الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

# Data Requirements for Human Drugs Submission

*Content of the Dossier*

**Version 4.0**

| | |
|---|---|
| Date of issue | 22 June 2011 |
| Date of implementation | 22 September 2011 |

# Data Requirements for Human Drugs Submission

*Content of the Dossier*

**Version 4.0**

Saudi Food & Drug Authority

Drug Sector

| | |
|---|---|
| *For Inquiries* | *SDR.Drug@sfda.gov.sa* |
| *For Comments* | *Drug.Comments@sfda.gov.sa* |

Please visit SFDA's website at
https://www.sfda.gov.sa/en/regulations?tags=2

for the latest update

**Saudi Food and Drug Authority**

**Vision and Mission**

## Vision

To be a leading international science-based regulator to protect and promote public health

## Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

## Document Control

| Version | Author | Date | Comments |
|---|---|---|---|
| 1.0 | Executive Directorate of Product Evaluation and Standards Setting | 22 June 2011 | Draft |
| 1.1 | Executive Directorate of Product Evaluation and Standards Setting | 24 June 2013 | Updated |
| 1.2 | Executive Directorate of Product Evaluation and Standards Setting | 12 April 2014 | Updated |
| 1.3 | Executive Directorate of Product Evaluation and Standards Setting | 15 July 2014 | Updated |
| 2.0 | Drug Sector | 9 March 2017 | Updated |
| 2.1 | Drug Sector | 24 October 2017 | Updated |
| 3.0 | Executive Directorate of Regulatory Affairs | 13 October 2022 | Updated |
| 4.0 | Executive Directorate of Regulatory Affairs | 03 August 2025 | Update (Next page shows the updated details) |

## What is New in this version?

The following table shows the update to the previous version:

| Section | Description of change |
|---|---|
| **Introduction** | **Add:** c) Well-Established Use application (WEU) |
| **1.0: Cover letter** | **Update:** Including the registration status worldwide. |
| **1.7.2: CPP or Free sales** | **Update:** The CPP submission is optional and no longer required for new MA applications within all regulatory pathways. |
| **1.7.9: Patent information** | **Add**: The related SFDA's reference. |
| **Additional Data** | **Add:** any SFDA exemption, advice or prior communication / Requirement for advanced therapy medicinal products |
| **3.2.S Drug Substance (Drug Master File)** | **Add:** Requirement for products containing viral vectors. |
| **3.2.S.1.2 Structure** | **Update:** For Biotech. |
| **3.2. S.3.2. Impurities** | **Update:** To cover degradation products, solvents, and elemental impurities and mandates a comprehensive risk assessment for N-nitrosamines across all potential contamination sources. |
| **3.2.S.4.2 Analytical Procedures** | **Updated:** Detailed documentation of calculation formulas and methods, including the use of raw data and scientific justification for any correction factors. |
| **3.2.P.2.1.2 Excipients** | **Add**: a restriction, stating that thiomersal is not permitted in pediatric vaccines intended for children under one year of age. |
| **3.2.P.2.2.1 Formulation Development (Scored tablets)** | **Update:** Requires score line description in product information, mandates testing on one batch per strength, and splitting method details. |
| **3.2.P.5.2 Analytical Procedures** | **Updated:** Detailed documentation of calculation formulas and methods, including the use of raw data and scientific justification for any correction factors. |
| **Characterization of Impurities 3.2.P.5.5** | **Updated:** mandates a risk assessment report for potential nitrosamine inclusion, considering sources like drug substance, excipients, water, solvents, manufacturing, packaging, and stability. |
| **3.2.R Regional Information** | **Add:** Specific requirements for biosimilars (comparative quality exercise) and advanced therapy medicinal products (shipping validation studies). |

