemical Abstracts Service (CAS) registry number.**

The chemical names listed should be consistent with those appearing in the scientific literature and those appearing on the product labelling information (e.g. in the summary of product characteristics (SmPC) and package leaflet, also known as the patient information leaflet (PIL)). Where several names exist the preferred name should be indicated.

3.2.S.1.2***Structure (name, manufacturer)***

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

This information should be consistent with that provided in section 3.2.S.1.1. For APIs existing as salts the molecular mass of the free base or acid should also be provided.

3.2.S.1.3***General properties (name, manufacturer)***

A list should be provided of physicochemical and other relevant properties of the API.

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed, including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane and acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2–6.8, dose/solubility volume), polymorphism, pH and pKa values, ultraviolet (UV) absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity and partition coefficient (see table in the QOS-PD). This list is not intended to be exhaustive but provides an indication as to the type of information that could be included.

Some of the most relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The physical description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities and quantitative aqueous pH solubility profile

The following should be provided for all options for the submission of API data.

- The solubilities in a number of common solvents should be provided (e.g. in water, alcohols, dichloromethane and acetone).
- The solubilities over the physiological pH range (pH 1.2–6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. from literature references), it should be generated in-house.
- For solid oral dosage forms, the dose/solubility volume should be provided as determined according to the formula:

$$\text{dose/solubility volume} = \frac{\text{largest dosage strength (mg)}}{\text{the minimum concentration of the drug (mg/ml)*}}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2–6.8) and temperature (37 ± 0.5 °C).

According to the Biopharmaceutics Classification System (BCS), highly soluble (or highly water soluble)APIs are those with a dose/solubility volume of ≤ 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5°C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a *BCShighly soluble* API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml = 400 ml).

Polymorphism

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (*5*) the following list explains where specific data should be located in the PD:

- The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3.
- The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant.
- The literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1.
- If a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCShighly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1–3.2.S.4.5.

Additional information is included in the sections mentioned in the above bullet points of these guidelines. In addition, 3.2.P.2.2.3 discusses considerations for control of the polymorphic form of the API in the FPP.

Particle size distribution

As recommended in ICH's *CTD-Q Questions and answers/location issues* document (*5*), the studies performed to determine the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of these guidelines for additional information).

Information from the literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

Reference documents: ICH Q6A (*6*).

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 *Manufacturer(s) (name, manufacturer)*

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing andstorage of the API should be listed. If certain companies are responsible onlyfor specific steps (e.g. milling of the API), this should be clearly indicated. This includes any manufacturing sites responsible for the preparation and supply of intermediates to the API manufacturer.

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The list of manufacturers or companies should specify the *actual addresses* of the production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.

A valid manufacturing authorization for the production of APIs should be provided. If available, a certificate of GMP compliance should be providedin the PD in Module 1. For manufacturers of API intermediates, the basis forestablishing that these sites are operating under GMP should be provided.

3.2.S.2.2 *Description of manufacturing process and process controls (name, manufacturer)*

The description of the API manufacturing process represents the applicant'scommitment for the manufacture of the API. Information should be providedto adequately describe the manufacturing process and process controls. Forexample: a flow diagram of the synthetic process(es) should be provided thatincludes molecular formulae, weights, yield ranges, chemical structures ofstarting

materials, intermediates, reagents and API reflecting stereochemistry,and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process shouldbe submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, processcontrols, equipment and operating conditions (e.g. temperature, pressure,pH, time).

Alternate processes should be explained and described with the samelevel of detail as the primary process. Reprocessing steps should be identifiedand justified. Any data to support this justification should be either referencedor filed in 3.2.S.2.5.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF may be indicated for confidential information. In this case, if detailed information is presented in the Restricted part, the information to be provided for this section of the PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps, including purification procedures. However, for sterile APIs, full validation data on the sterilization process should be provided in the Open part (in cases where there is no further sterilization of the final product).

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

As discussed in ICH Q7 (*7*) the point at which the *API starting material* is introduced into the manufacturing process is the starting point for the application of GMP requirements. The API starting material itself needs to be proposed and its choice justified by the manufacturer and accepted as such by assessors. The API starting material should be proposed taking into account the complexity of the molecule, the proximity of the API starting material to the final API, the availability of the API starting material as a commercial chemical and the quality controls placed upon the API starting material. This justification should be documented in the dossier

In situations where the API starting material is a complex molecule and only a minimal number of synthetic steps from the final API, a further molecule called the starting material for synthesis should be proposed and its choice justified by the applicant. The starting material for synthesis defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as starting materials for synthesis (see section 3.2.S.2.3 for further guidance). In the case where the precursor to the API is obtained by fermentation, or is of plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

A one-step synthesis may be accepted in exceptional cases, for example, where the API starting material is covered by a CEP, or where the API starting material is an API accepted through the APIMF or API prequalification procedure, or when the structure of the API is so simple that a one-step synthesis can be justified, e.g. ethambutol..

In addition to the detailed description of the manufacturing process as per ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites for one API manufacturer,a comprehensive list in tabular form should be provided comparing the processesat each site and highlighting any differences; this includes preparation of theAPI intermediates from external suppliers. The manufacturing details describedin this section should either be declared to be identical for all intermediatemanufacturers involved in the preparation of the API, or each alternativemanufacturing process employed should be described in this section, for eachintermediate manufacturer, using the same level of detail as that supplied for theprimary manufacturing process..

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended; however their use can be justified on presentation of sufficient data demonstrating that recovered solvents meet appropriate standards as outlined in ICH Q7 (*7*).

Where polymorphic or amorphous forms have been identified, the form resulting from the synthesis should be stated.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details) the particle size reduction method(s) (e.g. milling or micronization) should be described.

Justification should be provided for use of alternative manufacturing processes. Alternative processes should be explained with the same level of detail as for the primary process. It should be demonstrated that batches obtained by the alternative processes have the same impurity profile as obtained by the principal process. If the impurity profile obtained is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

It is acceptable to provide information on pilot-scale manufacture, provided it is representative of production scale and scale-up is reported immediately to FDA according to the requirements of the FDA variation guidelines (*9*).

3.2.S.2.3 Control of materials (name, manufacturer)

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate (details in 3.2.A.2).

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section.

The following requirements apply to the fourth option for submission of API information, where full details are provided in the dossier.

The API starting material should be fully characterized and suitable specifications proposed and justified, including, at a minimum, control for identity, assay, impurity content and any other critical attribute of the material.For each API starting material, the name and address of the manufacturing site(s) of the manufacturer(s) should be indicated. A brief description of the preparation of the API starting material should be provided for each manufacturer, including the solvents, catalysts and reagents used. A single set of specifications should be proposed for the starting material that applies to material from all sources. Any future changes to the API starting material manufacturers, mode of preparation or specifications should be notified.
Any future changes to the API starting materialmanufacturers, mode of preparation or specifications should be notified.

