DIRECTORATE GENERAL OF DRUG ADMINISTRATION (DGDA)

MINISTRY OF HEALTH & FAMILY WELFARE

GUIDELINE FOR THE SUBMISSION OF BANGLADESH COMMON TECHNICAL DOCUMENT: MODULES 2 (QUALITY OVERALL SUMMARY) and 3 (QUALITY)

This document provides instructions to applicants intending to submit applications for the registration of medicines. These guidelines are governed by the Directorate General of Drug Administration's (DGDA) current thinking on safety, quality, and efficacy of medicines. The DGDA reserves the right to request additional information to establish the safety, quality, and efficacy of a medicine in keeping with current knowledge at the time of the evaluation of a medicine. The DGDA is committed to ensuring that all registered medicines are of the required quality, safety, and efficacy. It is important that applicants adhere to the quality requirements in this module to avoid delays in the processing and evaluation of applications.

Version 1 released for pilot implementation and comments
June 2015

GENERAL TABLE OF CONTENTS

MESSAGE FROM THE DIRECTOR GENERAL, DIRECTORATE GENERAL OF DRUG ADMINISTRATION

The Directorate General of Drug Administration (DGDA) of Bangladesh is changing and improving its medicines registration system to ensure the safety and efficacy of medicines as well as to strengthen the potential for the exportation of medicines. The DGDA is therefore adopting the Common Technical Document (CTD) formats and guidelines for the preparation of registration dossiers for pharmaceuticals that are submitted with the application for registration.

The DGDA is also planning to implement PharmaDex to track registration applications and to enhance its capacity to successfully manage the registration process in a timely manner.

The Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Bangladesh office has been providing technical assistance to the DGDA under the terms of cooperative agreement number AID-OAA-A-11-00021 in this regard. The DGDA established a Taskforce Team to review the CTD modules and customize modules 2 and 3 of these guidelines to the Bangladesh context. With the support of SIAPS, the team was able to have a clear understanding of the process.

To adopt the CTD and implement PharmaDex, a series of workshops were conducted for DGDA officials as well as other stakeholders.

It is hoped that the CTD will be adopted on a pilot basis within six months. Thanks are offered to all members of the Taskforce Team and the SIAPS team for their continuous support for the implementation of the CTD.

Major Gen Md. Jahangir Hossain Mollik
Director General, Directorate General of Drug Administration &
Licensing Authority of Drugs

ACRONYMS

API	active pharmaceutical ingredient
BCS	Biopharmaceutical Classification System
BP	British Pharmacopoeia
CoA	certificate of analysis
CTD	Common Technical Document
DGDA	Directorate General of Drug Administration
DMF	drug master file
EMA	European Medicines Agency
EU	European Union
FDC	fixed-dose combination
FPP	finished pharmaceutical product
FPRC	Finished Product Release Control
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	international nonproprietary name
IPI	inactive pharmaceutical ingredient
IR	infrared
NCE	new chemical entity
Ph Eur	European Pharmacopoeia
PI	prescribing information
PIL	patient information leaflet
QOS	Quality Overall Summary
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
USFDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
VP	validation protocol
VR	validation report
WHO	World Health Organization

MODULE 2 QUALITY OVERALL SUMMARY

MODULE 2.1 TABLE OF CONTENTS

MODULE 2.2 BACKGROUND OF THE QUALITY OVERALL SUMMARY

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in module 3 (Quality) of the dossier, which contains the chemical, pharmaceutical, and biological data relevant to the application. The QOS should contain the summary data of what is already provided in module 3 or in other parts of the Common Technical Document (CTD). The QOS should include sufficient information from each section of module 3 to provide the quality reviewer with an overview of the quality of the product. The QOS should also emphasize critical key parameters of the medicine and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrate information from sections in module 3 and supporting information from other modules, including cross-referencing to volume(s) and page number(s) in other module(s).

This QOS should normally not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document may be longer, but normally should not exceed 80 pages of text, excluding tables and figures. *For a sample template of the QOS, refer to WHO Quality Overall Summary - Product Dossier (QOS-PD), 2014-12-11.*[1]

Although, the CTD is organized by modules, the guidance providing recommendations for applicants on preparing the CTD is organized by topic: quality, safety, and efficacy. As a result, guidance discussed in module 2 is divided into three sections:

- Guidance on the quality section of the CTD (module 2, Quality Overall Summary [QOS], and module 3) may be found in the ICH M4Q: The CTD — Quality.
- Guidance on the safety section of the CTD (module 2, the Nonclinical Overview and the Nonclinical Written and Tabulated Summaries, and module 4) may be found in the ICH M4S: The CTD — Safety.[2]
- Guidance on the efficacy section of the CTD (module 2, the Clinical Overview and the Clinical Summary, and module 5) may be found in the ICH guideline M4E: The CTD — Efficacy.[2]

The Bangladesh CTD guidelines are intended to be used along with other International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) requirements for the registration of pharmaceuticals for human use. For general information about the CTD, as well as specific information about module 1, see the *Guideline for the*

[1] http://apps.who.int/prequal/ (go to A-Z Listings of Documents).

Submission of Bangladesh CTD: General Guidelines and Module 1. For information on safety and efficacy, refer to the ICH M4S and M4E guidelines.[2]

The CTD guidelines, together with the other DGDA guidelines available on its website, provide detailed information about the contents of an application. These guidelines apply to applications to register medicines and all related variations. Applicants should not modify the overall organization of the CTD. If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary, or overview.

Module 1 - Administrative Information and Prescribing Information

Relevant administrative documentation and the proposed label for use in Bangladesh should be submitted in module 1 of the CTD dossier. This module should be divided into the relevant sections, as described in Part B of module 1.

Module 2 - Summary of the Dossier

Module 2 of the CTD dossier contains the summaries and overviews for the quality, nonclinical, and clinical sections of the dossier (refer to ICH guidelines M4Q, M4S, and M4E).[2] The module begins with a general introduction to the medicine, including its pharmacological class, mode of action, and proposed clinical use. The summary of quality information should be provided according to the World Health Organization's (WHO) Quality Overall Summary–product dossier (QOS-PD) template.

Module 3 - Quality

Module 3 of the dossier contains the chemical, pharmaceutical, and biological data relevant to the application. This information should be structured as described in the Bangladesh CTD Module 2 (Quality Overall Summary) and 3 (Quality) guidelines. Also, refer to the ICH Guidelines M4Q (M4Q (R1): QUALITY Module 2: Quality Overall Summary (QOS) and Module 3: Quality.[3]

Module 4 - Nonclinical Study Reports

Module 4 of the dossier contains the nonclinical (pharmacotoxicological) data relevant to the application. Exemptions apply to multisource (generic) products.

