



FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REGISTRATION OF ALLOPATHIC DRUGS

(HUMAN & VETERINARY)

JUNE 2012

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1 OBJECTIVE

This revised guideline presents a common format for the preparation of an application that will be submitted to the Food and Drugs Authority (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.

SCOPE

This revised guideline is developed in pursuance of Section 118 of the Public Health Act, 2012, Act 851, 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.

LIST OF ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
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
C_{max}: 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 Conference 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

In the context of this guideline, the following words/phrases are defined as follows.

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 37°C

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.

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

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 - British Pharmacopoeia, United States Pharmacopoeia, Extra Pharmacopoeia, International Pharmacopoeia and European Pharmacopoeia.

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.

Innovator pharmaceutical product: Means a pharmaceutical product, which was first registered (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of registration).

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 chemical or biologically Active Pharmaceutical Ingredient (API) that has not previously been registered as an ingredient of any pharmaceutical product.

New drug: means a generic copy of an innovator product:

- i) That has not been previously registered as a pharmaceutical or biological product in Ghana, or
- ii) Which has been marketed in Ghana for a period of not less than ten (10) years or any other period to be determined by the Authority from time to time, for public health reasons

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.

INTRODUCTION

This guideline applies only to allopathic drugs. This guideline prescribes the minimum information required for submission of documentation as well as the appropriate format and organisation of the requisite data.

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.

In this new format, each application is organised into modules, together with the associated technical guidelines. Applicants should not modify the overall organisation of this format.

Applicants are requested to carefully read this guideline, fill in application form, prepare dossier and submit one original hard-copy and one electronic copy (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.

The guideline is divided into 5 modules:

- Module 1: Administrative information and prescribing information
- Module 2: Common technical document summaries
- Module 3: Quality
- Module 4: Non-Clinical study reports for New Chemical Entities Only
- Module 5: Clinical Study Reports

The annexes are:

- Annex I: Application form for Registration of Allopathic Drug
- Annex II: Model Stability Report for Active Pharmaceutical Ingredients (APIs)
- Annex III: Model Stability Report for Finished Pharmaceutical Products
- Annex IV: Labelling Guidelines
- Annex V: Application form for renewal of registration
- Annex VI: Guidelines on variation
- Annex VII: Summary of Product Characteristics
- Annex VIII: Package insert
- Annex IX: Sample schedule
- Annex X: FDA Guideline for Interchangeability of generic drugs

- Annex XI: Labelling template
- Annex XII: Stability studies Guidelines

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 printed submission, information, data, tables, diagrams, attachments must be legible of font size 12 or more and shall be presented on A4 and 80g/m² paper. 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.

Dossiers should be securely **bound** and **arranged** sequentially and could be submitted in separately bound volumes for the different parts but shall be numbered serially (eg volume 1 of 2) for ease of reference. The dossier covers shall be made of a material which is thick and hard enough not to collapse in standing position.

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. One original hard-copy and one electronic copy 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 standard for new chemical entities.
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. Refer to annex V
2. Submit 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. 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. Annex VI

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 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 twelve (12) months** 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 Drug 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 Drug 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 Expedited review applications – applications under this category shall be processed within three (3) months.

Processing of new applications

A new application will be processed within 6 months of receipt of the application. The applicant will be required to provide any requested additional data within 12 months. In case additional time is required, a formal request must be submitted to the FDA.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.0. Cover letter

1.1 Table of contents of the application including module 1 (module 1-5)

1.2 Application information

1.2.1 Trade/Proprietary name

Trade/Proprietary name means the (trade or brand) name which is unique to a particular drug and by which it is generally identified. Refer to FDA Guidelines for labelling.

1.2.2 Approved / INN / generic name

Approved / INN / generic name means the internationally recognised non-proprietary name of such a drug.

1.2.3 Dosage form of the product

Dosage form of the product shall mean the form in which the drug is presented, eg. eye drops, emulsion, ointment, suppository, tablet, capsule, solution, suspension, injections.

1.2.4 Strength of the product

Strength of the product shall be given per unit dosage form or per specified quantity: e.g. mg per tablet, mg per capsule, mg per ml, mg per 5ml, mg per gram, etc.

1.2.5 Commercial presentation

Commercial presentation of the product shall mean the presentation of the product to be registered i.e. list all pack sizes intended for marketing. eg 10 x 1tablets, 10 x 10tablets, 10 x 1 capsules, 200mls, 1ml vial etc.

1.2.6. Nature and content of container

The container/closure description should include all parts of the primary packaging including desiccant, void filler or adsorbent cotton filler. Dimensions/volume/capacity may be listed. Shape and colour of the bottle and the cap type (including plastic e.g. PP), should be stated. E.g.: Blisters: colour and transparent/opaque, with number of units per card and cards per box.]

[e.g. sealed LDPE bag, placed inside a round white HDPE bottle with plain PP screw cap and aluminium tagger (packs of 100 Tablets & 1000 Tablets)]

1.2.7 Description of the drug

Description of the drug shall mean a full visual appearance of the drug as marketed including colour, size, shape and other relevant features [e.g.: White coloured, biconvex capsule-shaped film-coated tablet having a score on one side and “XL 5” debossed on the other side.]

1.2.8 Country of Origin

Country of Origin means the country of manufacture or production, of the medicine to be registered or country of product release.

1.2.9 Category of distribution

POM (Prescription only medicines)

P (Pharmacist initiated medicine)

OTC (Over-the-counter medicine)

1.2.10 Pharmacological classification and indication

Specify clinical indication(s) which are supported by relevant information in Module 2 and 5 of the application dossier.

1.2.11 Proposed Shelf life of the product

Proposed Shelf life of the product means the specified length of time prior to use for which pharmaceutical products are inherently subject to deterioration are deemed to remain fit for use under prescribed conditions.

1.2.12 Applicant

The name, physical address, telephone number, fax number, and e-mail address of the applicant/license holder.

1.2.13 Name and complete address(es) of the manufacturer(s) of the FPP

The name, physical address, telephone number, fax number, and e-mail address of the manufacturer shall be provided.

Where different activities of manufacture of a given product are carried out at different manufacturing sites, the information on the following should be provided.

- Name of the Manufacturer
- Full Physical address of the Manufacturing Site
- Activity at the manufacturing site

A copy of a valid manufacturing License shall be provided for each site. Only products entirely manufactured at sites that are cGMP compliant by FDA shall be eligible for registration.

1.2.14. Manufacturing and registration/international registration status

The applicant shall provide the regulatory situation of the medicine to be registered in the country of origin and other countries.

List the countries in which this product:

- Has been registered. (Attach Certificate (s) of registration)
- Has been withdrawn from any market
- Where an application for marketing in any country has been rejected, suspended, deferred or withdrawn.