In general, the starting material described in the PD should:

- be a synthetic precursor of one or more synthesis steps prior tothe final API intermediate. Acids, bases, salts, esters and similarderivatives of the API, as well as the racemate of a single enantiomerAPI, are not considered final intermediates;

- be a well-characterized, isolated and purified substance with itsstructure fully elucidated including its stereochemistry (whenapplicable);

- have well-defined specifications that include, among others, oneor more specific identity tests and tests and limits for assay andspecified, unspecified and total impurities;
- be incorporated as a significant structural fragment into thestructure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

The carry-over of impurities of the starting materials for synthesis into the final API should be considered and discussed.

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are without risk of transmitting agents of animal spongiform encephalopathies.

When available a CEP demonstrating compliance with recommendations on transmissible spongiform encephalopathy (TSE) should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q6A (*6*).

3.2.S.2.4 Controls of critical steps and intermediates (name, manufacturer)

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Where the APIMF procedure is used, a cross-reference to the Restricted partof the APIMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant (*4*).

The following requirements apply to the fourth option for submission of API information where full details are provided in the dossier.

The critical steps should be identified. These can include: steps where significant impurities are removed or introduced; steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation; steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

Reference documents: ICH Q6A (*6*).

3.2.S.2.5***Process validation and/or evaluation (name, manufacturer)***

Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

Where the APIMF procedure is used, a cross-reference to the Restricted part of the APIMF is considered sufficient for this section of the PD.

The following requirements apply to the fourth option for submission of API information where full details are provided in the dossier.

The manufacturing processes for all APIs are expected to be properly controlled. If the API is prepared as sterile, a complete description should be provided of the aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternative processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 *Manufacturing process development (name, manufacturer)*

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or biowaiver, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the API data provided in Section 3.2.S.4.4.

Where the APIMF procedure is used, a cross-reference to the Restricted partof the DMF~~APIMF~~ is considered sufficient for this section of the PD.

3.2.S.3 Characterization (name, manufacturer)

3.2.S.3.1 *Elucidation of structure and other characteristics (name, manufacturer)*

Confirmation of structure based on, e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Elucidation of structure

The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data from the studies performed to elucidate and/or confirm the structure of the API. The QOS-PD should include a list of the studies performed and a conclusion from the studies (e.g. whether the results support the proposed structure).

For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

For APIs that are described in an officially recognized pharmacopoeia it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with an officially recognized pharmacopoeial reference standard. See section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the comparative biostudies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identicality of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for interconversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided, such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API processability, pharmaceutical product manufacturability and product quality and performance, including stability, dissolution and bioavailability. The unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants filing for marketing authorization with the FDAand API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly soluble.* In the absence of published data for APIs that are not

BSC highly soluble, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize thepolymorphic forms of an API. Demonstration of a non-equivalent structure bysingle crystal X-ray diffraction is currently regarded as the definitive evidenceof polymorphism. XRPD can also be used to provide unequivocal proof ofpolymorphism. Other complementary methods, including microscopy, thermalanalysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) andspectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR))are helpful to further characterize polymorphic forms. Where polymorphismis a concern, the applicants/manufacturers of APIs should demonstrate that asuitable method, capable of distinguishing different polymorphs, is availableto them.

Decision tree 4(1) of ICH Q6A (*6*) can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the FPP and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the API batches used in comparative bioavailability or biowaiver studies by the above-mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:

- specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated API including appropriate limits on the weight ratio of API to solvent (with data to support the proposed limits);

- a description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs that are not *BCShighly soluble* contained in solid FPPs, or liquid FPPs containing undissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behaviour of the FPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the API should be provided, including characterization of the batch(es) used in the comparative bioavailability or biowaiver studies. API specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically, based on the standard deviation of the test results from the previously mentioned studies. The following example is provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X µm;
- d50 XX µm–XXX µm;
- d90 not less than (NLT) 90% of total volume less than XXXX µm.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.

Reference documents: ICH Q6A (*6*).

3.2.S.3.2***Impurities (name, manufacturer)***

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines (*10*–*12*). Additional information elaborating on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins of the impurities. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.

The tables in the QOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the QOSPD, the term “origin” refers to how and where the impurity was introduced (e.g. “Synthetic intermediate from Step 4 of the synthesis” or “Potential by-product due to rearrangement from Step 6 of the synthesis”). It should also be indicated if the impurity is a metabolite of the API.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the API. For APIs available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products the maximum hourly dose of the API should also be included.

It is acknowledged that APIs of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the API and the extent of the chemical modification steps, the principles regarding the control of impurities (e.g. reporting, identification and qualification) could be extended to

apply to APIs of semi-synthetic origin. As an illustrative example, an API whose precursor molecule was derived from a fermentation process or a natural product of plant or animal origin, which has subsequently undergone several chemical modification reactions, would generally fall within the scope of the ICH impurity guidelines, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not. It is understood that there is some latitude for these types of APIs.

Identification of impurities

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph. As a result each PD is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis. For these reasons the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having an MDD ≤ 2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph, which could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an officially recognized pharmacopoeiais generally considered to be qualified.The following is an additional option for qualification of impurities in existing APIs:

The limit for an impurity present in an existing API can be accepted by comparing the results of tests for impurities found in the existing API with those observed in an innovator product using the same validated, stabilityindicating analytical procedure (e.g. comparative (high-performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the impurity profile may also be compared to a

different registered FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. samples of a similar age) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or registered FPPare not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or registered FPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) according to the applicable ICH guidelines (e.g. Q3A (*10*), Q3C (*12*)).

The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the API from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. In cases where a large number of batches have been tested it is acceptable to summarize the results of all the batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided (e.g. “Impurities D, E and F listed in *The International Pharmacopoeia* (Ph.Int.) monograph are not potential impurities from the proposed route of synthesis used by manufacturer X”). If acceptable

justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of the impurities listed in the pharmacopoeia.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last step solvents used in the process should always be routinely controlled in the final API.

For guidance on acceptable residual solvent limits refer to ICH Q3C (*12*). The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C option I or 3.2 mg/day on the basis of permitted daily exposure (PDE).

The absence of known, established highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidance (e.g. EMEA/CHMP/QWP/ 251344/2006 (*13*) or USFDA Guidance for Industry. *Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches*(*14*)) or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the FPP (e.g. an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents (EMEA/CHMP/SWP/4446/2000 (*15*)) or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, good distribution practices (GDP) or any other

relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents: ICH Q6A, Q3A, Q3C (*6*, *10*, *12*).