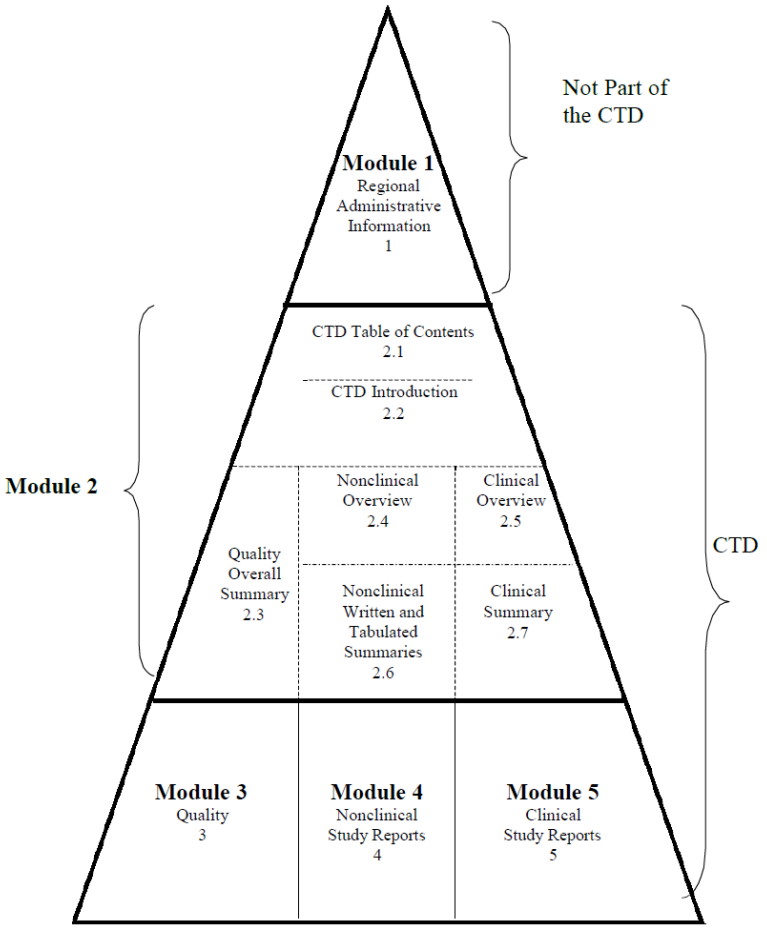
[2] http://www.ich.org/products/ctd.html.
[3] http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

Module 5 - Clinical Study Reports

Module 5 of the dossier contains the clinical data relevant to the application. In most circumstances, the clinical studies included in module 5 of the dossier will be international studies used to establish the pharmacodynamics, pharmacokinetics, safety, and efficacy of the medicine across an international patient population. However, where there is evidence to suggest that the pharmacokinetics or pharmacodynamics of the product may vary across the populations that will use the medicine in Bangladesh, the applicant should consider submitting studies relevant to those target populations. These reports should be presented in the order described in the Bangladesh CTD Module 2 (Clinical Overview), Guideline for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products, Bangladesh: Annexure 3, and CTD Module 5 (Bioequivalence Studies) guidelines. Also, refer to the ICH guidelines M4E (M4E (R1): Efficacy and Module 2: Clinical Overview and Clinical Summary Module 5 Clinical Study Reports.[2]

In cases concerning well-known active pharmaceutical ingredients, the DGDA may grant exemption from the submission of bioequivalence study reports in module 5.

Schematic of the Organization of the ICH CTD



MODULE 2.3 BODY OF DATA OF QUALITY OVERALL SUMMARY

2.3.S Active Pharmaceutical Ingredient (API) [Name, Manufacturer]

2.3.S.1 General Information [Name, Manufacturer]

Information from section 3.2.S.1 of module 3 should be included here.

2.3.S.2 Manufacture [Name, Manufacturer]

Information from section 3.2.S.2 of module 3 should be included here.

- 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 materials of appropriate quality.
- A flow diagram, as provided in section 3.2.S.2.2 of module 3, should be imported directly to this section.
- A description of the source and starting material and raw materials of biological origin used in the manufacture of the API, as described in section 3.2.S.2.3 of module 3.
- A discussion of the selection and justification for critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in section 3.2.S.2.4 of module 3.
- A description of process validation and/or evaluation, as described in section 3.2.S.2.5 of module 3.
- A brief summary of major manufacturing changes made throughout the development process and conclusions from the assessment used to evaluate product consistency, as described in section 3.2.S.2.6 of module 3. The QOS should also cross-reference the nonclinical and clinical studies that used batches affected by these manufacturing changes. For more information, also refer to the ICH guidelines M4S and M4E sections of the application.

2.3.S.3 Characterization [Name, Manufacturer]

<u>For New Chemical Entities (NCE):</u>

A summary of the interpretation of evidence of structure and isomerism, as described in section 3.2.S.3.1 of module 3, should be included.

When the API is chiral, please specify whether specific stereoisomers or a mixture of stereoisomers were used in the nonclinical and clinical studies. Information should

also be given as to the stereoisomer of the API 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 characterization data (for example, primary and higher order structure and biological activity), as described in section 3.2.S.3.1 of module 3, should be included.

For NCE and Biotech:

The QOS should summarize the data on potential and actual impurities arising from the synthesis, manufacture, and/or degradation, and should summarize the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarize the impurity levels in batches of the API used in the nonclinical 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 section 3.2.S.3.2 of module 3, with graphic representation, where appropriate, should be imported directly to this section.

2.3.S.4 Control of Active Pharmaceutical Ingredient [Name, Manufacturer]

A brief summary of the justification for the specifications, the analytical procedures, and validation should be included.

Specifications from section 3.2.S.4.1 of module 3 should be imported directly to this section.

A tabulated summary of the batch analyses from section 3.2.S.4.4 of module 3, with graphic representation, where appropriate, should be imported directly to this section.

2.3.S.5 Reference Standards or Materials [Name, Manufacturer]

Information from section 3.2.S.5 of module 3 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System [Name, Manufacturer]

A brief description and discussion of the information from section 3.2.S.6 of module 3 should be included.

2.3.S.7 Stability [Name, Manufacturer]

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, and the retest date or shelf life, where relevant, as described in section 3.2.S.7.1 of module 3.

The post-approval stability protocol, as described in section 3.2.S.7.2 of module 3, should be included.

A tabulated summary of the stability results from section 3.2.S.7.3 of module 3, with graphic representation, where appropriate, should be imported directly to this section.

Note: A separate section 2.3.S should be provided for each API. For example, for a second substance, the sections would be labeled 2.3.S [name 2, manufacturer]. For a substance coming from another manufacturer, the sections would be labeled 2.3.S [name, manufacturer 2].

2.3.P Pharmaceutical Product [Name, Dosage Form]

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

Information from section 3.2.P.1 of module 3 should be provided.

The description and composition of the pharmaceutical product from section 3.2.P.1 of module 3 should be imported directly to this section.

2.3.P.2 Pharmaceutical Development [Name, Dosage Form]

A discussion of the information and data from section 3.2.P.2 of module 3 should be presented. A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be imported directly to this section, where relevant.

2.3.P.3 Manufacture [Name, Dosage Form]

Information from section 3.2.P.3 of module 3 should be included here.

- 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 a product of appropriate quality.