Also attach a valid Certificate of Pharmaceutical Product from the country of origin as per the WHO certification scheme and issued in the name of Ghana or with Ghana included in the list of importing countries.

In the case of loan license manufacturing, the following should also be submitted;

- A copy of the valid manufacturing contract agreement
- Supporting documentation from the competent drug regulatory authority for the manufacturing licence code.

1.2.15 Copy of Certificate (s) of Suitability of the European Pharmacopoeia (CEP) (including any annexes)

The latest, valid European Certificate of Suitability (CEP) (including any annexes) should be provided where applicable.

1.2.16 Authorised Local Representative (local agent)

Every applicant who is not resident in Ghana shall appoint one local representative who must be a company incorporated in Ghana and authorized by FDA to import medicinal products and must hold a wholesale dealers License.

1.2.17 Declaration

The applicant/license holder should indicate that the information submitted is true and correct. Information on the name, position and signature of the applicant should be provided. The application should be dated and stamped by the applicant.

1.3 Prescribing information

1.3.1 Product information for Health Professionals (For All Products subject to Medical Prescription)

Provide copies of the proposed Summary of Product Characteristics (SmPC – see Annex VII for structure) aimed at medical practitioners and health professionals. It should be written in English, should be legible, indelible and comprehensible.

The SmPC is an essential part of registration and cannot be altered without the prior approval of FDA through a post approval variation.

1.3.2 Patient information leaflet

Provide four (4) copies of package insert (PIL -see Annex VIII) and any information intended for distribution with the product to the patient. The patient information leaflet (PIL) should be in conformity with the SmPC. It should be written in English, should be legible, indelible and comprehensible.

The PIL is an essential part of registration and cannot be altered without the prior approval of FDA through a post approval variation.

1.3.3. Labelling (outer and inner labels)

Provide four (4) copies of the proposed outer and inner labels. It should be written in English, should be legible, indelible and comprehensible.

The labelling is an essential part of registration and cannot be altered without the prior approval of FDA through a post approval variation.

1.4 Samples

Samples of the product and certificate of analysis of the FPP (s) and measuring devices as per the FDA sample schedule (refer Annex IX) should be provided for laboratory analysis and also to enable visual inspection of the product and product package.

All products submitted for registration shall have at least 60% of its shelf life remaining. This notwithstanding, products with a shelf life of less than 24 months shall have at least 80% of its shelf life remaining at the time of submission.

MODULE 2: CTD SUMMARIES- CHEMICAL, PHARMACEUTICAL, NON-CLINICAL AND CLINICAL OVERVIEWS AND SUMMARIES

2.1 CTD Table of contents (module 2-5)

2.2 CTD Introduction

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

2.3 QUALITY OVERALL SUMMARY (QOS)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of Module 3. The QOS should not include detailed information, data or justification that will be included in Module 3 or in other modules of the document.

The QOS should include sufficient information from each section to provide the Quality Evaluator with an overview of Module 3. The QOS should also emphasise critical key parameters of the product and provide, for instance, justification in cases where guideline 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, including cross-referencing to volume and page number in other Modules.

The QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

2.3.S DRUG SUBSTANCE (ACTIVE PHARMACEUTICAL INGREDIENT)

2.3.S.1 General Information

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture

Information from 3.2.S.2 should be included:

- Information on the manufacturer
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- *A flow diagram, as provided in 3.2.S.2.2;*
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4.
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.

A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterisation

For NCE:

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included.

When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

For NCE and Biotech:

The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System

A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (name, dosage form)

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture

Information from 3.2.P.3 should include:

- Information on the manufacturer.
- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.
- *A flow diagram, as provided under 3.2.P.3.3.*
- A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (name, dosage form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (name, dosage form)

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (name, dosage form)

A brief description and discussion of the information in 3.2.P.7 should be included.

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

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment

Biotech:

A summary of facility information described under 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation

A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

2.3.A.3 Excipients

2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under “3.2.R” should be included, where appropriate.

2.4 OVERVIEW AND SUMMARY OF NON CLINICAL AND CLINICAL DOCUMENTATION

General Principles of Nonclinical Overview and Summaries

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical product, and the implications of the nonclinical findings for the safe use of the pharmaceutical product (i.e., as applicable to labelling) should be addressed in the Overview.

2.4.1 NEW CHEMICAL ENTITIES ONLY

2.4.1.1 NONCLINICAL OVERVIEW

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed 30 pages.

General Aspects

The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical product. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from this guideline should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects.

This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed.

For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guideline. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries.

2.4.1.1.2 Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

- Overview of the nonclinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, anti-product antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed.

Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, C_{max}, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to:

- Pharmacodynamics
- toxic signs
- causes of death
- pathologic findings
- genotoxic activity- the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data

- the carcinogenic risk to humans- if epidemiologic data are available, they should be taken into account
- fertility, embryofetal development, pre-and post-natal toxicity
- studies in juvenile animals
- the consequences of use before and during pregnancy, during lactation, and during pediatric development
- local tolerance
- other toxicity studies/ studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect / phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- animal species used
- numbers of animals used
- routes of administration employed
- dosages used
- duration of treatment or of the study
- systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended.
- the effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

2.5 CLINICAL OVERVIEW

Preamble

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarisation of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the

strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should:

- Describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- Assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.
- Provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).
- Provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage risks.
- Address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved.
- Explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them.
- Explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

Table of Contents

- 2.5.1 Product Development Rationale
- 2.5.2 Overview of Biopharmaceutics
- 2.5.3 Overview of Clinical Pharmacology
- 2.5.4 Overview of Efficacy
- 2.5.5 Overview of Safety
- 2.5.6 Benefits and Risks Conclusions
- 2.5.7 Literature References

Refer ICH M4E_R1 for detailed discussion of content of the clinical overview section.

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Nonclinical Written Summaries

Introduction

This guideline is intended to assist authors in the preparation of nonclinical pharmacology,

pharmacokinetics, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasised that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

General Presentation Issues

Order of Presentation of Information within Sections

- When available, in vitro studies should precede in vivo studies.
- Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Non-human primate
- Other non-rodent mammal
- Non-mammals

Routes of administration should be ordered as follows :

- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures.

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries

Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100-150 pages.

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Refer ICH M4S_R2 for detailed discussion of content of the non-clinical written and tabulated summaries.

2.7 : CLINICAL SUMMARY

Preamble

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions.