# Table of Contents

## ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| **BA** | Bioavailability |
| **BE** | Bioequivalence |
| **BP** | British Pharmacopoeia |
| **BSE** | Bovine Spongiform Encephalopathy |
| **CEP** | Certificates of Suitability |
| **COO** | Country of Origin |
| **CPP** | Certificate of Pharmaceutical Product |
| **CRFs** | Case Report Forms |
| **eCTD** | Common Technical Document |
| **DMF** | Drug Master File |
| **EU** | European Union |
| **GCC** | Gulf Cooperation Council |
| **GCP** | Good Clinical Practice |
| **GLP** | Good Laboratory Practice |
| **GMO** | Genetically Modified Organism |
| **GMP** | Good Manufacturing Practice |
| **ICH** | International Conference on Harmonisation |
| **IV/IVC** | *In vitro*/*In vivo* Correlation |
| **NCE** | New Chemical Entity |
| **Non-GMO** | Non-Genetically Modified Organism |
| **PD** | Pharmacodynamics |
| **Ph. Eur.** | European Pharmacopoeia |
| **PIL** | Patient Information Leaflet |
| **PK** | Pharmacokinetics |
| **QOS** | Quality Overall Summary |
| **RMP** | Risk Management Plan |
| **SDR** | Saudi Drug Registration System |
| **SFDA** | Saudi Food and Drug Authority |
| **SPC** | Summary of Product Characteristics |
| **TSE** | Transmissible Spongiform Encephalopathy |
| **US FDA** | Food and Drug Administration of the United States |
| **USP** | United States Pharmacopoeia |
| **WHO** | World Health Organization |
| **WEU** | Well-Established Use application |

## INTRODUCTION

The information presented in this guidance is based on recommendations of the:

- WHO, as described in the *"Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part (2010)"*;
- ICH, as described in the *"M4Q (R1), M4S(R2), and "M4E(R1) (2002)"*; and
- EU, as described in the *"Notice to Applicants, Volume 2B: Presentation and content of the dossier (2006)"*.

The data requirements for each application will differ, depending on the drug submission type. However, all the required data should be in accordance with the eCTD structure *(i.e. applicants should not modify the overall organization of the eCTD as outlined in this guideline)*:

a) In case of **New Chemical Entity (NCE), Biologicals and Biosimilars** ALL the eCTD Modules are required.

b) In case of **Generic Products**:

In preparing the dossier for generic products, it is acknowledged that certain modules or sections of the eCTD would generally not be applicable and should be marked as such (and not to be deleted).

Please note that for applications of generic drug of a non-SFDA registered reference product should include in addition to the bioequivalence requirements, a comprehensive literature review of the active substance to support the generic product registration. The literature review should be submitted in module 2.5 clinical overview and covers the following aspects:

- The search should be as extensive and relevant as possible
- The rationale for the development of the active substance as well as the generic product. The search should support the efficacy and safety of the active ingredient in each proposed indication.
- Bioequivalence and bioavailability data of the generic product.
- Safety and efficacy of the active substance in each of the proposed indications.

- Methodology of the search used should be stated in detail (database used, keywords used, and filters applied as well as date and time the search was carried on).
- Provide a tabular listing of the identified literature with their citations and arrange the studies according to the following:
  - Start with the key clinical studies (e.g. confirmatory studies).
  - Well-designed, adequately powered, and preferably multicenter studies.
  - Studies that have registered protocol or registered in clinical trials registries (provide registration status).
  - Evidence from non-randomized controlled trials should be located in a separate section of the table.
  - Post marketing safety studies.
  - If possible, provide study reports for each identified study.

Summarize serious adverse events related to the product (from randomized controlled trials and observational studies as well as periodic safety update reports (PSUR) of the reference product).

– ***Module 1: Regional Administrative Information***

This Module is required to be submitted. It should contain documents specific to SFDA; e.g., application form, proposed labelling, alcohol-content declaration, patents information ... etc. The content and format of this module is further illustrated in this guideline.

– ***Module 2: Common Technical Document Summaries***

The following sections are required to be submitted under Module 2:

- 2.1 Table of Contents of Module 2-5.
- 2.2 Introduction:

This section should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page.

- 2.3 Quality Overall Summary:

The whole section is required and should reflects the information provided in Module 3.

- 2.5 Clinical Overview:

**2.5.2** *"Overview of Biopharmaceutics":* The summary of the comparative bioequivalence/bioavailability study reports should be provided under this section. In addition, critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) *(e.g., dosage form/strength proportionality and influence of food on exposure)* should be provided under this section.

– ***Module 3: Quality***

The whole section is required and the information should be presented according to the structured format described in this guideline.

– ***Module 4: Non-Clinical Study Reports***

Generally not applicable for generic products, however some exceptions may apply.

– ***Module 5: Clinical Study Reports***

It is anticipated that only the following relevant sections of Module 5 will normally be required.

- 5.1 Table of contents for Module 5
- 5.2 Tabular listing of all clinical studies
- 5.3 Clinical study reports
    - 5.3.1 Reports of biopharmaceutical studies
        - 5.3.1.2 Comparative BA & BE Study Reports

The comparative bioavailability/bioequivalence study reports should be presented in Module 5 under section **5.3.1.2** *"Comparative BA & BE Study Reports"*.