- A flow diagram, as provided in section 3.2.P.3.3 of module 3, should be imported directly to this section.
- A brief description of the process validation and/or evaluation, as described in section 3.2.P.3.5 of module 3, should be provided.

2.3.P.4 Control of Inactive Pharmaceutical Ingredients (Excipients) [Name, Dosage Form]

A brief summary of the quality of excipients, as described in section 3.2.P.4 of module 3, should be included here.

2.3.P.5 Control of Pharmaceutical Product [Name, Dosage Form]

A brief summary of the justification for the specifications, a summary of the analytical procedures and validation, and characterization of impurities should be provided.

Specifications from section 3.2.P.5.1 of module 3 should be imported directly to this section.

A tabulated summary of the batch analyses provided under section 3.2.P.5.4 of module 3, with graphic representation, where appropriate, should be imported directly to this section.

2.3.P.6 Reference Standards or Materials [Name, Dosage Form]

Information from section 3.2.P.6 of module 3 (tabulated presentation, where appropriate) should be included here.

2.3.P.7 Container Closure System [Name, Dosage Form]

A brief description and discussion of the information in section 3.2.P.7 of module 3 should be included here.

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 regarding storage conditions and shelf life (and in-use storage conditions and shelf life, if applicable), should be given. A tabulated summary of the stability results from section 3.2.P.8.1 of module 3, with graphic representation, where appropriate, should be imported directly to this section.

The post-approval stability protocol, as described in section 3.2.P.8.2 of module 3, should be provided.

Note: A separate section 2.3.P should be provided for each dosage form. For example, for a second dosage form, the sections would be labeled 2.3.P [name, dosage form 2].

2.3.A Appendices

2.3.A.1 Facilities and Equipment

For Biotech:

A summary of facility information described under Appendix 3.2.A.1 of module 3, Facilities and Equipment, should be included here.

2.3.A.2 Adventitious Agents Safety Evaluation

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

A tabulated summary of the reduction factors for viral clearance from Appendix 3.2.A.2 of module 3, Adventitious Agents Safety Evaluation section of module 3, should be imported directly to this section.

2.3.A.3 Novel Excipients

A brief discussion of information described under section 3.2.A.3 of module 3 should be included.

2.3.R Regional Information

A brief description of information specific to the region, as provided under section 3.2.R Regional Information, should be included, where appropriate.

MODULE 3 QUALITY

MODULE 3.1 TABLE OF CONTENTS

MODULE 3.2 BODY OF DATA

3.2.S Active Pharmaceutical Ingredient (Name, Manufacturer)

Neither the complete nor the open part of the drug master file (DMF) should be sent directly to the DGDA.

The information should be submitted in the dossier under the headings provided below.

The documentation must comply with the WHO Good Manufacturing Practices[4] that has been adopted by the DGDA.

Starting materials for in situ API preparation are treated as APIs.

For a mixture of API(s) or API(s) with inactive pharmaceutical ingredients (IPI), the blending of the ingredients is considered as the first step in the manufacture of the final product, and therefore does not fall under the definition of an API even though it may take place in a different facility. The resultant mixture, or partially completed final product (e.g., coated or uncoated granules) is regarded as a finished pharmaceutical product (FPP) intermediate.

The only exceptions can be made where the API cannot exist on its own, for example, due to insufficient stability without a stabilizing agent.

The mixing of the API with an IPI or another API therefore forms part of the manufacturing procedure for the final product, which is addressed in section 3.2.P.3 of module 3, while the API(s) used in such mixtures should be included in section 3.2.S of module 3, according to the requirements of sections 3.2.S.1 to 3.2.S.7 and 3.2.R.6 of module 3. The formulation, API, and IPI specifications and control procedures, packaging materials, stability, and pharmaceutical development of the FPP intermediate are addressed in sections 3.2.P.3, 3.2.S.2, 3.2.P.4, 3.2.P.7, 3.2.P.8, and 3.2.P.2, respectively, in accordance with the requirements of the relevant sections.

In case of blood fractions, a Plasma Master File should be included in the dossier, if applicable.

A separate 3.2.S should be submitted for:

- Each API (in the case of a fixed-dose combination product);
- Each API manufacturer applied for;

[4] http://dgda.gov/bd.

- Those sections that are relevant to the FPP manufacturer in terms of testing of the API (e.g., section 3.2.S.4).

3.2.S.1 General Information (Name, Manufacturer)

3.2.S.1.1 Nomenclature (Name, Manufacturer)

The brand name, generic name, or international nonproprietary name (INN), or chemical description of the API(s), should be provided.

3.2.S.1.2 Structure (Name, Manufacturer)

The structural formula (indicating stereochemistry, where appropriate), systematic name, the empirical formula, and the relative molecular mass should be provided.

3.2.S.1.3 General Properties (Name, Manufacturer)

The physical and chemical properties of the API, including, for example, solubility, particle size, and hygroscopicity, should be indicated.

The solubility of each API should be specified in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents should include water and the solvent(s) relevant to the product formulation.

If the API has a low solubility in water in accordance with the Biopharmaceutical Classification System (BCS) definition, the solubility should be quantified (mg/ml).

Evidence of the occurrence of isomers, chirality, and polymorphism, where applicable, should be indicated. The absence of isomers, chirality, and/or polymorphism should be confirmed.

For a multisource product, the API must be identical in structure and stereochemistry to the API used as the reference product (pharmacopoeia structure).

3.2.S.2 Manufacture (Name, Manufacturer)

3.2.S.2.1 Manufacturer(s) (Name, Manufacturer)

The name, business, and physical address of each manufacturer of the API being applied (including any intermediate manufacturer) should be provided.

No API from any manufacturer, other than the approved manufacturer(s), may be used.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (Name, Manufacturer)

A short description of the synthesis and a flow chart that includes: the structures and stereochemistry of starting materials and intermediates; reagents, catalysts, solvents, isolation, and purification; and any other relevant aspects. Note that specifications and control procedures for substances used in this process are not generally required. (The specific processes carried out by any intermediate manufacturer should be identified.)

Other relevant aspects, for example, preparation of sterile material (full description of aseptic or sterilization process, including conditions), should be included or if there is no further sterilization of the FPP.

See 3.2.R. below for alternative to this section.

3.2.S.2.3 Control of Materials (Name, Manufacturer)

1. Full details of tests and specifications for pharmaceutical ingredients used in the production of the primary production lot should be provided; refer to the applicable guideline of the WHO Technical Report Series: biological products: general recommendations.[5]

2. In the case of biological medicines produced using the cell bank or seed lot system, the history (origin and sources) and preparation of the seed lot and/or cell lines should be described with specific reference to the tests that are carried out on such a seed lot or cell bank to establish and maintain the integrity. Refer to the European Medicines Agency (EMA)[6] and or the applicable guideline of the WHO Technical Report Series: biological products: general recommendations.

3. Particulars of the composition of all culture media used in the preparation and testing of a biological medicine should be given. All raw materials of animal or human origin must be specified as well as suppliers (indicating the country of origin) and the certificate of analysis (CoA).