The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

Table of Contents

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

- 2.7.1.1 Background and Overview
- 2.7.1.2 Summary of Results of Individual Studies
- 2.7.1.3 Comparison and Analyses of Results Across Studies
- 2.7.1.4 Appendix

2.7.2 Summary of Clinical Pharmacology Studies

- 2.7.2.1 Background and Overview
- 2.7.2.2 Summary of Results of Individual Studies
- 2.7.2.3 Comparison and Analyses of Results Across Studies
- 2.7.2.4 Special Studies
- 2.7.2.5 Appendix

2.7.3 Summary of Clinical Efficacy

- 2.7.3.1 Background and Overview of Clinical Efficacy
- 2.7.3.2 Summary of Results of Individual Studies
- 2.7.3.3 Comparison and Analyses of Results Across Studies
- 2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations
- 2.7.3.5 Persistence of Efficacy and/or Tolerance Effects
- 2.7.3.6 Appendix

2.7.4 Summary of Clinical Safety

- 2.7.4.1 Exposure to the Drug
- 2.7.4.2 Adverse Events
- 2.7.4.3 Clinical Laboratory Evaluations
- 2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety
- 2.7.4.5 Safety in Special Groups and Situations
- 2.7.4.6 Post-marketing Data
- 2.7.4.7 Appendix

2.7.5 Literature References

2.7.6 Synopses of Individual Studies

Refer ICH M4E_R1 for detailed discussion of content of the clinical summary.

MODULE 3: CHEMICAL-PHARMACEUTICAL DOCUMENTATION

This module is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products.

3.1 TABLE OF CONTENTS OF MODULE 3

A Table of Contents for the filed application should be provided.

3.2 BODY OF DATA

The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guideline.

3.2.1 PARTICULARS OF ACTIVE PHARMACEUTICAL INGREDIENT(S) [API(S)]/ DRUG SUBSTANCE

The information on the API can be submitted according to the following order of preference:

- Provide the latest, valid European Certificate of Suitability (CEP) with all annexes.
- Provide a Drug Master File(s) [DMF(s)] submitted by the API manufacturer.

Certificates of Suitability of the European Pharmacopoeia (CEP)

The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant who refers to the CEP.

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

Along with the CEP the applicant should supply the following information in the dossier, with data summarized in the QOS

- *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and PhEur monograph, e.g. solubilities and polymorphs as per guidance in this section.
- *3.2.S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per 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 PhEur monograph and any additional tests and acceptance criteria that are not controlled in the CEP and PhEur 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 tests 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 pilot scale, 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.6 Container-closure system* – specifications including descriptions and identification of primary packaging components.
- *3.2.S.7 Stability* – exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

Drug Master File (DMF) for the active pharmaceutical ingredient

Provide a Drug Master File(s) [DMF(s)] submitted by the API manufacturer. The DMF should contain all the information listed under **Section 3.2.S**

For use of the DMF option, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.

For a drug product containing more than one drug substance, the information requested for both options —3.2.1 above should be provided in its entirety for each drug substance.

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

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

- Recommended International Nonproprietary Name (INN);
- Compendial name if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
- Chemical Abstracts Service (CAS) registry number.

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

3.2.S.1.2 Structure

NCE & Generics:

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.

Biotech:

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

3.2.S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

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, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc. 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 more relevant properties to be considered for APIs are discussed below in greater detail.

Physical description

The 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/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. water, alcohols, dichloromethane, acetone).

The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. literature references), it should be generated in-house.

For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

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

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature ($37 \pm 0.5^\circ\text{C}$).

As per the Biopharmaceutics Classification System (BCS), *highly soluble (or highly water soluble)* APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at $37 \pm 0.5^\circ\text{C}$, 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 *BCS highly soluble* API as its dose/solubility volume is greater than 250 ml ($400 \text{ mg}/1.0 \text{ mg/ml} = 400 \text{ ml}$).

Polymorphism

As recommended in ICH's *CTD-Q Questions and answers/location issues* document the following refers to *where* specific data should be located in the product dossier:

- 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 *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

Additional information is included in the referenced sections of this guideline.

Particle size distribution

As recommended in ICH's *CTD-Q Questions and Answers/Location Issues* document, the studies performed to identify the particle size distribution of the API should be provided in Section 3.2.S.3.1 (refer to this section of this guideline for additional information).

Information from literature

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

Reference ICH Guidelines: Q6A and Q6B
WHO Generic guideline 2012

3.2.S.2 Manufacturer

3.2.S.2.1 Manufacturer(s)

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 and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API), this should be clearly indicated.

The list of manufacturers/companies should specify the *actual addresses* of 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 licence should be provided for the production of APIs. If available, a certificate of GMP compliance should be provided in the dossier in Module 1.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

NCE and Generic drugs:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be 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, process controls, equipment and operating

conditions (e.g., temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

As discussed in ICH Q7 and WHO Technical Report Series, No. 957 Annex 2, the point at which the *API starting material* is introduced into the manufacturing process is the starting point of 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*.

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 from fermentation, or is from plant or animal origin, such a molecule can be considered the API starting material regardless of complexity.

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences.

Biotech:

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps,

equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3, major equipment (details provided in 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in 3.2.S.2.4.)

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4.).

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used for storage of the drug substance (details in 3.2.S.6.) and storage and shipping conditions for the drug substance should be described.

Reference ICH Guidelines: Q5A, Q5B, and Q6B

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

Materials used in the manufacture of the drug substance (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 (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterisation. (Details in 3.2.A.2 for both NCE and Biotech).

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the dossier, 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 dossier.

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

Reference ICH Guidelines: Q6A and Q6B
WHO Generic guide 2012

Biotech:

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information for biologically-sourced materials should be provided. (Details in 3.2.A.2.)

Source, history, and generation of the cell substrate

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.

Cell banking system, characterisation, and testing

Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s)) should be provided as described in Q5B and Q5D.

Reference ICH Guidelines: Q5A, Q5B, Q5C and Q5D

3.2.S.2.4 Controls of Critical Steps and Intermediates

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.

The critical steps should be identified. These can be among others: 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 ICH Guidelines: Q6A and Q6B
WHO Generic Guidance 2012

Additionally for Biotech: Stability data supporting storage conditions should be provided.
Reference ICH Guideline: Q5C

3.2.S.2.5 Process Validation and/or Evaluation

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

Biotech:

Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2.S.2.6 Manufacturing Process Development

NCE and Generics:

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q3A

Biotech:

The developmental history of the manufacturing process, as described in 3.2.S.2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see Q6B for additional guidance). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q6B

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

NCE and Generics:

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 dossier should include quality assurance (QA) certified and legible copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The dossier should include a list of the studies performed and a conclusion from the studies (e.g. if 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 identity 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 racemisation 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 centers 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/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants 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 *BCS 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 the polymorphic forms of an API. Demonstration of a nonequivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance [ssNMR]) are helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

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 *BCS highly 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 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 ICH Guideline: Q6A
WHO Generic Guide 2012

Biotech:

For desired product and product-related substances, details should be provided on primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.
Reference ICH Guideline: Q6B

3.2.S.3.2 Impurities

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. Additional information to provide further guidance 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. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the

API monograph.