3.2.S.4 Control of the API (name, manufacturer)

3.2.S.4.1 *Specification (name, manufacturer)*

The specification for the API should be provided.

As defined in ICH's Q6A guideline (*6*), a specification is:

> ''A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. 'Conformance to specifications' means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.''

Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control or quality assurance department) should be provided in the PD, including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS-PD template under the headings: tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

- The *standard* declared by the applicant could be an officially recognized compendial standard (e.g. BP, JP, Ph.Eur., Ph.Int., USP) or an in-house (manufacturer's) standard.
- The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC or laser diffraction), the source refers to the origin of the analytical procedure (e.g. BP, JP, Ph.Eur., Ph.Int., USP or in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified together with the proposal on the frequency of non-routine testing.

The ICH Q6A guideline (*6*) outlines recommendations for a number of universal and specific *tests* and criteria for APIs.

Reference documents: ICH Q6A, Q3A, Q3C (*6*, *10*, *12*) and officially recognized pharmacopoeias.

3.2.S.4.2***Analytical procedures (name, manufacturer)***

The analytical procedures used for testing the API should be provided.

Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided. Unless modified it is not necessary to provide copies of officially recognized compendial analytical procedures.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, gas chromatography (GC) methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. *2.3.R.2)*. These tables should be used to summarize the in-house analytical procedures of the FPP manufacturer for determination of the residual solvents, assay and purity of the API, in section 2.3.S.4.2 of the QOS-PD. Other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and thin-layer chromatography (TLC) can also be used if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantified against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the API as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the API, i.e. between 80 and 120%. In cases where the response factor is outside this range it may still be acceptable to use the API, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in-house method. Unspecified impurities may be quantified using a solution of the API as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%). The test for related substances in the Ph.Int. monograph for lamivudine serves as a typical example.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the satisfactory performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods

should include SSTs for resolution and repeatability. For HPLC methods to control API-related impurities, this is typically done using a solution of the API with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternative peaks can be used if justified (e.g. choice of a toxic impurity). In accordance with the Ph.Int. section on Methods of analysis the repeatability test should include an acceptable number of replicate injections. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution. For TLC methods, the SSTs should verify the ability of the system to separate and detect the analyte(s) (e.g. by applying a spot corresponding to the API at a concentration corresponding to the limit of unspecified impurities).

Reference documents: ICH Q2 (*16*), *WHO Technical Report Series*, No. 943, Annex 3 (*17*).

3.2.S.4.3 *Validation of analytical procedures (name, manufacturer)*

Analytical validation information, including experimental data for the analytical procedures used for testing the API, should be provided.

Copies should be provided of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay and impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. *2.3.R.2)*. These tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS-PD.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated as suitable to control the impurity profile of the API from the intended source(s).

In general verification is not necessary for compendial API assay methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognized compendial standard is claimed and an inhouse method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalence of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For impurity methods the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference documents: ICH Q2 (*16*).

3.2.S.4.4 ***Batch analyses (name, manufacturer)***

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date and production site of relevant API batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scaleup and, if available, production-scale batches. These data are used to establish the specifications and evaluate consistency in API quality.

Analytical results should be provided from at least two batches of at least pilot scale from each proposed manufacturing site of the API and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The FPP manufacturer's test results should be summarized in the QOS-PD.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

Reference documents: ICH Q6A, Q3A, Q3C,(*6*, *10*, *12*)

3.2.S.4.5***Justification of specification (name, manufacturer)***

Justification for the API specification should be provided.

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially recognized compendial standard(s). If the officially recognized compendial methods have been modified or replaced a discussion of the modifications or replacement method(s) should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. for impurities or particle size distribution) and does not need to be repeated here, although a cross-reference should be provided.

Reference documents: ICH Q6A, Q3A, Q3C (*6*, *10*, *12*), and officially recognized pharmacopoeias.

3.2.S.5 *Reference standards or materials (name, manufacturer)*

Information on the reference standards or reference materials used for testing of the API should be provided.

Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP manufacturer in routine API and FPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity and assay tests). These could be classified as primary or secondary reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. BP, JP, Ph.Eur., Ph.Int., USP) where one exists, and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API and/or the FPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR and mass spectrometry (MS) analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference

substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water/solvent free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantified by an assay procedure, e.g. HPLC or DSC) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

Reference standards should normally be established for specified impurities. Refer to 3.2.S.4.2 for additional guidance.

Reference documents: ICH Q6A (*6*), *WHO Technical Report Series*, No. 943, Annex 3 (*17*).

3.2.S.6 Container-closure system (name, manufacturer)

A description of the container-closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction.

The WHO *Guidelines on packaging for pharmaceutical products* (*18*) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for APIs.

Primary packaging components are those that are in direct contact withthe API or FPP. The specifications for the primary packaging components shouldbe provided and should include a specific test for identification (e.g. IR).

The name and address of the manufacturer of the API should be stated on the container, regardless of whether relabelling is conducted at any stage duringthe API distribution process.

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 *Stability summary and conclusions (name, manufacturer)*

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

The WHOguidelines *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (*19)* should be consulted for recommendations on the core stability data package required for the prequalification of APIs and FPPs.

As outlined in the FDA stability guidelines, the purpose of stability testing is to: “provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light.”

The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions and commitments).

Stress testing

As outlined in the ICH Q1A guidance document (*20*), stress testing of the API can help identify the likely degradation products which, in turn, can help to establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Stress testing may be carried out on a single batch of the API. For examples of typical stress conditions refer to section 2.1.2 of *WHO Technical Report Series*, No. 953, Annex 2, section 2.1.2 (*19*), as well as, “A typical set of studies of the degradation paths of an active pharmaceutical ingredient”, in: *WHO Technical Report Series*, No. 929, Annex 5, Table A1 (*21*).

The objective of stress testing is not to completely degrade the API but to cause degradation to occur to a small extent, typically 10–30% loss of API by assay when compared with non-degraded API. This target is chosen so that some degradation occurs, but not enough to generate secondary products. For this reason the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition.

The tables in the QOS-PD template should be used to summarize the results of the stress testing and should include the treatment conditions (e.g. temperatures, relative humidities, concentrations of solutions and durations) and the observations for the various test parameters (e.g. assay, degradation products). The discussion of results should highlight whether mass balance was observed.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B (*22*). If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API, it is sufficient to state “protect from light” on labelling, in lieu of photostability studies when the container-closure system is shown to be light protective.

When available it is acceptable to provide the relevant data published in the scientific literature (including, but not limited to, WHO Public Assessment Reports (WHOPARs), European Public Assessment Reports (EPARs)) to support the identified degradation products and pathways.

Accelerated and long-term testing

Available information on the stability of the API under accelerated and longterm storage conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified.