4. Particulars should be given of the other biological source material from which a biological medicine (e.g., blood fractions) is extracted, including the origin of the culture or blood.

[5] http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

[6] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000082.jsp&mid=WC0b01ac0580027547.

3.2.S.2.4 Controls of Critical Steps and Intermediates (Name, Manufacturer)

Submit information relevant for the FPP manufacturer (e.g., sterile material).
Critical Steps: Tests and acceptance criteria (with justification, including experimental data) performed at critical steps identified in section 3.2.S.2.2 above on 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. For details, refer to ICH Guidelines: Q6A and Q6B.

Additionally for Biotech: Stability data supporting storage conditions should be provided. For details, refer to ICH Guideline Q5C.

3.2.S.2.5 Process Validation and/or Evaluation (Name, Manufacturer)

Provide full validation data on the aseptic processing and sterilization process, where there is no further sterilization of the FPP.

3.2.S.2.6 Manufacturing Process Development (Name, Manufacturer)

For NCEs, refer to ICH M4Q.[3]

3.2.S.3 Characterization (Name, Manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (Name, Manufacturer)

Provide structure (including stereochemistry) elucidation for NCEs.

Proof of correctness of structure for a well-known API (e.g., infrared [IR] spectrometric comparison against an official standard, such as US or BP pharmacopoeia) may be acceptable. In the case of enantiomers, an additional test is required to confirm its identity.

If the API is not described in a monograph of any of the official pharmacopoeias, no official standard is available, in which case sufficient evidence (nuclear magnetic resonance, IR, mass spectrometry, elemental analysis, etc., with interpretation) should be provided in support of the structure and stereochemistry.

3.2.S.3.2 Impurities (Name, Manufacturer)

Provide a description of impurities, indicating the possible source of impurities and a clear distinction between actual and possible impurities.

Provide a description of possible degradation products.

3.2.S.4 Control of Active Pharmaceutical Ingredient (Name, Manufacturer)

3.2.S.4.1 Specifications (Name, Manufacturer)

Include the API manufacturer's and FPP manufacturer's (if different) specifications of the API in tabulated format, not narrative. Indicate clearly if these specifications are the same.

Additional specifications (e.g., isomers, chirality, polymorphs, as well as impurities, particle size distribution, residual solvents, where relevant) should be submitted for all APIs.

Specifications and the control procedures for the particle size of APIs that have a low solubility in water in accordance with the BCS definition and for those which the DGDA may request should be submitted, and the solubility quantified, unless justified. Particle size should be given in International Systems of Units (SI). Exemption from this requirement may be granted if the API is administered as a clear solution.

3.2.S.4.2 Analytical Procedures (Name, Manufacturer)

Include detailed methods used for quality testing (identification, assay, determination of related substances, residual solvents, etc.), including chromatograms for the API manufacturer and FPP manufacturer (if different). When pharmacopoeia methods are used, these should be current and may be referred to.

3.2.S.4.3 Validation of Analytical Procedures (Name, Manufacturer)

Include validation reports, where relevant. In-house methods require full validation. Pharmacopoeia methods require system suitability and linearity, where applicable.

3.2.S.4.4 Batch Analyses (Name, Manufacturer)

For NCEs, extensive batch analysis is required; also for batches used in clinical studies.

Submit valid CoAs from the API manufacturer relating to at least two batches for NCEs and generics.

3.2.S.4.5 Justification for Specifications (Name, Manufacturer)

Full justification is required for in-house standards claimed. For details refer to ICH Q6A.[3]

No justification is required for pharmacopoeia standards claimed unless there are additional tests.

3.2.S.5 Reference Standards or Materials (Name, Manufacturer)

For NCEs and well-known non-compendial APIs, at least the following information on the primary reference standard should be provided:

- Purification method, if applicable
- Establishment of purity (potency)
- CoA, with a potency statement

If a pharmacopoeia monograph is claimed, the pharmacopoeia standard should be used.

Secondary standards should always be established against the pharmacopoeia/primary standard. Refer to WHO Technical Report Series 943, Annex 3 (2009)[7] for more details.

3.2.S.6 Container Closure System (Name, Manufacturer)

A description of the container closure system(s) should be provided, including the identity of construction materials for each primary packaging component, and their specifications. The specifications should include a 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 construction materials with the API, including absorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability (Name, Manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (Name, Manufacturer)

The storage requirements for the API, as specified by the manufacturer of the API and/or prescribed in the pharmacopoeia or acceptable standard reference, should be specified, and a description of the API container closure system should be included.

[7] http://apps.who.int/prequal/info_general/documents/TRS953/TRS_953-Annex3.pdf.

If a specific storage temperature is not specified in any acceptable reference, an instruction to protect from excessive heat, freezing, moisture, and light should be included, unless justified.

The proposed retest period should be indicated.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment (Name, Manufacturer)

The post-approval stability protocol and stability commitment should be provided. For more details, please refer to the ICH guidelines Q1A and Q5C.

3.2.S.7.3 Stability Data (Name, Manufacturer)

1. Include results of stability studies performed on the API obtained by the route of synthesis described in section 3.2.S.2.2 when stored in the proposed container closure system.

2. Provide the conditions under which degradation products are formed (stress testing).

3. A validated stability-indicating assay method, described in full, should be used in these studies, unless the method for related substances is specific and quantitative, such as using High Performance Liquid Chromatography (HPLC) technique.

4. Supporting chromatograms, where relevant, should be included in the methods or validation section.

5. Stability data on NCE APIs should be generated according to the stability guideline (refer to ICH Q1B); for well-known chemical entities supporting literature may be submitted.

6. For biological medicines, stability of the primary production lot and all intermediates (if not used immediately) should be provided.

3.2.P Pharmaceutical Product (Name, Dosage Form)

3.2.P.1 Description and Composition of the Pharmaceutical Product (Name, Dosage Form)

1. The formulation should show the INN or approved names, generic, and/or chemical names of all APIs, and polymorph (if relevant), and approved names of IPIs, including those that do not remain in the final product after

manufacturing, for example, granulating agents and gases used for flushing. IPIs not present in the final product should be indicated.

The ingredients for in-situ preparations, pre-mixes, FPP intermediates, cores, coating, etc. should be listed/grouped together and identified accordingly.

2. The name and the quantity of the API and the name and quantity provided under “Composition” in the package insert and patient information leaflet (PIL) should correspond. The name and quantity of the API per dosage unit should also correspond to the final product specifications.

   Justification should be provided for deviations.

   The theoretical quantity of the base of the API should be indicated if a compound, for example, a hydrate, solvate, or salt, is used.

   If the moisture content or other characteristic of an API is relevant to the quantity of the IPIs used in the formulation, this should be mentioned in a footnote.

3. A product may contain more than one API provided that:

   a) each API makes a contribution to the claimed indications;
   b) the effect of combining the APIs in one product does not decrease the safety, efficacy, or quality (including stability) of the product significantly;
   c) the product provides rational concurrent therapy for a significant proportion of the target population (e.g., tuberculostatic combinations).