- 5.3.1.3 *In vitro*/*In vivo* Correlation (IV/IVC) study reports: if available
- 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human studies: Bioanalytical or analytical methods for BA/BE or *in vitro* dissolution studies should ordinarily be provided in the clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.
- 5.3.7 Case Report Forms and Individual Patient Listings: only Case Report Forms (CRFs) for subjects who experienced serious adverse events should be included. All CRFs should be available upon request.
- 5.4 Literature references

c) **Well-Established Use application**[1] (WEU):

When an active substance has been used for more than 10 years in a stringent regulatory authority, and its efficacy and safety have been well established for the claimed therapeutic indication, the application for marketing authorization may be based on published scientific literature.

For medicinal products with a well-established medicinal use, the following shall apply:

- The applicant shall submit Modules 1, 2 and 3 as described in this guideline.
- For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics. For further details, applicants should refer to SFDA's *Regulatory Guidance for Literature Based Support of Efficacy and Safety of Medicines*.

The following shall apply in order to demonstrate the well-established medicinal use:

- Factors which have to be taken into account in order to consider a well-established medicinal use of medicinal products are:
  - the time over which a substance has been used (must not be less than 10 years),
  - quantitative aspects of the use of the substance,

[1] Date of implementation: 01 February 2026

- the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and
- the coherence of scientific assessments.

- The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative efficacy and safety studies. All documentation, both favourable and unfavourable, must be communicated. It is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.
- Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

## Considerations for Quality Module:

**The following are recommendations for the presentation of the information in the Quality Module for different scenarios that may be encountered with any application:**

- **For a drug product containing more than one drug substance:** one complete "3.2.S" section should be provided for one drug substance, followed by other complete "3.2.S" sections for each drug substance.
- **For a drug substance from multiple manufacturers:** one complete "3.2.S" section should be provided for the drug substance from one manufacturer, followed by other complete "3.2.S" sections for each drug substance manufacturer.
- **For a drug product with multiple strengths:** one complete "3.2.P" section should be provided with the information for the different strengths provided within the subsections. One complete copy of the dossier should be provided for each strength.
- **For a drug product with multiple container closure systems** (e.g. bottles and unit dose blisters): one complete "3.2.P" section should be provided with the information for the different presentations provided within the subsections.
- **For multiple drug products** *(e.g. tablets and a parenteral product)*: a separate dossier is required for each drug product.
- **For a drug product supplied with reconstitution diluent(s)**, the information on the diluent should be provided in a separate part "3.2.P" if the diluent is co-packaged with the drug product. However, if the diluent is not co-packaged with the drug product, the compatibility of the diluent with the drug product should be discussed in 3.2.P.2.6.

## TABLE 1: THE eCTD STRUCTURE FOR HUMAN DRUGS SUBMISSION

| Section | Requirements |
|---|---|
| **Module 1** | **Regional Administrative Information** |
| 1.0 | Cover letter |
| 1.2 | Application Form |
| 1.3 | Product Information |
| 1.3.1 | Summary of Product Characteristics (SPC) |
| 1.3.2 | Labeling |
| 1.3.3 | Patient information leaflet (PIL) |
| 1.3.3.1 | Arabic leaflet |
| 1.3.3.2 | English leaflet |
| 1.3.4 | Artwork (*Mock-up*s) |
| 1.3.5 | Samples |
| 1.4 | Information on the experts |
| 1.4.1 | Quality |
| 1.4.2 | Non-clinical |
| 1.4.3 | Clinical |
| 1.5 | Environmental Risk Assessment |
| 1.5.1 | Non-Genetically Modified Organism (Non-GMO) |
| 1.5.2 | GMO |
| 1.6 | Pharmacovigilance |
| 1.6.1 | Pharmacovigilance System |
| 1.6.2 | Risk Management Plan |
| 1.7 | Certificates and Documents |
| 1.7.1 | GMP Certificate |
| 1.7.2 | CPP or Free-sales |
| 1.7.3 | Certificate of analysis – Drug Substance / Finished Product |
| 1.7.4 | Certificate of analysis – Excipients |
| 1.7.5 | Alcohol-content declaration |
| 1.7.6 | Pork- content declaration |
| 1.7.7 | Certificate of suitability for TSE |
| 1.7.8 | The diluents and coloring agents in the product formula |
| 1.7.9 | Patents Information |
| 1.7.10 | Letter of access or acknowledgment to DMF |
| 1.8 | Pricing |
| 1.8.1 | Price list |
| 1.8.2 | Other documents related |
| 1.9 | Responses to questions |