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* on the control of impurities (e.g. reporting, identification and qualification) could also be extended 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 that has subsequently undergone *several* chemical modification reactions generally would fall within this scope, whereas an API whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. 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 product dossier 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 a maximum daily dose =2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that 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 pharmacopoeia* is 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 impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different prequalified 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. age of samples) 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 prequalified FPP are 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 prequalified 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) as per the applicable ICH guidelines (e.g. Q3A, Q3C).

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 the cases where a large number of batches have been tested it is acceptable to summarize the results of the total number of 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 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 pharmacopoeial listed impurities.

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. 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 guidances (e.g. EMEA/CHMP/QWP/251344/2006 or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches, December 2008) 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 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, 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 Q3A, Q3C, Q6A and Q6B
WHO Generic guidance 2012

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

The specification for the API 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.”

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 dossier including specifications from each API manufacturer as well as those of the FPP manufacturer.

The FPP manufacturer(s) API specification could be summarized in a tabular form 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 or a 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, laser diffraction), the *source* refers to the origin of the analytical procedure 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 along with the proposal on the frequency of non routine testing.

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

Reference documents: ICH Q3A, Q3C, Q6A, FDA officially recognised list of publications WHO Generic guidance 2012

3.2.S.4.2 Analytical Procedures

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 dossier, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided.

Although HPLC is normally considered the method of choice for determining API-related impurities, other chromatographic methods such as GC and 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 quantitated 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 quantitated 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 system suitability tests (SSTs) represent an integral part of the method and are used to ensure the adequate 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 alternate 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
WHO Generic guidance 2012

3.2.S.4.3 Validation of Analytical Procedures

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

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 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 in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalency 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 analyzed should be the API spiked with impurities at concentrations equivalent to their specification limits.

Reference ICH Guidelines: Q2A, Q2B, and Q6B
WHO Generic guidance 2012

3.2.S.4.4 Batch Analyses

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, scale-up and, if available, production-scale batches.

This data is 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 dossier.

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 ICH Guidelines: Q3A, Q3C, Q6A, and Q6B
WHO Generic guidance 2012

3.2.S.4.5 Justification of Specification

A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc. 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 may have been discussed in other sections of the dossier (e.g. impurities, particle size distribution) and does not need to be repeated here, although a cross-reference to their location should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A and Q6B
WHO Generic guidance 2012

3.2.S.5 Reference Standards or Materials

Information should be provided on the reference standard(s) used to generate data in the dossier, 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, 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 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, 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 (quantitated by an assay procedure, e.g. HPLC, DSC, etc.) 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 ICH Guidelines: Q6A and Q6B
WHO Generic drug guidance 2012

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 drug substance, including sorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

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 WHO guideline *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* should be consulted for recommendations on the core stability data package required for product registration.

Stress testing of the API can help identify the likely degradation products, which can in turn help 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.

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 active 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.

Photostability testing should be an integral part of stress testing. The standard conditions are described in ICH Q1B. If “protect from light” is stated in one of the officially recognized pharmacopoeia 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.

Accelerated and long-term testing

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

The required long-term storage conditions for APIs for the registration of the product is either $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$ or $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$. Studies covering the proposed re-test period at the above mentioned long-term storage conditions will provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to WHO Zone IVb. Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30°C is inappropriate for the API. For APIs intended for storage in a refrigerator and those intended for storage in a freezer refer to the FDA stability guideline. APIs intended for storage below -20°C should be treated on a case-by-case basis.

To establish the re-test 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 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 dossier.

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

Proposed storage statement and re-test period

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

A re-test period should be derived from the stability information and should be displayed on the container label.

For APIs known to be labile (e.g. certain antibiotics), it is more appropriate to establish a shelf-life rather than a re-test period

Reference ICH Guidelines: Q1A, Q1B, Q1D, Q1E and Q5C
WHO Generic guidance 2012

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

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

When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

Where the submission includes long-term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary.

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); and

- applicable parameters specific to the API.

Any differences in 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, Q1B, Q1D, Q1E
WHO Generic drug guidance

3.2.S.7.3 Stability Data

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 re-test 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, Q1B, Q1D, Q1E, Q2
WHO Generic drug guidance.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

A description of the drug product 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, modified (delayed or extended)), as well as any other distinguishable characteristics.

- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any with justification) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer’s specifications)
- Description of accompanying reconstitution diluent(s)
For FPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable, information on the diluent(s) should be provided in a separate FPP portion (“3.2.P”), as appropriate.

- 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.

Reference ICH Guidelines: Q6A and Q6B
WHO Generic drug guidance 2012

3.2.P.2 Pharmaceutical Development

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 application. 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 drug product 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 application.

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 lifecycle of the product (ref: ICH Q8).

For a discussion of additional pharmaceutical development issues specific to the development of Fixed-Dose Combinations, reference should be made to WHO Technical Report Series, No. 929, Annex 5, Section 6.3.2.

Reference documents: ICH Q6A, Q6B, Q8, Q9 and Q10
WHO Generic drug guidance 2012

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The compatibility of the drug substance 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 drug substance that can influence the performance of the drug product should be

discussed.

For fixed-dose combinations, the compatibility of drug substances with each other should be discussed.

In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. SmPC or product leaflet) that the excipients are present in the comparator product.

3.2.P.2.1.2 Excipients

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

When choosing excipients, those with a compendial monograph are generally preferred. Use of excipients in concentrations outside of established ranges is discouraged and generally requires justification.

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

3.2.P.2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical 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 requirements for bioequivalence studies should be taken into consideration example when formulating multiple strengths and/or when the product is eligible for a biowaiver.

For product that have a functional score or break line, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the dossier 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.

The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand).

The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the FPP specification(s). The tablet description in the FPP specification and in the product information (e.g. summary of product characteristics, labelling, package leaflet) should reflect the presence of a score.

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

Where relevant in the case of non-functional, labelling should state that the score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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, 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). 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 period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or $\pm 12.5\%$ of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Reference: WHO Generic drug guidance 2012

3.2.P.2.2.2 Overages

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 the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

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

3.2.P.2.2.3 Physicochemical and Biological Properties

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

3.2.P.2.3 Manufacturing Process Development

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

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

Provide the formulation in tabular form for a typical batch and for an administration unit, e.g. one tablet, 5 ml of oral solution, or the contents of an ampoule or bag of large volume parenteral solution.

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, 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.

Reference: ICH Q8).

WHO Generic drug guidance 2012

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

Plastic containers: Ph Eur 3.2.2, 3.2.2.1, USP <661>

Rubber/Elastomeric closures: USP <381> , Ph Eur 3.2.9

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

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

A device is required to be included with the container closure system for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such), any time the package provides for multiple doses.

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

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

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 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 guideline (WHO Technical Report Series, No. 953, Annex

2, 2009), 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.