4. Each pharmaceutical ingredient should be listed with its quantity per dosage unit. This would include the vehicle(s), solvent(s), or base(s) (excluding quantities of coating solvents). In the absence of an approved name (INN) or chemical name, a chemical description or characterization of the substance should be given. If so required and relevant, the proprietary name of the IPI may be included in addition to the approved name.

   The approved name for each ingredient should be standardized throughout the application.

   Where applicable, special characteristics of the IPI, for example, lyophilised, micronised, solubilised, emulsified, or form (e.g., anhydrous, monohydrate) and/or source (e.g., the botanical source of starch) should be indicated.

The grade of IPIs, also when a pharmacopoeia monograph covers more than one grade (e.g., viscosity of methyl cellulose), and the type of water (e.g., purified, water for injection), where relevant, should be indicated.

The use of IPIs that are not described in official pharmacopoeia is strongly discouraged and should be justified. This includes flavorant, fragrance, colorant, and ink.

5. The purpose of each IPI should be briefly described. If the IPI is used for multiple purposes in the formulation, each purpose should be mentioned.

   The name of each API and IPI should correspond and the quantities correlate with those reflected in the batch formulation submitted in section 3.2.P.3.2 of module 3, and the batch manufacturing record submitted or made available for inspection.

6. Some IPIs are single chemical entities, while others are combinations. Some are chemically transformed (e.g., modified starch). For excipients that are mixtures of chemically related or unrelated components, for example, polyol esters (mixture of mono, di, and tri esters), direct compression excipients, solutions, or film coating formulations, or excipients that are chemically modified, the nature and quantity of each such excipient should be specified.

   The qualitative composition of inks should be specified.

   The composition of these mixtures/combinations could be attached to the formulation information or included separately on the next page.

7. Any overages for the API should be given separately. The label claim quantity should be provided and the excess quantity indicated as the actual quantity or as a percentage. For example, 500 mg + 5 mg (= 1 %) overage.* (*Use the asterisk to indicate the justification for the overage.)

   The reason for the overage should be indicated/justified, for example, with reference to batch results, in section 3.2.P.2.2.2 of module 3.

8. If a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the API will depend on the potency and the IPI(s) that will be used to adjust the bulk quantity should be made. The manner in which the adjustment will be made should also be specified.

   If the moisture content or other characteristic of an IPI is relevant to the quantity of the IPI used in the formulation, this should be mentioned in a footnote.

9. Permitted flavoring and coloring agents (that comply with directives of the European Union [EU] or the register of the US Food and Drug Administration [USFDA]), in many instances because of their complexity, may be described in terms of their main constituents only, provided that a conclusive identification is given in the relevant section.

   The Color Index Numbers or the colorant reference number, in accordance with the EU or USFDA directive on colorants, should be included in the formulation.

   The use of dyes, printing ink, coating materials, flavorants, and organic solvents is subject to the same safety and quality requirements that apply to medicinal substances.

10. The content of alcohol, if included in medicines for oral administration, should comply with the requirements of the Alcohol Content of Medicines guideline (EMA or USFDA guidelines).

11. If a vehicle is added up to the required volume or mass of the product, the actual or estimated quantity of that vehicle may be indicated. Expressions such as “add up to” and “q.s.” are acceptable. Solutions added to adjust the pH should be described in terms of composition and strength (e.g., normality, molarity), but it is not necessary to state the actual quantity added as none or only minute quantities may be required.

12. In the case of capsules, the fill mass as well as the capsule size, composition, and mass should be indicated.

13. The theoretical mass should be indicated for uncoated tablets. In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit should be indicated and the IPIs used for each should be grouped separately.

14. For biological medicines, the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine that is offered for sale in a dried form should be supplied.

15. Toxicity levels per dosage unit should be indicated for all solvents and for other ingredients when required by the DGDA. Levels should be indicated as per the most recent edition of The Complete Drug Reference by United States Pharmacopoeia or other related document.

3.2.P.2 Pharmaceutical Development (Name, Dosage Form)

A pharmaceutical development report (generally of not more than 25 pages on A4 paper) should be submitted with each application. It should include at least an overall conclusion and the following information:

3.2.P.2.1 Components of the Pharmaceutical Product (Name, Dosage Form)

3.2.P.2.1.1 Active Pharmaceutical Substance(s) (Name, Dosage Form)

- Comment on the synthesis of the API(s);
- Discussion of all the physicochemical properties, for example, solubility (in terms of BCS classification), water content, particle size distribution, crystal properties, polymorphs, chirality, isomers, and stability of the API that can influence the performance of the final product.
- The compatibility of the API with excipients listed in section 3.2.P.1 should be discussed.
- Provide studies (literature) on the proposed excipients. If the excipients are the same as those of the reference product, this information is not required.
- In the case of fixed-dose combination (FDC) products, extensive studies on API-API compatibility under various conditions (aqueous medium and solid state) should be provided. For well-established combinations, literature information may suffice, if available. In general, the pharmaceutical development and quality aspects of FDC products should be in accordance with the WHO Technical Report Series No. 929, “Guidelines for Registration of Fixed-dose Combination Medicinal Products” (2005)[8] or the most recent revision.

3.2.P.2.1.2 Inactive Pharmaceutical Ingredients or Excipients (Name, Dosage Form)

- Submit an explanation of the function of the excipients.
- For multisource products, state whether excipients are the same as in the reference product.
- Non-compendial excipients should be avoided in generic products. Safety/toxicity profile of the excipients should be submitted if it is non-compendial.
- All the excipients used during the development should be clearly listed in tabulated form (see the sample table below).

[8] http://apps.who.int/medicinedocs/en/d/Js19979en/.

List of Excipients Used

Inactive Ingredient Name(s)	Dosage Strength	Dosage Unit	Pharmacopoeia Reference	Maximum Potency Allowed

3.2.P.2.2 Final Pharmaceutical Product (Name, Dosage Form)

3.2.P.2.2.1 Formulation Development (Name, Dosage Form)

- Data or literature (including the qualitative composition of the innovator product) on any interactions likely to occur, or that may occur, under given circumstances between the API and excipients should be provided.
- For multisource products, include a tabulated comparison of the qualitative composition, appearance, physical parameters, impurity profiles, and other relevant parameters of the test and reference/innovator products.
- Discussion of the relevant physicochemical parameters (e.g., dissolution and choice of medium, effect of pH) should be provided. The dissolution conditions and acceptance criteria should be derived from the multipoint comparative data generated for the batch used in the bioequivalence/biowaiver studies.
- Provide information on tablet “scoring,”, if applicable

    - Functional scoring:

        - Provide data from a study on the uniformity of dosage units of the tablet halves in terms of United States Pharmacopoeia (USP) or European Pharmacopoeia (Ph Eur)/British Pharmacopoeia (BP) recommendations. The data generated should support and be in line with the dosage and directions outlined in the PI/PIL.

    - Non-functional scoring:

        - This should be explained / justified. It should be indicated as non-functional in the PI/PIL.