| Module 2[2] | Common Technical Document Summaries |
|---|---|
| 2.1 | Table of Contents of Module 2-5 |
| 2.2 | Introduction |
| 2.3 | Quality Overall Summary |
| | Introduction |
| 2.3.S | Drug substance |
| 2.3.S.1 | General Information |
| 2.3.S.2 | Manufacture |
| 2.3.S.3 | Characterization |
| 2.3.S.4 | Control of Drug Substance |
| 2.3.S.5 | Reference Standards or Materials |
| 2.3.S.6 | Container/Closure System |
| 2.3.S.7 | Stability |
| 2.3.P | Drug Product |
| 2.3.P.1 | Description and Composition of the Drug Product |
| 2.3.P.2 | Pharmaceutical Development |
| 2.3.P.3 | Manufacture |
| 2.3.P.4 | Control of Excipients |
| 2.3.P.5 | Control of Drug Product |
| 2.3.P.6 | Reference Standards or Materials |
| 2.3.P.7 | Container/Closure System |
| 2.3.P.8 | Stability |
| 2.3.A | Appendices |
| 2.3.A.1 | Facilities and Equipment |
| 2.3.A.2 | Adventitious Agents Safety Evaluation |
| 2.3.A.3 | Novel Excipients |
| 2.3.R | Regional Information |
| 2.4 | Nonclinical Overview |
| 2.5 | Clinical Overview |
| 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 | References |
| 2.6 | Non-Clinical Written and Tabulated Summaries |
| 2.6.1 | Introduction |
| 2.6.2 | Pharmacology Written Summary |
| 2.6.2.1 | Brief Summary |

[2] Module 2 should reflect the information provided in modules 3, 4 and 5.

| | |
|---|---|
| 2.6.2.2 | Primary Pharmacodynamics |
| 2.6.2.3 | Secondary Pharmacodynamics |
| 2.6.2.4 | Safety Pharmacology |
| 2.6.2.5 | Pharmacodynamic Drug Interactions |
| 2.6.2.6 | Discussion and Conclusions |
| 2.6.2.7 | Tables and Figures |
| 2.6.3 | Pharmacology Tabulated Summary |
| 2.6.4 | Pharmacokinetics Written Summary |
| 2.6.4.1 | Brief Summary |
| 2.6.4.2 | Methods of Analysis |
| 2.6.4.3 | Absorption |
| 2.6.4.4 | Distribution |
| 2.6.4.5 | Metabolism (interspecies comparison) |
| 2.6.4.6 | Excretion |
| 2.6.4.7 | Pharmacokinetic Drug Interactions |
| 2.6.4.8 | Other Pharmacokinetic Studies |
| 2.6.4.9 | Discussion and Conclusions |
| 2.6.4.10 | Tables and Figures |
| 2.6.5 | Pharmacokinetics Tabulated Summary |
| 2.6.6 | Toxicology Written Summary |
| 2.6.6.1 | Brief Summary |
| 2.6.6.2 | Single-Dose Toxicity |
| 2.6.6.3 | Repeat-Dose Toxicity |
| 2.6.6.4 | Genotoxicity |
| 2.6.6.5 | Carcinogenicity |
| 2.6.6.6 | Reproductive and Developmental Toxicity |
| 2.6.6.7 | Local Tolerance |
| 2.6.6.8 | Other Toxicity Studies (if available) |
| 2.6.6.9 | Discussion and Conclusions |
| 2.6.6.10 | References |
| 2.6.7 | Toxicology Tabulated Summary |
| 2.7 | Clinical Summary |
| 2.7.1 | Summary of Biopharmaceutic 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 |
| 2.7.3.3.1 | Study Populations |
| 2.7.3.3.2 | Comparison of Efficacy Results Across All Studies |
| 2.7.3.3.3 | Comparison of Results in Sub-Populations |
| 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 |
| 2.7.4.1.1 | Overall Safety Evaluation Plan and Narratives of Safety Studies |
| 2.7.4.1.2 | Overall Extent of Exposure |
| 2.7.4.1.3 | Demographic and Other Characteristics of Study Population |
| 2.7.4.2 | Adverse Events |
| 2.7.4.2.1 | Analysis of Adverse Events by Organ System or Syndrome |
| 2.7.4.2.2 | Narratives |
| 2.7.4.3 | Clinical Laboratory Evaluations |
| 2.7.4.4 | Vital Signs, Physical Findings, Observations Related to Safety |
| 2.7.4.5 | Safety in Special Groups and Situations |
| 2.7.4.5.1 | Intrinsic Factors |
| 2.7.4.5.2 | Extrinsic Factors |
| 2.7.4.5.3 | Drug Interactions |
| 2.7.4.5.4 | Use in Pregnancy and Lactation |
| 2.7.4.5.5 | Overdose |
| 2.7.4.5.6 | Drug Abuse |
| 2.7.4.5.7 | Withdrawal and Rebound |
| 2.7.4.5.8 | Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability |
| 2.7.4.6 | Post-Marketing Data |
| 2.7.4.7 | Appendix |
| 2.7.5 | References |
| 2.7.6 | Synopses of Individual Studies |