The storage conditions and the lengths of studies chosen should besufficient to cover storage and shipment. Refer to the WHO *stability guidelines*in WHO Technical Report Series, No. 953, Annex 2, (1*9*).

To establish the retest period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The stability testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the tables in the QOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container-closure system and completed (and proposed) test intervals. The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. Ranges of analytical results where relevant and any trends that were observed should be included. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or

"conforms". Where methods are different from those described in S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

Refer to WHO Technical Report Series, No. 953, Annex 2, (19),for further information regarding the minimum data required at the time of submitting the dossier, storage conditions, container-closure system, test specifications and testing frequency

Proposed storage statement and retest period

A storage statement should be established for display on the label, based on the stability evaluation of the API. The FDA stability guidelines include a number of recommended storage statements that should be used when supported by the stability studies.

A retest period should be derived from the stability information and should be displayed on the container label.

After this retest period a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf-life than a retest period (ICHQ1A *20*).

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be done at the time of assessment of the PD, if justified. Applicants should consult the ICH Q1E guideline (*23*) for further details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated conditions and the data show

little or no variability, the proposed retest period could be up to twice the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Reference documents: ICH Q1A (*20*), Q1B (*22*), Q1D (*24*), Q1E (*23*), *WHO Technical Report Series*, No. 953, Annex 2 (*19*).

3.2.S.7.2 *Post-approval stability protocol and stability commitment (name, manufacturer)*

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available long-term stability data on primary batches do not cover the proposed retest period granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the retest period. A written commitment (signed and dated) to continue long-term testing over the retest period should be included in the dossier when relevant.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted through the proposed retest period on at least three production batches. Where stability data were not provided for three production batches, a written commitment (signed and dated) should be included in the dossier.

The stability protocol for the commitment batches should be provided and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;

- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains stable and can be expected to remain stable within the retest period in all future batches.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability. In certain situations, additional batches should be included. A written commitment (signed and dated) to ongoing stability studies should be included in the dossier.

Refer to section 2.1.11 of *WHO Technical Report Series*, No. 953, Annex 2 (*19*), for further information on ongoing stability studies.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference documents: ICH Q1A (*20*), Q1B (*22*), Q1D (*24*), Q1E (*23*), *WHO Technical Report Series*, No. 953, Annex 2 (*19*).

3.2.S.7.3 *Stability data (name, manufacturer)*

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

The actual stability results used to support the proposed retest period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests) it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”.

Reference documents: ICH Q1A (*20*), Q1B (*22*), Q1D (*24*), Q1E (*23*),*WHO Technical Report Series*, No. 953, Annex 2 (*19*).

3.2.P **Drug product (or finished pharmaceutical product (FPP))**

3.2.P.1 **Description and composition of the FPP (name, dosage form)**

A description of the FPP and its composition should be provided. The information provided should include, for example:

- **Description of the dosage form**

  The description of the FPP should include the physical description, available strengths, release mechanism (e.g. immediate or modified (delayed or extended)), as well as any other distinguishable characteristics, e.g.

  “The proposed XYZ 50-mg tablets are available as white, oval, filmcoated tablets, debossed with ‘50’ on one side and a break-line on the other side.

  The proposed XYZ 100-mg tablets are available as yellow, round, film-coated tablets, debossed with ‘100’ on one side and plain on the other side.”

- **Composition, i.e. list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications).**

  The tables in the QOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and a percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables where applicable.

  All components used in the manufacturing process should be listed, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "contains 2% overage of the API to compensate for manufacturing losses").

  The components should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and, if applicable, their grades (e.g. "microcrystalline cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilized or emulsified).

  The function of each component (e.g. diluent or filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent or antimicrobial preservative) should be stated. If an excipient performs multiple functions the predominant function should be indicated.

  The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends or imprinting inks). This information (excluding the

solvents) is to be listed in the product information (e.g. summary of product characteristics, labelling and package leaflet).

■**Description of accompanying reconstitution diluent(s)**

For FPPs supplied with reconstitution diluent(s) that are commercially available or that have been assessed and considered acceptable in connection with another PD with the FDA,a brief description of the reconstitution diluents(s) should be provided.

For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another PD with the FDA, information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

■**Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g.

> "The product is available in HDPE bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s) (cards of 5 × 2, 10 cards per package)."

Reference documents: ICH Q6A (*6*).

3.2.P.2 Pharmaceutical development (name, dosage form)

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

Pharmaceutical development information should include, at a minimum:

- the definition of the quality target product profile (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 critical quality attributes (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 drug product of the desired quality;
- discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product (ICH Q8) (*25*).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs reference should be made to section 6.3.2 of *WHO Technical Report Series,* No. 929, Annex 5 ~~(*21*)~~.

Reference documents: ICH Q6A (*6*), Q8 (*25*), Q9 (*26*), Q10 (*27*).

3.2.P.2.1 ***Components of the FPP (name, dosage form)***

3.2.P.2.1.1 ***Active pharmaceutical ingredient (name, dosage form)***

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

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

Guidance on compatibility studies is provided in Appendix 3 of the WHO *Guidelines for registration of fixed-dose combination medicinal products* (*WHO Technical Report Series*, No. 929, Annex 5, 2005) (*21*). 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. in the SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 ***Excipients (name, dosage form)***

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

When choosing excipients those with a compendial monograph are generally preferred and may be required in certain jurisdictions. Other resources are available for information on acceptable excipients and their concentrations, such as the US Food and Drug Administration (FDA) inactive ingredient guide (IIG) list (*28*) and the *Handbook of pharmaceutical excipients* (*29*). Use of excipients in concentrations outside established ranges is discouraged and generally requires justification (*30*). In addition, available guidelines should be referenced which discuss particular excipients to be avoided, for example azo-colourants as listed in the EMA Guideline CPMP/463/00 (*31*). Other guidance such as the WHO *Guidelines on development of paediatric medicines: (WHO Technical Report Series, No. 970, 2012, Annex 5)*(*32*) may provide useful general guidance in this regard.

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

Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.

Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2.P.2.2 *Finished pharmaceutical product (name, dosage form)*

3.2.P.2.2.1 *Formulation development (name, dosage form)*

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

dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed, when appropriate.

The FDAdefines an established pharmaceutical 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 and QOS-PD should be completed with the exception of P.2.2.1 (a). In addition, a product quality review should be provided as outlined in Appendix 2.

The requirements for bioequivalence studies should be taken into consideration, for example, when formulating multiple strengths and/or when the product(s) may be eligible for a biowaiver. WHO reference documents (e.g. *WHO Technical Report Series*, No. 937, Annex 7) (*33*) should be consulted.

Product scoring may be recommended or required, for example, when scoring is included as part of SmPC of comparator products, or when division into fractional doses may be necessary according to approved posology.