- Pre-formulation testing;
- Clinical trial formulations;
- Discussion or explanation of novel formulations and novel IPI composition, function, and safety;

- Any differences in the formulation during the development should be indicated clearly in tabulated form;
- Stability (may refer to section 3.2.P.8);
- Discussion of the stability of the final product formulation, the parameters and specifications used during stability, and to confirm quality for lot release;
- Conclusion on stability and shelf-life allocation.

3.2.P.2.2.2 Overages (Name, Dosage Form)

Provide the following information:

- A justification/explanation for overages.
- Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable, unless justified.

3.2.P.2.2.3 Physicochemical and Biological Properties (Name, Dosage Form)

- Parameters relevant to the performance of the final 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.
- Show that no precipitation will occur with poorly soluble APIs formulated at a non-physiological pH or formulated with co-solvents.

3.2.P.2.3 Manufacturing Process Development (Name, Dosage Form)

The selection and optimization of the manufacturing process described in 3.2.P.3.3, the critical aspects, in particular, should be explained. Where relevant, the method of sterilization should be explained and justified, and compatibility with production equipment (e.g., filter media).

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.

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 storage, transportation (shipping), and use of the final product should be discussed. This discussion should consider, for example: choice of materials; protection from moisture and light; compatibility of the construction materials with the dosage form (including sorption to container and leaching, injections with rubber closures); safety of construction materials; and performance, such as reproducibility of the dose

delivery from the device when presented as part of the FPP product (e.g., inhalers/aerosols).

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 limit testing for non-sterile products, and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. This should be determined on at least one stability batch (aging).

For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed, as well as in-use stability testing, whether there is a preservative or not, including eye drops. Also see 3.2.P.8.

3.2.P.2.6 Compatibility (Name, Dosage Form)

The compatibility of the FPP with:

- Reconstitution diluent(s);
- IV solutions: provide data or reference to primary references;
- Dosage devices (e.g., precipitation of API in solution; sorption on injection administration sets; adsorption by in-line filters) should be addressed to provide appropriate and supportive information for the labeling.

3.2.P.3 Manufacture (Name, Dosage Form)

3.2.P.3.1 Manufacturer(s) (Name, Dosage Form)

If more than one pharmaceutical manufacturing facility/site is involved in any of the manufacturing or packaging processes, the complete name and physical address of each site should be given, the various stages of manufacturing and packaging at each site clearly identified, and the declaration of similarity included in section 1.7.5. of module 1. If all the stages of manufacturing and packaging are performed at one site, a statement confirming this will suffice.
An inspection flow diagram, also of FPP intermediates, clearly indicating the sites and processes, including clear distinction between primary and secondary packers, should be included. (section 1.7.10 of module 1).

3.2.P.3.2 Batch Formula (Name, Dosage Form)

The batch manufacturing formulation, also for FPP intermediates, and the batch size(s) (number of dosage units) should be included. If more than one batch size is indicated, the batch formulation for each of the batch sizes should be given.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (Name, Dosage Form)

The following should be submitted:

- A comprehensive flow diagram, detailing the various stages of manufacturing.

- A comprehensive description of the manufacturing procedures, detailing the various stages of manufacturing, derived from the master manufacturing documents.
  The type and size of manufacturing equipment (including sieve sizes in metric units), duration of treatment, temperature, light and humidity conditions, machine settings (e.g., rotation speed or rpm), and other relevant details should be indicated.

  For sterile manufacturing, the grades of clean areas should also be indicated.

- A brief description of the packaging procedure:

  A brief description of the packaging procedure reflecting the stages, temperature, humidity, and other conditions applicable for the packaging of specific dosage forms (e.g., effervescent tablets and granules) should be included.

  For sterile manufacturing, the grades of clean areas should also be indicated.

  The frequency of all in-process control tests (analytical, microbiological, physical, packaging, and labeling) should be shown in the flow diagram or specified in the description.

- Either a copy of the Master Batch Manufacturing and Packaging Document or Records for a batch or the Batch Records should be available for inspection, or be available on request.

3.2.P.3.4 Controls of Critical Steps and Intermediates (Name, Dosage Form)

The frequency of all in-process control tests (analytical, microbiological, physical, packaging, and labeling) should be shown in the flow diagram or specified in the description.

3.2.P.3.5 Process Validation and/or Evaluation (Name, Dosage Form)

A process validation protocol (VP) or validation report (VR) should be submitted.

The validation of the maximum holding time of the final product before packaging, and the holding time of FPP intermediates before further processing should also be addressed. The conditions during storage and/or shipping should be covered.

If different sterilization methods are used, validation of each method should be addressed in the VP or VR that is provided. This would include a description of the sterilization processes, aseptic manipulation, in-process controls, and grades of clean areas. Validation should include the validation of the maximum holding time before packing into the final container, and the holding time of FPP intermediates before further processing.

New Applications for Registration:

A VP or a VR should be included in 3.2.P.3.5. If the VP is submitted, the VR should be submitted only if and when requested by the DGDA.

Applications for Change in Applicant/Manufacturer/Packer/Laboratory

A VP or VR should be submitted with each application for a change in manufacturer or laboratory, or a change in the applicant where it also involves a change in the manufacturer.

If the validation has already been done, it should be indicated as such in the application, and the VP and VR have to be submitted.

3.2.P.4 Control of Inactive Pharmaceutical Ingredients (Name, Dosage Form)

The approved name of each ingredient should concur with that reflected in the formulation in section 3.2.P.1.

3.2.P.4.1 Specifications (Name, Dosage Form)

Compendial and Non-Compendial

1. Specifications (titles and the limits) of all the IPIs and also the IPIs of FPP intermediates, should be listed. Adherence to current pharmacopoeia requirements (BP, USP, and Ph Eur), where applicable, is recommended, in which case it is not necessary to list specifications. Any deviation from such specifications should be fully substantiated (e.g., non-inclusion of a specific impurity specification due to a different route of synthesis).

Use of any other pharmacopoeia should be justified and acceptable to the DGDA. In the latter case, copies of the relevant monographs should be included.

More than one pharmacopoeia may be used for the IPIs provided that each individual reference is used fully, and not partially or selectively. For example:

- the USP may be used for starch and the BP for lactose;
- an individual IPI may be referenced fully in two or more recognized pharmacopoeia simultaneously;
- an in-house specification consisting of all parameters and that includes the most stringent criteria of acceptance of two or more recognized pharmacopoeia.

For non-pharmacopoeia entities, the specifications should be at the pharmacopoeia level, i.e., based on current pharmacopoeia requirements for similar pharmacopoeia entities. (See ICH Q6A.**Error! Bookmark not efined.**)

2. Functionality specifications that confirm the IPI characteristics should be indicated.

3. Colorants and flavorants should comply with either one of the following:

    - At least a specification and control procedure regarding the chemical identification, a statement that the flavorants comply with the general requirements, and that the colorants comply with the purity criteria. At least a specification and control procedure regarding chemical identification and a statement that it complies with the directives of the EU or the register of the USFDA.