Reference: WHO Generic drug guidance

3.2.P.2.6 Compatibility

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

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

3.2.P.3.1 Manufacturer(s)

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.

The list of manufacturers/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 included in this section.

A valid manufacturing licence for pharmaceutical production, as well as a registration certificate, 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*).

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/countries which provided the WHO-type certificate(s), 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 differences in site of manufacture, specifications, formulation, etc. Note that only minor differences are likely to be acceptable. Differences in container labelling need not normally be justified.

Regulatory situation in other countries

The countries in which the product has been registered, withdrawn from the market and/or application for registration been rejected, deferred or withdrawn should be listed (*Module 1*).

Reference: WHO Generic drug guidance 2012

3.2.P.3.2 Batch Formula

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.

Provide a table in the application form to summarize the batch formula of the FPP for each proposed commercial batch size and 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, 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.

Ph.Int., Ph.Eur., BP, USP, JP, In-House) and, if applicable, their grades (e.g. “Microcrystalline Cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilised, emulsified).

3.2.P.3.3 Description of Manufacturing Process and Process Controls

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 homogeniser) 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 prior to final packaging 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.

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

Additionally for Biotech see 3.2.A.1 for facilities, if appropriate.

Reference ICH Guideline: Q6B, ICH Q8, Q9, Q10
WHO Generic drug guidance 2012

3.2.P.3.4 Controls of Critical Steps and Intermediates

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, 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/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; and
- parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bioburden testing.

Reference documents: ICH Q2, Q6A, Q8, Q9, Q10,
WHO Generic drug guidance 2012

3.2.P.3.5 Process Validation and/or Evaluation

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 sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2A.2, if necessary.

The following information should be provided for all other products:

- a) a copy of the *process validation protocol*, specific to an FPP, described below;
- b) a *commitment* that three consecutive, production-scale batches of the FPP will be subjected to *prospective validation* in 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; and
- 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 dossier in lieu of (a) and (b) above.

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 will need to be re-validated once further scale-up is proposed after registration.

The process validation protocol should include inter alia 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/storage bins for uniformity testing of the final blend);
- the testing parameters/acceptance criteria including in-process and release

specifications and including 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/evaluating results; and
- the proposed timeframe for completion of the protocol.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

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, 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.

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, 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 EU “List of permitted food colours”, and the USFDA “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).

Information that is considered confidential may be submitted directly to the FDA by the supplier with reference to the specific related product.

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

Reference documents: ICH Q6A
WHO Generic drug guidance 2012

3.2.P.4.2 Analytical Procedures

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

Reference documents: ICH Q2 and Q6B

3.2.P.4.3 Validation of Analytical Procedures

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

Reference documents: ICH Q2, Q2B, and Q6B

3.2.P.4.4 Justification of Specifications

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 as per the FDA officially recognised list of publications should be provided.

3.2.P.4.5 Excipients of Human or Animal Origin

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 from plant origin a declaration to this effect will suffice.

For these excipients from 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, Q5D, Q6B

WHO Generic drug guidance

3.2.P.4.6 Novel Excipients

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

3.2.P.5 Control of FPP

3.2.P.5.1 Specification(s)

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

As defined in ICH 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 dossier.

Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of shelf-life.

The specifications should be provided in a tabular form in the dossier and should include the tests, acceptance criteria and analytical procedures. The analytical procedure should include the types, sources and versions for the methods:

- the *standard* declared by the applicant could be as per the FDA officially recognised list of publications 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), the *source* refers to the origin of the analytical procedure (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) and the *version* (e.g. *code number/version/date*) should be provided for version control purposes.

The following information provides guidance for 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 equal or greater than 5 mg and equal or greater than 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; and

Transdermal dosage forms: peel or shear force, mean weight per unit area, dissolution.

Unless there is appropriate justification, the acceptable limit for the API content of the FPP in the release specifications is $\pm 5\%$ 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 skip testing justification has been accepted, the specifications should include a footnote, stating at minimum the following skip testing requirements: at minimum every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and 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, Q3C, Q6A, Q6B
WHO Generic drug guidance 2012

3.2.P.5.2 Analytical Procedures

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

All analytical test procedures, including biological and microbiological methods where relevant, must be described in sufficient detail to enable the procedures to be repeated if necessary.

Information on the summary of analytical procedures and validation information used for determination of assay, related substances and dissolution of the FPP should be provided in a tabular form in 2.3.R.2.

Reference documents: ICH Q2
WHO Generic drug guidance 2012

3.2.P.5.3 Validation of Analytical Procedures

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

Copies of the protocol and reports for method validation including representative chromatograms/tracings for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the dossier) as well as those proposed for routine testing should be provided.

The monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial as per the FDA officially recognised list of publications for 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), equivalency 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 related compound methods, the sample analyzed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

Reference documents: ICH Q2A and Q2B, Q6B
WHO Generic drug guidance 2012

3.2.P.5.4 Batch Analyses

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

Information 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) on relevant FPP batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested 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.

These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The testing results should include 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 dossier 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”. This 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 minimum as both the average and range of individual results.

Reference documents: ICH Q3B, Q3C, Q6A, Q6B
WHO Generic drug guidance 2012

3.2.P.5.5 Characterisation of Impurities

Information on the characterisation 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, Q3C, Q6A, Q6B
WHO Generic drug guidance 2012

3.2.P.5.6 Justification of Specification(s)

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, differences from the officially recognized compendial standard(s) as per the FDA officially recognised list of publications, etc. 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, dissolution method development) may have been discussed in other sections of the dossier and does not need to be repeated here, although a cross-reference to their location should be provided.

Reference documents ICH Q6A and Q6B
WHO Generic drug guidance 2012

3.2. P.6 Reference Standards or Materials

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 and Q6B
WHO Generic drug guidance 2012

3.2.P.7 Container Closure System

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.

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, filler);
- used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions and powders/granules for such);
- used as a protective barrier to help ensure stability or sterility; and 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).

Where appropriate, critical dimensions, with drawings should be provided. Specifications for film and foil materials should include limits for thickness or area weight.

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

Reference document: ICH
WHO Generic drug guidance 2012

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. 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 design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the API and the dosage form. Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, the test procedures applied to the stability tests on the finished product should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded.

Characterize the possible degradants identified by stress stability testing during development pharmaceuticals (compatibilities of the APIs with each other and with the excipients as well as the effect of temperature on the rate of degradation reactions). The tests for degradants should be validated to demonstrate that they are specific to the FPP being examined and are of adequate sensitivity.

For long-term and accelerated stability studies, refer to FDA Guidelines on stability studies

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/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000's). If applicable, the in-use period and storage conditions should be stated in the product information.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". This 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), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". Dissolution results should be expressed at minimum as both the average and range of individual results.

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.