If the proposed FPP is a functionally scored tablet a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity for split portions containing less than 5 mg or less than 5% of the weight of the dosage unit portion, or mass uniformity for other situations) 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. SmPC, labelling and package leaflet) should reflect the presence of a score.

If splitting of a tablet is intended for preparation of 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 the tablet into equal doses.

Additional quality data may be required to support special dosinginstructions (for example, crushing) stated in product information.

In vitro dissolution or drug release

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

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed and medium) should be provided. Data should also 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. Use of a single point test or a dissolution range should be justified based on the solubility and/ or biopharmaceutical classification of the API.

For slower dissolving immediate-release products (e.g. Q = 80% in 90 minutes), a second time point may be warranted (e.g. Q = 60% in 45 minutes).

Delayed release (enteric coated) products are intended to resist gastricfluid but disintegrate in intestinal fluid; therefore dissolution should includeacid and buffer phases with separate criteria for each. Refer to compendialmonographs for examples.

Modified-release FPPs should 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 should 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 point, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 20% or ±10% of thetargeted value. Dissolution results should be submitted for several lots, includingthose lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

3.2.P.2.2.2***Overages (name, dosage form)***

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

Justification of an overage to compensate for loss during manufacture should be provided, including information on 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 (name, dosage form)***

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.
When polymorphism is an issue for the API as discussed in 3.2.S.3.1, it may be necessary to provide information on the form present in the FPP, for example,when the manufacturing process may affect the form. Such studies may not benecessary when sufficient information has been provided on the polymorphismobserved during API stability studies.

3.2.P.2.3***Manufacturing process development (name, dosage form)***

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

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

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

For products that meet the criteria of an established pharmaceutical product,in order to fulfil the requirements of section P.2.3, section P.2.3 (b) of the dossier and QOS-PD should be completed and a product quality review should be submitted as outlined in Appendix 2. 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. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence FPP quality and performance should 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 scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time and granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ICH Q8 ~~(25)~~).

3.2.P.2.4***Container-closure system (name, dosage form)***

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

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

- Glass containers: USP <660>

  Ph.Eur. 3.2.1: (34, *35*);
- Plastic containers: Ph.Eur. 3.2.2, 3.2.2.1(*36*, *37*);

  USP <661>, <671>
- Rubber/elastomeric closures: USP <381>

  Ph.Eur. 3.2.9 (*38*, *39*).

Table A6.1 outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure

Table 2 outlines the general recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials.

Table A6.1

General recommendations for the various dosage forms for one-time studies to establish the suitability of the container-closure system contact materials

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

× Information should be submitted. – Information does not need to be submitted.

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

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

For solid oral dosage forms and solid APIs, compliance with regulations on plastic materials coming into contact with food (for example (EU) No. 10/2011 (*40*)) can be considered acceptable.

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

A dosage device is required to be included with the container-closure system for administration of oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules), 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.’’

For a device accompanying a multidose container, the results of a study should be provided demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume), generally at the lowest intended dose.

A sample of the device should be provided with Module 1.

3.2.P.2.5 *Microbiological attributes (name, dosage form)*

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

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of studies on 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 Ph.Eur. 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 stability guidelines (*WHO Technical Report Series*, No. 953, Annex 2, 2009 (*19*)), 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 (name, dosage form)*

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

Where a dosage device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders or granules for such 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.

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

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 *Manufacturer(s) (name, dosage form)*

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated (*WHO good distribution practices for pharmaceutical products* (*41*)).

The list of manufacturers or companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

For a mixture of an API with an excipient, the blending of the API with the excipient is considered to be the first step in the manufacture of the final product and, therefore, the mixture does not fall under the definition of an API. The only exceptions are in the cases where the API cannot exist on its own. Similarly, for a mixture of APIs, the blending of the APIs is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be listed in this section.

A valid manufacturing authorization for pharmaceutical production, as well as a marketing authorization, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements (Module 1, 1.2.2).

For each site where the major production step(s) are carried out, when applicable, attach a WHO-type certificate of GMP issued by the competent authority in terms of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (Module 1, 1.2.2).

Justification for any differences to the product in the country or countries issuing the WHO-type certificate(s)

When there are differences between the product for which this application is submitted and that marketed in the country or countries which provided the WHO-type certificate(s), it is necessary to provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for example for differences in site of manufacture, specifications and formulation. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

A listing should be provided of the countries in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1, 1.2.2).
Reference documents: WHO Technical Report Series, No. 961, Annex 3 (*42*) and No. 957, Annex 5 (*41*).

3.2.P.3.2***Batch formula (name, dosage form)***

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the FPP for each proposed commercial batch size and to express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen or silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. “1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses”).

The components should be declared by their proper or common names, quality standards (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and, if applicable, their grades (e.g. “Microcrystalline cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized or emulsified).

3.2.P.3.3***Description of manufacturing process and process controls (name, dosage form)***

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges

for critical steps should be justified in Section 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP (product prior to final packaging, e.g.tablets in HDPE drums)should be stated. The holding time should be supported by the submission of stability data if longer than 30 days. For an aseptically processed FPP, sterile filtration of the bulk and filling into final containers should preferably be continuous; any holding time should be justified.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

The information above should be summarized in the QOS-PD template and should reflect the production of the proposed commercial batches. See Glossary (section 2) for definitions of pilot-scale and production-scale batches.

For the manufacture of sterile products the class (e.g. A, B or C) of the areas should be stated for each activity (e.g. compounding, filling and sealing), as well as the sterilization parameters, including for equipment, container-closure system and terminal sterilization.

Reference documents: ICH Q8 (*25*), Q9 (*26*), Q10 (*27*).

3.2.P.3.4***Controls of critical steps and intermediates (name, dosage form)***

Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Examples of applicable in-process controls include:

- granulations: moisture (limits expressed as a range), blend uniformity (e.g. low-dose tablets), bulk and tapped densities and particle size distribution;
- solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- semi-solids: viscosity, homogeneity, pH;
- transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;
- metered dose inhalers: fill weight or volume, leak testing, valve delivery;
- dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;
- liquids: pH, specific gravity, clarity of solutions;
- parenterals: appearance, clarity, fill volume or weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, prefiltration and/or pre-sterilization bioburden testing.

Reference documents: ICH Q2 (*16*), Q6A (*6*), Q8 (*25*), Q9 (*26*), Q10 (*27*), *WHO Technical Report Series*, No. 929, Annex 5 (*21*).

3.2.P.3.5***Process validation and/or evaluation (name, dosage form)***

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g. validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

For products that meet the criteria of an established pharmaceutical product, a product quality review as outlined in Appendix 2 may be submitted in lieu of the information below.