4. Microbial limits and control procedures for all organic ingredients of natural origin should be included (e.g., maize starch is an organic IPI of natural origin [test], but selenium dioxide is an inorganic IPI of natural origin [no test]).

5. Empty capsule specifications should include the description, moisture content, disintegration time, and microbial limits.

6. The absence of diethylene glycol should be specified for propylene glycol and glycerine if the dosage form is for oral or parenteral administration.

7. Specifications and control procedures should be included for intermediate preparations used as ingredients in the formulation as well as for each of the

ingredients contained in the intermediate preparation. If stock preparations of the intermediate preparation are used, specification and control procedures to ensure the stability and confirm the identity should be included.

8. For biological medicines:

    a) Specifications for the primary production lot used in the manufacture of the final filling lot of a biological medicine and specifications for all ingredients for the diluent should be listed.
    b) Tests for a biological source material should include tests to confirm the identification, safety, and potency of the primary production or bulk lot used in the manufacture of the final filling lot.
    c) Parameters and criteria of acceptance to confirm the identification, safety, and potency of the product should be provided.

3.2.P.4.2 Analytical Procedures (Name, Dosage Form)

Control procedures for all IPIs should be fully described. These should include physicochemical tests, purity tests, solubility and assay, and any other relevant tests. When pharmacopoeia methods are used, they should be current and may be referred to.

3.2.P.4.3 Validation of analytical procedures (Name, Dosage Form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate. (Refer to ICH Guidelines Q2R1, Q6B.[9])

3.2.P.4.4 Justification for Specifications (Name, Dosage Form)

Justification for the proposed excipient specification should be provided, where appropriate. (Refer ICH Guidelines Q3C and Q6B.[9])

3.2.P.4.5 Excipients of Human or Animal Origin (Name, Dosage Form)

Refer to section 3.2.A.3 and ICH M4Q.**Error! Bookmark not defined.**

3.2.P.4.6 Novel Excipients (Name, Dosage Form)

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

[9] http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html.

3.2.P.5 Control of Pharmaceutical Product (Name, Dosage Form)

3.2.P.5.1 Specification(s) (Name, Dosage Form)

1. Specifications (titles and limits) should be listed for in-process controls, FPP intermediate controls, final product controls (batch release), stability controls, and the reconstituted or diluted final product (if applicable). (If the in-process controls are submitted in section 3.2.P.3.3 of module 3, a cross reference will suffice.) In-process controls should be clearly identified as such, including those performed on bulk (e.g., liquids and semi-solids prior to packaging).
   If a product is included in a recognized pharmacopoeia, any deviation from the relevant monograph should be justified.

2. The description of the final product and the description given under “Identification” in the package insert should correspond. The description should be such that visual identification of counterfeit medicines is facilitated, where possible.

3. If any specification is not appropriate for a particular product, an explanation should be included. Other parameters not appropriate for stability testing should also be included (e.g., a specification for residual organic solvents used during the coating procedure or sterility).

   The limits and acceptance criteria for each parameter (physical, chemical, and microbial, if applicable) should be fully described. To state "complies" for acceptance criteria is not acceptable.

Physical and Other Properties

4. At least the following physical and other properties additional to those listed in the Stability Guideline, should be specified, as appropriate, for the dosage form, unless the omission is justified:

   a) Tablets, lozenges, capsules, suppositories

      Theoretical mass, average mass and mass limits, uniformity of dosage units, divisibility of scored tablet with the relevant mass uniformity of the divided tablet.

      Intactness of coating, in the case of coated tablets, if the coating has a protective purpose. If not appropriate for a particular product (e.g., film coat), an explanation should be included.

Microbial testing, as lot release requirement for capsules, is not a requirement if microbial testing of the empty capsules is performed and submitted in section 3.2.P.4 of module 3.

For soft gelatin capsules containing oily liquid, peroxide value /acid value/ iodine value and any other appropriate parameter, suspension content uniformity of each should be provided.

b) Emulsions, suspensions, solutions:

Alcohol content, tonicity (eye and nasal preparations), fill volume or mass, deliverable volume. Peroxide value/acid value/iodine value and any other appropriate parameter for oily preparations should be included

c) Powders, granules (including those for reconstitution), metered dose inhalation aerosols: Fill volume or mass.

d) Ointments, creams

Peroxide value/acid value/iodine value and any other appropriate parameter for oily preparations should be included.

e) Parenterals

Evaluation of FPP intermediates for parenterals should also include homogeneity, and FPP intermediate sterile powders should also include evaluation of sterility and bacterial endotoxin testing.

f) FPP intermediate (defined in the WHO Guideline to Good Manufacturing Practices as partially completed final product, pre-mixes, microspheres, granules, coated granules, sterile powders, etc.).

FPP intermediates should also include evaluation of homogeneity and other appropriate parameters relevant to the FPP intermediate product/dosage form.

Assay/Content

5. The limits of acceptance for the content of each active ingredient should be expressed as a percentage of the label claim. Limits greater than 5.0 % of the label claim should be justified, except in the case of vitamins.

6. Uniformity of dosage units should be in accordance with the general requirements of the current editions of the official pharmacopoeia. Note that

the uniformity has been harmonized in the ICH region (see ICH guideline Q4B Annex 6).[10]

Also refer to the WHO Technical Report Series 929, "Guidelines for the Registration of Fixed-dose Combination Medicinal Products" (2005) or the most recent revision.

FPP intermediates, including parenterals, should also be evaluated for homogeneity. (Refer paragraph 4. above.)

Dissolution and Disintegration

7. Batch release and stability specifications for all solid oral dosage forms, including chewable tablets and suspensions, where applicable, should include a requirement for the dissolution of the API(s) (generally single point for immediate release, multipoint for modified release), unless otherwise determined by the DGDA.

8. Disintegration time, where relevant, for example, for chew tablets, matrix tablets, and soft gelatin capsules, should be determined on all batches on which dissolution is not determined as a requirement for lot release as well as for stability. Disintegration time may be used as a lot release requirement for preparations containing multivitamins and minerals, unless a dissolution requirement for a specific product is included in the USP, in which case dissolution should be done as a lot release requirement.

Preservative Efficacy

9. The preservative efficacy of relevant dosage forms and/or presentations (e.g., multi-dose vials, eye drops) should be specified in section 3.2.P.5.1 and presented in section 3.2.P.8 of module 3. However, once established for the lowest limit of preservative content specification, it is not a routine batch test requirement.

Endotoxins

10. For a product from a non-biological origin that has endotoxin levels, the validation data, as required by the USP/BP/Ph Eur, should be submitted.

11. If the endotoxin levels are not determined according to the method in a recognized pharmacopoeia, the validation data should be submitted for evaluation.

[10] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q4B/Q4B_Annex_6_Step_4.pdf.

3.2.P.5.2 Analytical Procedures (Name, Dosage Form)

All control procedures, other than those from a recognized pharmacopoeia, should be described in full, with calculations included, where relevant.
If an analysis is not technologically possible (e.g., complex extracts), an explanation and alternative quality criteria should be submitted.