Reference document: ICHQ1A, Q1B, Q1C, Q1D, Q1E, Q3B, Q6A and Q6B
WHO Generic drug guidance 2012
FDA Guidelines for stability testing

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

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

When available long term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf-life.

Where the submission includes long-term stability data on three production batches covering the proposed shelf-life, a post approval commitment is considered unnecessary.

Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed shelf-life.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed shelf-life and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf-life.
- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf-life.

The stability protocol used for longterm studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified

Reference documents: ICH Q1A and Q5C

3.2.P.8.3 Stability Data

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 characterisation of impurities is located in 3.2.P.5.5.

The actual stability results/reports used to support the proposed shelf-life should be provided 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”. Dissolution results should be expressed at minimum as both the average and range of individual results.

Reference documents: ICH Q1A, Q1B, Q1C, Q1D, Q1E, Q2 and Q5C

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Biotech:

A diagram should be provided illustrating the manufacturing flow including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multi-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

3.2.A.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi).

This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

Reference ICH Guidelines: Q5A, Q5D, and Q6B

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5). For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3).

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.S.2.4 and 3.2.P.3.4).

Viral Testing of Unprocessed Bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5).

Reference ICH Guidelines: Q5A, Q5D, and Q6B

3.2.A.3 Novel Excipients

For novel excipients: a dossier should be established containing the same data as required for new active substances:

- a) A strict definition of the excipient, its function and its conditions of use. If the excipient is complex or is made of a mixture of compounds, the composition should be specified in qualitative and quantitative terms.

b) For novel excipients and for excipients presented as a mixture of compounds the following should be taken into consideration:

- i. Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.
- ii. The provisions concerning additives in foodstuffs: any criteria which are based on the toxicological data, with cross-references to these data. The quality specifications which have been laid down in the directives are satisfactory as long as the routine control tests used are validated.
- iii. The international specifications (FAO/WHO/JECFA), and other publications such as the Food Chemical Codex.
- iv. For medicinal products for cutaneous use, data on the starting material in cosmetic products.
- v. Data concerning the toxicology of the novel excipient should be presented according to the dosage form and the route of administration of the medicinal product (if applicable).

c) Documentation on chemistry of excipients is required for all new excipients, just as Chemistry of New Active Substances.

3.2.R REGIONAL INFORMATION

3.2.R.1 Production documentation

3.2.R.1.1 Executed production documents

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. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the executed production documents for these batches should be submitted.

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:

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

g) sampling plan with regard to the:

- steps where sampling should be done (e.g. drying, lubrication, 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);

h) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);

i) for sterile products, reference to SOPs in appropriate sections and a list of all relevant SOPs at the end of the document;

j) theoretical and actual yield;

k) compliance with the GMP requirements.

Reference documents: WHO Generic Drug Guidance 2012

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

MODULE 4: NONCLINICAL STUDY REPORTS FOR NEW CHEMICAL ENTITIES ONLY

This guideline presents the organisation of the nonclinical reports in the applications that will be submitted. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual-animal data is in the study report or as an appendix to the study report.

4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the Common Technical Document.

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology

- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

- 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
 - 4.2.3.3.1 In vitro
 - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
 - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
 - 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

- 4.2.3.5.1 Fertility and early embryonic development
- 4.2.3.5.2 Embryo-fetal development
- 4.2.3.5.3 Prenatal and postnatal development, including maternal function
- 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
- 4.2.3.6 Local Tolerance
- 4.2.3.7 Other Toxicity Studies (if available)
 - 4.2.3.7.1 Antigenicity
 - 4.2.3.7.2 Immunotoxicity
 - 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
 - 4.2.3.7.4 Dependence
 - 4.2.3.7.5 Metabolites
 - 4.2.3.7.6 Impurities
 - 4.2.3.7.7 Other

References:

Non-Clinical Safety Studies For The Conduct Of Human Clinical Trials For Pharmaceuticals (ICH M3[R2]) modification;

<http://www.ema.europa.eu/pdfs/human/ich/028695en.pdf>

EMA: Non- Clinical Scientific Guidelines;

<http://www.ema.europa.eu/htms/human/humanguidelines/nonclinical.htm>

CTD M4S (R2) SAFETY; *<http://www.ich.org/LOB/media/MEDIA556.pdf>*

4.3 Literature References

MODULE 5: CLINICAL STUDY REPORTS

This module provides guidance on the organization of the study reports, other clinical data, and references within an application for registration of a pharmaceutical product. These elements should facilitate the preparation and review of a marketing application.

This module is not intended to indicate what studies are required for successful registration.

It indicates an appropriate organization for the clinical study reports that are in the application. This module recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as —not applicable or —no study conducted should be provided when no report or information is available for a section or subsection.

5.1 NEW CHEMICAL ENTITIES ONLY

5.1.1 Table of Contents of Module 5:

A Table of Contents for study reports should be provided

5.1.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 5.1.1. of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section 5.1.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.1.3 Clinical Study Reports

5.1.3.1 Reports of Biopharmaceutic Studies

Bioavailability (BA) studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or Bioequivalence (BE) studies may use Pharmacokinetics (PK), Pharmacodynamics (PD), clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.1.3.1, and referenced in Sections 5.1.3.1.1 and/or 5.1.3.1.2.

5.1.3.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form
- dosage form proportionality studies, and
- food-effect studies.

5.1.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

4.2.1 the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,

4.2.2 the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and

4.2.3 similar drug products from different manufacturers.

5.1.3.1.3 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in Section 5.1.3.1.3. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the module 3.

5.1.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutical studies or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Section 5.1.3.1.4 and referenced in the appropriate individual study reports.

5.1.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used *in vitro* or *ex vivo* to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

5.1.3.2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies should be provided in Section 5.1.3.3.

5.1.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

5.1.3.2.3 Reports of Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in this section.

5.1.3.3 Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences.

These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity.

The PK studies whose reports should be included in Sections 5.1.3.3.1 and 5.1.3.3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faeces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Section 5.1.3.3.1 to 5.1.3.3.2, as appropriate.

These studies should characterise the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in Sections 5.1.3.3.1 and/or 5.1.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorised as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organised in Sections 5.1.3.3.3 and 5.1.3.3.4, respectively. In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-PK-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in Section 5.1.3.3.5.

5.1.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

5.1.3.3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

5.1.3.3.3 Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section.

5.1.3.3.4 Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors, should be placed in this section.

5.1.3.3.5 Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials, should be placed in this section.

5.1.3.4 Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in Section 5.1.3.5. This section should include reports of

- 1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers)
- 2) short-term studies of the main clinical effect, and
- 3) PD studies of other properties not related to the desired clinical effect.

Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects should be placed in Section 5.1.3.4.1, and the reports for those studies conducted in patients should be placed in Section 5.1.3.4.2. In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5.1.3.5, not in Section 5.1.3.4.