The following information should be provided for all other products:

a. a copy of the process validation protocol, specific to this FPP, described below;
b. a commitment that three consecutive, production-scale batches of this FPP will be subjected to prospective validationin accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification after registration by the FDA inspection team;
c. if the process validation studies have already been conducted (e.g. for sterile products), a copy of the process validation report should be provided in the PD in lieu of a. and b. above.

One of the most practical forms of process validation, mainly for nonsterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then analysed statistically to verify the “normality” of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Certain product characteristics may occasionally be skip-tested. Thus, subvisual particulate matter in

parenteral preparations may be determined by means of electronic devices, or tablets or capsules tested for their dissolution profile if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme would need to be revalidated once further scale-up is proposed after marketing approval is granted.

The process validation protocol should include, but not be limited to, the following:

- a reference to the current master production document;
- a discussion of the critical equipment;
- the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;
- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender or storage bins for uniformity testing of the final blend);
- the testing parameters and acceptance criteria including inprocess and release specifications and comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
- the analytical procedures or a reference to appropriate section(s) of the dossier;
- the methods for recording and evaluating results;
- the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs to take place in a well-controlled manufacturing area (e.g. a strictly controlled environment using highly reliable procedures and with appropriate in-process controls). A

detailed description of these conditions, procedures and controls should be provided, together with actual copies of the standard operating procedures for the following:

- washing, treatment, sterilization and depyrogenation of containers, closures and equipment;
- filtration of solutions;
- lyophilization process;
- leaker test of filled and sealed ampoules;
- final inspection of the product;
- sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral FPPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide) or radiation. It should be noted that terminal steam sterilization, when practical, is considered to be the method of choice to ensure sterility of the final FPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as Fo range, temperature range and peak dwell time for an FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, bacteria retention, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic processing of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling containers with culture media under normal conditions, followed by incubation. Refer to current WHO GMP guidelines for details.

Reference documents: ICH Q8 (*25*), Q9 (*26*), Q10 (*27*), *WHO Technical Report Series*, No. 961, Annex 3 (*42*).

3.2.P.4 Control of excipients (name, dosage form)

3.2.P.4.1 *Specifications (name, dosage form)*

The specifications for excipients should be provided.

The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final FPP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen or silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph.

If the standard claimed for an excipient is a non-compendial standard (e.g. in-house standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.

For products submitted to the FDA for registration, only excipients with an officially recognized pharmacopoeial monograph should be used. Exceptions may be justified.

For excipients of natural origin, microbial limit testing should be included in the specifications. Skip-testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soy bean oil or peanut oil) the absence of aflatoxins or biocides should be demonstrated.

The colours permitted for use are limited to those listed in the “Japanese pharmaceutical excipients”, the European Union (EU) “List of permitted food colours”, and the FDA “Inactive ingredient guide”. For proprietary mixtures, the supplier’s product sheet with the qualitative formulation should be submitted, in addition to the FPP manufacturer’s specifications for the product, including identification testing.

For flavours, the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU regulations).

Information that is considered confidential may be submitted directly to the FDAby the supplier who should make reference in the cover letter to the specific related product.

Other certifications of at-risk components may be required on a case-bycase basis.

If additional purification is undertaken on commercially available excipients, details of the process of purification and modified specifications should be submitted.

Reference documents: ICH Q6A (*6*).

3.2.P.4.2***Analytical procedures (name, dosage form)***

The analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for thetesting of excipients, with the exception of the validation of in-house methodswhere appropriate.

Reference document: ICH Q2 (*16*).

3.2.P.4.3***Validation of analytical procedures (name, dosage form)***

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

Reference document: ICH Q2 (~~*16*~~).

3.2.P.4.4***Justification of specifications (name, dosage form)***

Justification for the proposed excipient specifications should be provided, where appropriate.

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

3.2.P.4.5***Excipients of human or animal origin (name, dosage form)***

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, viral safety data) (details in 3.2.A.2).

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If the excipients are of plant origin a declaration to this effect will suffice.

For excipients of animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are without risk of transmitting agents of animal spongiform encephalopathies.. Materials of animal origin should be avoided whenever possible.

When available a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

Reference documents: ICH Q5A (*43*), Q5D (*44*), Q6B (*45*), WHO Technical Report Series, No. 908, Annex 1 (*46*).

3.2.P.4.6 *Novel excipients (name, dosage form)*

For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (non-clinical and/or clinical) should be provided according to the API and/or FPP format (details in 3.2.A.3).

The FDAmay choose not to accept the use of novel excipients in submitted PDs. For the purpose of these guidelines, a novel excipient is onethat has not been used (at a similar level and by the same route of administration) in a product approved by an SRA or WHO. If novel excipients are accepted, fullinformation should be provided in 3.2.A.3.

3.2.P.5 Control of FPP (name, dosage form)

3.2.P.5.1 *Specification(s) (name, dosage form)*

The specification(s) for the FPP should be provided.

As defined in ICH's Q6A guideline, a specification is:

> ''a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an API or FPP should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the API and/or FPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical

quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.''

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance department) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of the shelf-life.

The specifications should be summarized according to the tables in the QOS-PD template including the tests, acceptance criteria and analytical procedures (listing types, sources and versions for the methods).

- The standard declared by the applicant could be an officially recognized compendial standard (e.g. BP, JP, Ph.Eur., Ph.Int., USP) or an in-house (manufacturer's) standard.
- The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV or HPLC); the source refers to the origin of the analytical procedure (e.g. BP, JP, Ph.Eur., Ph.Int., USP, in-house) and the version (e.g. code number/version/ date)should be provided for version control purposes.

ICH's Q6A guideline outlines recommendations for a number of *universal* and *specific tests* and criteria for FPPs. Specifications should include, at a minimum, tests for appearance, identification, assay, purity, performance tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability and particle size), uniformity of dosage units, and, as applicable, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance on specific tests that are not addressed by ICH's Q6A guideline:

- fixed-dose combination FPPs (FDC-FPPs):
  - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
  - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should in general be calculated with reference to the worst case (the API with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards,
  - a test and limit for content uniformity is required for each API present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit,
  - for the API(s) present at ≥ 5 mg and ≥ 5% of the weight of the dosage unit, a test and limit for weight variation may be established in lieu of content uniformity testing;
- modified-release products: a meaningful API release method;
- inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in vivo studies where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- suppositories: uniformity of dosage units, melting point;
- transdermal dosage forms: peel or shear force, mean weight per unit area and dissolution.

Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is ± 5% of the label claim (i.e. 95.0–105.0%).

For products such as tablets, capsules and suppositories where a test for uniformity of single-dose preparations is required, a test and limit for content uniformity is required when the API is present in the FPP at less than 5 mg or less than 5% of the weight of the dosage unit. Otherwise, the test for mass uniformity may be applied.