3.2.P.5.3 Validation of Analytical Procedures (Name, Dosage Form)

1. The full validation data of the assay method of the API related to batch release should be submitted. Chromatograms confirming the separation of the API from the degradation products, if relevant, should be included.
2. It should be demonstrated that the assay method is stability-indicating, i.e., it should distinguish between the API(s) and the degradation product(s).

3. If the assay method used to determine the API content is not stability-indicating, it cannot be used for assaying after importation.

4. If the assay method (chromatographic) is taken from one of the latest recognized pharmacopoeias, other partial validation data (e.g., system suitability and specificity) should be submitted.

5. If an assay method different from the batch release method is used for stability testing, the validation of the assay method and a full description thereof should be submitted.

6. Supportive chromatograms for the validation should be submitted, if relevant.

7. All other quantitative assay methods (e.g., preservatives, degradation products, antioxidants, dissolution assay) should be validated and the validation data included.

   If not in accordance with the relevant pharmacopoeia, an explanation should be included for the deviation. All the relevant limits should also be justified by stability or batch data.

3.2.P.5.4 Batch Analyses (Name, Dosage Form)

1. Complete batch analysis data for at least two batches (pilot or production) of the final product should be submitted with the application.

2. For imported products, at least the identification and assay of the API content should be performed by an approved laboratory (Finished Product

Release Control [FPRC]) after importation. This is to verify that the product has not been affected adversely during transport.

3.2.P.5.5 Characterization of Impurities (Name, Dosage Form)

Information on the characterization of impurities should be provided, if not previously provided in section 3.2.S.3.2 (Impurities) (Refer to ICH Guidelines Q3B, Q5C, Q6A, Q6B.[9])

3.2.P.5.6 Justification for Specifications (Name, Dosage Form)

Justification for the proposed final product specifications should be provided. (Refer to ICH Guidelines Q3B, Q6A and Q6B.[9])

3.2.P.6 Reference Standards or Materials (Name, Dosage Form)

For NCEs and well-known non-compendial APIs, at least the following information on the primary reference standard should be provided:

- Purification method, if applicable
- Establishment of purity (potency)
- CoA, with a potency statement

If a pharmacopoeia monograph is claimed, the pharmacopoeia standard should be used.

Secondary standards should always be established against the pharmacopoeia/primary standard. For more details, refer to WHO Technical Report Series 943, Annex 3 (2007).[11]

3.2.P.7 Container Closure System (Name, Dosage Form)

1. The immediate container specifications (titles and limits), including the nature of the material, dimensions, and sketches, where applicable, as well as those of patient ready packs, the closure system, wadding, and any other component in direct contact with the product, where applicable, and a description of the control procedures, should be supplied.

   They should include:

   - The moisture and gas permeability of polyvinyl chloride (PVC), if not already supported by real time stability data of the product (not relevant for PVC forming a base layer of aluminum blisters); and

[11] http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf.

- Heat seal bond strength/intactness of the blister (integrity of the seal) – section 3.2.P.3.3 may be referred to for further details.

2. A description of the control procedures performed by the manufacturer of the final product should be given.

3. A brief description of the outer container, if any, should also be given. At least the nature of the material should be mentioned (e.g., outer cardboard carton).

4. The description of the container and that reflected in the package insert under "Presentation" and in the stability studies should correspond. To facilitate the visual identification of counterfeit medicines (also by the public), the description should include the type, color, and clarity of the container (e.g., clear plastic/silver aluminum blister).

5. If the product is packed in bulk containers, the type of material of the container should be described.

   The maximum period that the product may be stored (bulk) before final packaging should be given in section 3.2.P.3.3 of module 3. The nature of the container should be given in section 3.2.P.7 of module 3, with supporting data provided in section 3.2.P.8 of module 3.

6. The type of material and the dimensions, including sketches of ampoules, vials, aerosols, applicators, and administration sets should be given. Sketches of containers for oral dosage forms and blister packs are not required.

7. All pack sizes should be described in the submission.

8. If equivalent or more protective immediate container packaging material than that used in stability testing or approved (post-registration), is applied for, data to substantiate the claim should be submitted (e.g., USP permeation test).

9. Child-protective measures should be employed with regard to the retail sale of salicylates, paracetamol, and iron tablets or capsules. Smaller sales packs and blister packaging are regarded as suitable child protective measures.

3.2.P.8 Stability (Name, Dosage Form)

3.2.P.8.1 Stability Summary and Conclusion (Name, Dosage Form)

A tabulated summary of the data, clearly indicating the number and types /sizes (production, pilot, or experimental) of batches, packaging material, storage

conditions and storage period, and manufacturer of the API with API batch numbers, should be included for each final product manufacturer.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment (Name, Dosage Form)

The post-approval stability protocol and stability commitment should be provided. Refer to ICH guidelines Q1A and Q5C.

3.2.P.8.3 Stability Data (Name, Dosage Form)

All applications for registration of a medicine should be submitted with stability data, in accordance with the minimum requirements given in the Stability guideline.

3.2.A Appendices

3.2.A.1 Facilities and Equipment (Name, Manufacturer)

For Biotech:

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediates 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, sterilization, 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 (Name, Dosage Form, Manufacturer)

Information assessing the risk of 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 nonviral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information may 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 ICH guidelines Q5A, Q5D, and Q6B for more details.

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 sections 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 section 3.2.S.2.3.)

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk, or postviral 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 sections 3.2.S.2.4 and 3.2.P.3.4.) In accordance with ICH guidelines Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

In accordance with ICH guideline Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data may 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 sections 3.2.S.2.5 and 3.2.P.3.5.) For details, refer to the ICH guidelines Q5A, Q5D, and Q6B.

3.2.A.3 Novel Excipients

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

3.2.R Regional Information

Any additional medicinal substance and/or medicine product information specific to each region, e.g., in Asia, should be provided in section R of the application. Applicants should consult the appropriate regional guidance and/or regulatory authorities for additional guidance.

MODULE 3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

REFERENCES

1. Department of Health, Republic of South Africa, Medicines Control Council. Pharmaceutical and Analytical CTD/eCTD. http://www.mccza.com/genericDocuments/2.25_PA_CTD_Aug14_v4.pdf. Published June 2010. Revised August 2014. Accessed February 2014.
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4. European Medicines Agency. ICH: Topic M 4 Common Technical Document for the Registration of Pharmaceuticals for Human Use – Organisation CTD. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002721.pdf. Effective February 2004. Accessed February 2014.
5. WHO Technical Report Series 937. WHO Expert Committee on Specifications for Pharmaceutical Preparations. http://whqlibdoc.who.int/trs/who_trs_937_eng.pdf. Published 2006. Accessed February 2014.
6. WHO Technical Report Series 929. WHO Expert Committee on Specifications for Pharmaceutical Preparations. http://apps.who.int/prequal/info_general/documents/trs929/who_trs_929.pdf. Published 2005. Accessed February 2014.
7. Technical Report Series: biological products: general recommendations. http://www.who.int/biologicals/publications/trs/areas/biological_products/en/. Published 2009. Accessed February 2014.