5.1.3.4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in this section

5.1.3.4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

5.1.3.5 Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and non-proposed indications.

The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and individual guidance by region).

Within Section 5.1.3.5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control.

Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section 5.1.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate Section 5.1.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5.1.3.5 and referenced as necessary in other Sections 5.1.3.5, e.g., Section 5.1.3.5A, Section 5.1.3.5B.

5.1.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control: Placebo control (could include other control groups, such as an active comparator or other doses) No-treatment control Dose-response (without placebo) Active control (without placebo) External (Historical) control, regardless of the control treatment Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in Section 5.1.3.5.1. Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Section 5.1.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Section 5.1.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in Section 5.1.3.5.1.

5.1.3.5.2 Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in Section 5.1.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.1.3.5.3 Reports of Analyses of Data from More than One Study

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Section 5.1.3.5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.1.3.5.4 Other Study Reports

This section can include:

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports of clinical experiences with the medicinal product that are not included in Section 5.1.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Section 5.1.3.5.1
- Reports of ongoing studies

5.1.3.6 Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in Section 5.1.3.6.

5.1.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings that are described as appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

5.1.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.1.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

5.2 INTERCHANGEABILITY OF GENERIC DRUGS – (GENERIC DRUG APPLICATIONS ONLY)

5.2.1 Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.1.3.1, and referenced in Sections 5.1.3.1.1 and/or 5.1.3.1.2.

5.2.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form
- dosage form proportionality studies, and
- food effect studies.

5.2.1.1.1 Comparative BA and Bioequivalence (BE) Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,

- the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and
- similar drug products from different manufacturers.

5.2.1.1.1 General Notes on Bioequivalence Study Report

Multi-source drug products need to conform to the same standards of quality, efficacy and safety required of the originator's product. In addition, reasonable assurance must be provided that they are, as intended, clinically interchangeable with nominally equivalent market products. With some classes of products, including-most evidently parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of Good Manufacturing Practices and evidence of conformity with relevant pharmacopoeial specifications. For other classes of products, including biologicals such as vaccines, animal sera, and products derived from human blood and plasma, and products manufactured by biotechnology, the concept of interchangeability raises complex considerations that are not addressed in this document, and these products are consequently excluded from consideration. However, for most nominally equivalent pharmaceutical products (including most solid oral dosage forms), a demonstration of therapeutic equivalence can and should be carried out, and such assessment should be included in the documentation for registration. Orally or parenterally administered aqueous solutions will be assessed by chemical-pharmaceutical characteristics only. This guideline refers to the marketing of pharmaceutical products that are intended to be therapeutically equivalent, and thus interchangeable, but produced by different manufacturers. Bioequivalence studies are designed to compare the in vivo performance of a test pharmaceutical product (multi-source) compared to a reference pharmaceutical product.

Bio-equivalence study report should contain at least the following items as described in part 2 of the application form see Annex X:

- Description of study design. The most appropriate study type is two period, randomized, crossover study. If other study types were used (e.g. parallel group design), these should be justified by the applicant. In general, single-dose study with sufficiently long period for blood samples collection is acceptable.
 - Information about investigators, study site and study dates.
 - Data about preparations used: manufacturer, place of manufacture, batch number etc.
- Reference preparation in bio-equivalence study should be innovator preparation from an ICH associated countries or from WHO list of international comparator products if listed.

Reference: *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902):161–180.*

- Characterization of study subjects. Bioequivalence study should be normally performed in healthy volunteers. If patients were used, this should be justified by the applicant. Number of subjects should not be less than 24 unless otherwise justified. Study report should contain inclusion and exclusion criteria, listing of demographic data of all subjects.
- Description of study procedures. Administration of test products, meals, times of blood sampling or urine collection periods should be described in the clinical report.
- Description and validation of drug determination methods in investigated material. Analytical method should be validated over the measured drug concentration range.

Validation should contain methodology and results of sensitivity, specificity, accuracy, precision and repeatability determination.

All measured drug concentrations should be presented.

Calculation methodology of pharmacokinetic parameters. Preferred is noncompartmental analysis. If modelled parameters were used, these models should be validated for the compound. All measured and calculated pharmacokinetic parameters should be presented in the report.

Description of statistical methodology and results of statistical calculations. Statistical calculations should be based on the equivalence evaluation. The statistical method of choice is the two one-sided test procedure and the calculation of 90% confidence intervals of the test/reference ratios of pharmacokinetic parameters. The main parameters to assess the bioequivalence are area under the plasma concentration-time curve (AUC) and maximum concentrations (C_{max}) ratios.

The 90% confidence interval for the AUC-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. The 90% confidence interval for the C_{max}-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. In certain cases for drugs with an inherently high intra-subject variability, a wider acceptance range (e.g., 75-133%) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations. *Reference: EMEA, as described in "Guideline On The Investigation Of Bioequivalence 2010", available at: <http://www.ema.europa.eu/pdfs/human/qwp/140198enrev1fin.pdf>*

5.2.1.1.2 In Vitro – In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate *in vitro* data with *in vivo* correlations, should be placed in Section 5.1.3.1.3. Reports of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the module 3.

5.2.1.1.3 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or *in vitro* dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in Section 5.1.3.1.4 and referenced in the appropriate individual study reports.

5.2.1.2 In vitro dissolution tests

General aspects of *in vitro* dissolution experiments are briefly outlined in **Dissolution testing and Similarity of Dissolution Profiles (below)** including basic requirements how to use the similarity factor (*f*₂-test).

5.2.1.2.1 In vitro dissolution tests complementary to bioequivalence studies

The results of *in vitro* dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics. Unless otherwise justified, the specifications for the *in vitro* dissolution to be used for quality control

of the product should be derived from the dissolution profile of the test product batch that was found to be bioequivalent to the reference product (**see Dissolution testing and Similarity of Dissolution Profiles below**). In the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails. However, possible reasons for the discrepancy should be addressed and justified.

5.2.1.2.2a *In vitro* dissolution tests in support of biowaiver of strengths

Appropriate *in vitro* dissolution should confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Accordingly, dissolution should be investigated at different pH values as outlined in the previous section (normally pH 1.2, 4.5 and 6.8) unless otherwise justified. Similarity of *in vitro* dissolution (**see Dissolution testing and Similarity of Dissolution Profiles below**) should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) (i.e. batch (es)) used for bioequivalence testing. At pH values where sink conditions may not be achievable for all strengths, *in vitro* dissolution may differ between different strengths. However, the comparison with the respective strength of the reference medicinal product should then confirm that this finding is drug substance rather than formulation related. In addition, the applicant could show similar profiles at the same dose (e.g. as a possibility two tablets of 5 mg versus one tablet of 10 mg could be compared).