Skip-testing is acceptable for parameters such as identification of colouring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When justification for skip-testing has been accepted the specifications should include a footnote, stating, at a minimum, the following skip-testing requirements: at least every tenth batch and at least one batch annually is tested. In addition, for stabilityindicating parameters such as microbial limits, testing will be performed at release and at the end of shelf-life during stability studies.

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Reference documents: ICH Q3B (*11*), Q3C (*12*), Q6A (*6*).

3.2.P.5.2 *Analytical procedures (name, dosage form)*

The analytical procedures used for testing the FPP should be provided.

Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified it is not necessary to provide copies of analytical procedures described in officially recognized compendia.

Tables for summarizing a number of the different analytical procedures and the validation information (e.g. HPLC assay and impurity methods) can be found in the 2.3.R Regional information section of the QOS-PD

(i.e. 2.3.R.2). These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

Refer to section 3.2.S.4.2 of these guidelines for additional guidance on analytical procedures.

Reference document: ICH Q2 (*16*).

3.2.P.5.3***Validation of analytical procedures (name, dosage form)***

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP, should be provided.

Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay and impurity methods, and GC methods) can be found in the 2.3.R Regional information section of the QOSPD (i.e. *2.3.R.2*). These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the FPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. The same API or FPP obtained from different sources can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalence of the in-house and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For methods for the determination of related compounds, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference document: ICH Q2 (*16*).

3.2.P.5.4 *Batch analyses (name, dosage form)*

A description of batches and results of batch analyses should be provided.

Information on relevant FPP batches used to establish the specifications and evaluate consistency in manufacturing should be provided and should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches).

Analytical results generated by the company responsible for the batch release of the FPP (generally the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot scale, or in the case of an uncomplicated[1] FPP (e.g. immediate-release solid FPPs (with noted exceptions), or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

[1] The term "complicated FPP" includes but not limited to sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Other specific products under "complicated FPP" include ritonavir/lopinavir FDC tablets and FDCs containing rifampicin or an artemisinin. Please contact the FDA in case of doubt

The testing results should include those of tests on the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the PD and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. The discussion should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A ranged from 0.2 to 0.4%”). Dissolution results should be expressed, at a minimum, as both the average and the range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Appendix 1.

A discussion and justification should be provided for any incomplete analyses (e.g. for any parameters not tested according to the proposed specification).

Reference documents: ICH Q3B (*11*), Q3C (*12*), Q6A (*6*).

3.2.P.5.5 ***Characterization of impurities (name, dosage form)***

Information on the characterization of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

Reference documents: ICH Q3B (*11*), Q3C (*12*), Q6A (*6*).

3.2.P.5.6 *Justification of specification(s) (name, dosage form)*

Justification for the proposed FPP specification(s) should be provided.

A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, and differences from the officially recognized compendial standard(s). If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products or dissolution method development) may have been discussed in other sections of the PD and would not need to be repeated here, although a cross-reference should be provided.

ICH Q6A (*6*) should be consulted for the development of specifications for FPPs.

3.2.P.6 *Reference standards or materials (name, dosage form)*

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in "3.2.S.5 Reference standards or materials".

See section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

Reference documents: ICH Q6A (*6*), *WHO Technical Report Series*, No. 943, Annex 3 (*17*).

3.2.P.7 Container-closure system (name, dosage form)

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should

include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

The WHO *Guidelines on packaging for pharmaceutical products* (*18*) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP manufacturer) should be provided for the packaging components that are:

- in direct contact with the dosage form (e.g. container, closure, liner, desiccant and filler);
- used for drug delivery (including the device(s) for multidose solutions, emulsions, suspensions and powders or granules for reconstitution into solution, emulsion or suspension;
- used as a protective barrier to help ensure stability or sterility;
- necessary to ensure FPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the API or FPP.

The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

Information to establish the suitability (e.g. qualification) of the containerclosure system should be discussed in section 3.2.P.2. Comparative studies may be warranted for certain changes in packaging components (e.g. a comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability summary and conclusions (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

The WHO stability guidelines *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (*19*) should be consulted for recommendations on the core stability data package required for the registration of APIs and FPPs.

As outlined in the WHO stability guidelines, the purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of productrelated factors that influence the quality of the API or FPP, for example, interaction of API with excipients, container-closure systems and packaging materials.

Stress testing

As outlined in the WHO stability guidelines, photostability testing should be conducted on at least one primary batch of the FPP if appropriate. If “protect from light” is stated in one of the officially recognized pharmacopoeias for the API or FPP it is sufficient to state “protect from light” on labelling, in lieu of photostability studies, when the container-closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products or freeze–thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV. Refer to *WHO Technical Report Series*, No. 953, Annex 2, Appendix 1 (*7*) for information on climatic zones. the required long-term storage conditions for GHANA are 30 ºC ± 2 ºC/75% ± 5% RH. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in the WHO stability guidelines for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below −20 °C should be treated on a case-by-case basis.

Table 3

Minimum data required at the time of submitting the dossier (in the general case)

Storage temperature (ºC)	Relative humidity (%)	Minimum time period (months)
Accelerated 40 ± 2	75 ± 5	6

Long-term	30 ± 2	75 ± 5	6

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Refer to *WHO Technical Report Series*, No. 953, Annex 2 (19) for further information regarding the storage conditions. Reference should also be made to the WHO Prequalification of Medicines Programme web site for any exceptions to the stated requirements.

To establish the shelf-life, data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The stability testing programme should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the QOS-PD. Bracketing and matrixing of proportional strengths can be applied if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test point. Weight loss from plastic containers should be reported over the shelf-life.

Any in-use period and associated storage conditions should be justified with experimental data, for example, after opening, reconstitution and/or dilution of any sterile and/ormultidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000s). If applicable, the in-use period and storage conditions should be stated in the product information.

The information on the stability studies should include details such as

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- container-closure system including orientation (e.g. erect, inverted, on-side) where applicable;
- completed (and proposed) test intervals.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. The discussion should include ranges of analytical results and any trends that were observed. For quantitative tests (e.g. individual and total degradation product tests and assay tests) actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”. Dissolution results should be expressed, at a minimum, as both the average and range of individual results.

Applicants should consult ICH’s Q1E guideline (23) for details on the evaluation and extrapolation of results from stability data (e.g. if significant change was not observed within 6 months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to twice the period covered by the long-term data, but should not exceed the long-term data by more than 12 months).

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided.

The recommended labelling statements for use based on the stability studies, are provided in the WHO stability guidelines (*19*).

Reference documents: *WHO Technical Report Series*, No. 953, Annex 2 (*19*), ICH Q1A (*20*), Q1B (*22*), Q1C (*47*), Q1D (*24*), Q1E (*23*), Q3B (*11*), Q6A (*6*).

3.2.P.8.2 *Post-approval stability protocol and stability commitment (name, dosage form)*

The post-approval stability protocol and stability commitment should be provided.

Primary stability study commitment

When the available data on long-term stability of primary batches do not cover the proposed shelf-life granted at the time of assessment of the PD, a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

Commitment stability studies

The long-term stability studies for the commitment batches should be conducted throughout the proposed shelf-life on at least three production batches of each strength in each container-closure system. Where stability data were not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability studies

As described in the FDA stability guidelines and*WHO Technical Report Series*, No. 953, Annex 2 (19), an ongoing stability programme is established to monitor the product over its shelf-life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every

container-closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

Any differences between the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

Reference document: ICH Q1A ~~(*20*)~~.

3.2.P.8.3 *Stability data (name, dosage form)*

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterization of impurities is located in 3.2.P.5.5.

The actual stability results and reports used to support the proposed shelf-life should be provided in the PD. For quantitative tests (e.g. individual and total degradation product tests and assay tests), actual numerical results should be provided rather than vague statements such as “within limits” or “conforms”.

Dissolution results should be expressed, at a minimum, as both the average and range of individual results.

Reference documents: ICH Q1A ~~(*20*)~~, Q1B ~~(*22*)~~, Q1C ~~(*47*)~~, Q1D ~~(*24*)~~, Q1E ~~(*23*)~~, Q2 ~~(*16*)~~.

3.2.A **Appendices**

3.2.A.1 Facilities and equipment

Not applicable (i.e. not a biotech product).

3.2.A.2 Adventitious agents safety evaluation

3.2.A.3 Novel excipients

Novel excipients are not accepted by the FDA.

3.2.R Regional information

3.2.R.1 Production documentation

3.2.R.1.1 *Executed production documents*

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules), should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For solid oral dosage forms, pilot scale is generally, at a minimum, one-tenth that of full production scale or 100 000 tablets or capsules, whichever is the larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrate the uniformity of this batch. The data to establish the uniformity of the biobatch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided where relevant.

3.2.R.1.2***Master production documents***

Copies of the FPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

- master formula;
- dispensing, processing and packaging sections with relevant material and operational details;
- relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
- identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);
- process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range));
- list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;

- sampling plan with regard to the:
  - steps at which sampling should be done (e.g. drying, lubrication and compression),
  - number of samples that should be tested (e.g. for blend uniformity testing of low-dose FPPs, blend drawn using a sampling thief from x positions in the blender),
  - frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
- precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);
- for sterile products, reference to standard operating procedures (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;
- theoretical and actual yield;
- compliance with the GMP requirements.

Reference document: WHO Technical Report Series, No. 961 (*48*).

3.2.R.2 Analytical procedures and validation information

The tables presented in section 2.3.R.2 in the QOS-PD template should be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3 where relevant.

4.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the PD when appropriate.

References

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6. *ICH harmonised tripartite guideline: specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances – Q6A*. International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
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10. *ICH harmonised tripartite guideline: impurities in new drug substances – Q3A*. International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.
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19. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953).
20. *ICH harmonised tripartite guideline: stability testing of new drug substances and products – Q1A*. International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.
21. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: *WHO Expert Committee on*

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22. ICH harmonised tripartite guideline: *Stability testing: Photostability testing of new drug substances and products – Q1B*. International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.
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Appendix 1

Recommendations for conducting and assessing comparative dissolution profiles

The dissolution measurements of the two FPPs (e.g. test and reference (comparator) or two different strengths) should be made under the same test conditions. A minimum of three time-points (zero excluded) should be included, the time-points for both reference (comparator) and test product being the same. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30, 45 (60, 90, 120) minutes). The 15-minute time-point is critical to determine whether a product is very rapidly dissolving and to determine whether f_2 must be calculated. For extendedrelease FPPs, the time-points should be set to cover the entire duration of expected release, e.g. 1, 2, 3, 5 and 8 hours for a 12-hour release and additional test intervals for longer duration of release.

Studies should be performed in at least three media covering the physiological range, including pH 1.2 hydrochloric acid, pH 4.5 buffer and pH 6.8 buffer. *International Pharmacopoeia* buffers are recommended; other pharmacopoeial buffers with the same pH and buffer capacity are also accepted. Water may be considered as an additional medium, especially when the API is unstable in the buffered media to the extent that the data are unusable.

If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar (no calculations required). Otherwise:

- Similarity of the resulting comparative dissolution profiles should be calculated using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1+1/n \sum^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t are the mean per cent API dissolved in reference (comparator) and test product, respectively, at each time-point. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar.

- A maximum of one time-point should be considered when 85% dissolution of the reference (comparator) product has been reached. In the case where 85% dissolution cannot be reached due to poor solubility of the API, the dissolution should be conducted until an asymptote (plateau) has been reached.
- At least 12 units should be used for determination of each profile. Mean dissolution values can be used to estimate the similarity factor, f_2. To use mean data, the percentage coefficient of variation at the first time-point should be not more than 20% and at other time-points should be not more than 10%.
- When delayed-release products (e.g. enteric coated) are being compared, the recommended conditions are acid medium (pH 1.2) for 2 hours and buffer pH 6.8 medium.
- When comparing extended-release beaded capsules, where different strengths have been achieved solely by means of adjusting the number of beads containing the API, one condition (normally the release condition) will suffice.
- Surfactants should be avoided in comparative dissolution testing. A statement that the API is not soluble in any of the media is not sufficient and profiles in the absence of surfactant should be provided. The rationale for the choice and concentration of surfactant should be provided. The concentration of the surfactant should be such that the discriminatory power of the test will not be compromised.

Appendix 2

Product quality review requirements for *established multisource products*

For an established multisource product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and
QOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with no fewer than 10 consecutive batches manufactured over the period of the past 12 months or, where 10 batches were not manufactured in the past 12 months, no fewer than 25 consecutive batches manufactured over the period of the past 36 months and should include at least:

- a review of starting and primary packaging materials used in the FPP, especially those from new sources;
- a tabulated review and statistical analysis of quality control and inprocess control results;
- a review of all batches that failed to meet established specification(s);
- a review of all critical deviations or non-conformances and related investigations;
- a review of all changes carried out to the processes or analytical methods;
- a review of the results of the stability-monitoring programme;

- a review of all quality-related returns, complaints and recalls, including export-only medicinal products;
- a review of the adequacy of previous corrective actions;
- a list of validated analytical and manufacturing procedures and their revalidation dates.

Notes

- Reviews must include data from all batches manufactured during the review period.
- Data should be presented in tabular or graphical form, when applicable.
- The above listing of requirements is specific to the dossier assessment process requirements and does not relieve the applicant of related GMP requirements.