5.2.1.2.2.1 Dissolution testing and Similarity of Dissolution Profiles

1. General aspects of dissolution testing as related to bioavailability During the development of a medicinal product a dissolution test is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the drug. As soon as the composition and the manufacturing process are defined a dissolution test is used in the quality control of scale-up and of production batches to ensure both batch-to-batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. Furthermore, in certain instances a dissolution test can be used to waive a bioequivalence study. Therefore, dissolution studies can serve several purposes:

(i) Testing on product quality

To get information on the test batches used in bioavailability/bioequivalence studies and pivotal clinical studies to support specifications for quality control

To be used as a tool in quality control to demonstrate consistency in manufacture

To get information on the reference product used in bioavailability/bioequivalence studies and pivotal clinical studies.

(ii) Bioequivalence surrogate inference

To demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product

To investigate batch to batch consistency of the products (test and reference) to be used as basis for the selection of appropriate batches for the *in vivo* study.

Test methods should be developed based on general and/or specific pharmacopoeial requirements. In case those requirements are shown to be unsatisfactory and/or do not reflect the *in vivo* dissolution (i.e. biorelevance) alternative methods can be considered when justified that these are discriminatory and able to differentiate between batches with acceptable and non-acceptable performance of the product *in vivo*. Current state-of-the-art information including the interplay of characteristics derived from the BCS classification and the dosage form must always be considered.

5.3 SAFETY AND RESIDUES DOCUMENTATION (FOR VETERINARY PRODUCTS ONLY)

5.3.1 Requirements for Animal Safety

5.3.1.1 Laboratory Animal Studies

Laboratory animal studies will normally be required for new chemical entities proposed for use as veterinary drugs. The information available in the published scientific literature may be accepted in lieu of studies outlined in this section. For the purpose of this guideline, these studies are required to determine potential toxic effects for the target animal species. The basic toxicity data obtained in laboratory animals complement the data required to support the safety of a new drug in the target animal species. Depending on the intended route(s) of administration of the drug for the target animal species, the toxicity studies may be conducted by oral and/or parenteral routes of administration of drugs. The laboratory animal toxicity studies in general may be classified as acute, subchronic or chronic. Due regard should be given to the welfare of the study animals. The use of animals for research and testing should conform to the rigorous ethical standards that are compatible with the goals of science for benefiting humans or animals. Those using animals should employ the most humane methods on the smallest number of appropriate animals required to obtain valid information. For standards for use and care of animals a reference may be made to the Guide to the Care and Use of Experimental Animals.

5.3.1.2 Target Animal Safety Studies

The objectives of these studies are to document: signs and effects associated with the toxicity of the new drug for the test species and its organs, tissues and functions; minimum toxic dose; maximum non-toxic-effect dose; and margin of safety. The data required for the safety in the intended target animal species may vary according to the nature of the basic toxicological data, the intended use of the proposed drug and the intended use of the target animal. The basic toxicology data are generally obtained from studies in laboratory animals. The data to establish safety of the proposed drug to the intended target animal species are obtained from the studies conducted in the target animal species. For the design and conduct of these studies a reference may be made to the Target Animal Safety Guidelines for New Animal Drugs.

5.3.2 Requirements for Human Safety

This Part pertains to the drugs used in food-producing animals. However, basic toxicity data obtained in laboratory animals are used to complement the data required to support the safety of the drug residues in food-producing animals. Under certain circumstances, the microbiological safety assessment may be required for veterinary antimicrobial products intended for use in non-food-producing animals. Before a new drug intended to be used in food-producing animals can be sold on the market, manufacturers are required by law to submit scientific evidence demonstrating that the drug has been carefully assessed for the safety of drug residues in meat and other food products intended for human consumption. Microbiological safety assessment is also considered as a key aspect of the requirements for human safety of veterinary antimicrobials.

5.3.2.1 Laboratory Animal Toxicity Studies

Toxicity studies are used to determine toxic effects of veterinary drugs and/or their metabolites in laboratory animal species, usually rodents and non-rodents (e.g., dogs), so that adequate extrapolations can be made to estimate the potential risks of the residues of veterinary drugs for consumers ingesting foods of animal origin. All laboratory animal toxicity studies, except for tests of mutagenicity, submitted in support of human safety for use in food-producing animals are conducted using the oral route of administration. Data generated under the toxicity studies are used to establish a no observable effect level (NOEL) in the most sensitive species/strain. The established NOEL is then used to calculate an Acceptable Daily Intake for the specific drug and/or its metabolites by using an appropriate safety factor.

It is recommended that all toxicity studies be conducted in accordance with the guidelines on Good Laboratory Practice (GLP) as approved by the OECD (website: <http://www.oecd.org>).

Specific requirements for toxicity studies may vary from one drug to another depending on the class of veterinary drug and the extent of its proposed use.

5.3.2.2 Microbiological Safety Studies

In this section of the Human Safety Requirements, information is provided regarding the data requirements expected for demonstrating the microbiological safety of a drug product. This section pertains to antimicrobial drug products as well as products containing bacteria, for example, direct-fed microbial products.

5.3.2.2 Veterinary Antimicrobial Products

This section pertains to antimicrobial drug products (including antibacterials, antiparasitics and antivirals). However, information in this guidance is often targeted to antibacterial products. Sponsors submitting applications for other antimicrobial products may wish to consult with the FDA for the specific requirements for their submission. The impact of the use of antimicrobial products in food-producing animals on the development and the potential for enrichment and dissemination of antimicrobial resistant human bacterial pathogens is considered one of the principal aspects of the human safety review. The objective of this guidance is for the sponsor to provide information necessary for assessing the potential impact of the use of veterinary antimicrobial products on the development of antimicrobial resistance in bacteria of animal origin, which may affect antimicrobial therapy in veterinary and human medicine.

5.3.2.4 Residue (Chemistry) Studies

This Part describes the absorption of the test substance after administration to animals as well as the Absorption, Distribution, Metabolism and Excretion, ADME, patterns of the test substance. The extent and duration of persistence of residues of a veterinary drug or its metabolites in edible tissues of treated animals or food products obtained from them determines the withdrawal period (withholding time for milk) needed for the residues to fall below the Maximum Residue Limit (MRL). The summary of the residue-related studies, providing factual, concise descriptions of the test results.

REFERENCES

1. Guide to Care and Use of Experimental Animals, CCAC, 1993. (Website: <http://www.ccac.ca>)
2. Target Animal Safety Guidelines for New Animal Drugs. Office of New Animal Drug Evaluation. Centre for Veterinary Medicine, Food and Drug Administration, Rockville, MD 20855, USA. 2001.

3. Uses of Antimicrobials in Food Producing Animals. Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health, 2002. (http://www.hc-sc.gc.ca/dhp-mps/pubs/vet/amr-ram_final_report-rapport_06-27_cp-pc-eng.php
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