| Module 3 | Quality |
|---|---|
| 3.1 | Table of Contents of Module 3 |
| 3.2 | Body of data |
| 3.2.S | Drug Substance |
| 3.2.S.1 | General Information |
| 3.2.S.1.1 | Nomenclature |
| 3.2.S.1.2 | Structure |
| 3.2.S.1.3 | General Properties |
| 3.2.S.2 | Manufacture |
| 3.2.S.2.1 | Manufacturer(s) |
| 3.2.S.2.2 | Description of Process and Process Controls |
| 3.2.S.2.3 | Control of Materials |
| 3.2.S.2.4 | Control of Critical Steps and Intermediates |
| 3.2.S.2.5 | Process Validation and/or Evaluation |
| 3.2.S.2.6 | Manufacturing Process Development |
| 3.2.S.3 | Characterization |
| 3.2.S.3.1 | Elucidation of Structure and Other Characteristics |
| 3.2.S.3.2 | Impurities |
| 3.2.S.4 | Control of Drug Substance |
| 3.2.S.4.1 | Specifications |
| 3.2.S.4.2 | Analytical Procedures |
| 3.2.S.4.3 | Validation of Analytical Procedures |
| 3.2.S.4.4 | Batch Analyses |
| 3.2.S.4.5 | Justification of Specification |
| 3.2.S.5 | Reference Standards or Materials |
| 3.2.S.6 | Container/Closure Systems |
| 3.2.S.7 | Stability |
| 3.2.S.7.1 | Stability Summary and Conclusions |
| 3.2.S.7.2 | Post-approval Stability Protocol and Commitment |
| 3.2.S.7.3 | Stability Data |
| 3.2.P | Drug Product |
| 3.2.P.1 | Description and Composition of the Drug Product |
| 3.2.P.2 | Pharmaceutical Development |
| 3.2.P.2.1 | Components of the Drug Product |
| 3.2.P.2.1.1 | Drug substance |
| 3.2.P.2.1.2 | Excipients |
| 3.2.P.2.2 | Drug Product |
| 3.2.P.2.2.1 | Formulation Development |
| 3.2.P.2.2.2 | Overages |
| 3.2.P.2.2.3 | Physiochemical and Biological Properties |
| 3.2.P.2.3 | Manufacturing Process Development |

| | |
|---|---|
| 3.2.P.2.4 | Container Closure System |
| 3.2.P.2.5 | Microbiological Attributes |
| 3.2.P.2.6 | Compatibility |
| 3.2.P.3 | Manufacture |
| 3.2.P.3.1 | Manufacturer(s) |
| 3.2.P.3.2 | Batch Formula |
| 3.2.P.3.3 | Description of Manufacturing Process and Process Controls |
| 3.2.P.3.4 | Controls of Critical Steps and Intermediates |
| 3.2.P.3.5 | Process Validation and/or Evaluation |
| 3.2.P.4 | Control of Excipients |
| 3.2.P.4.1 | Specifications |
| 3.2.P.4.2 | Analytical Procedures |
| 3.2.P.4.3 | Validation of Analytical Procedures |
| 3.2.P.4.4 | Justification of Specifications |
| 3.2.P.4.5 | Excipients of Human or Animal Origin |
| 3.2.P.4.6 | Novel Excipients |
| 3.2.P.5 | Control of Drug Product |
| 3.2.P.5.1 | Specifications |
| 3.2.P.5.2 | Analytical Procedures |
| 3.2.P.5.3 | Validation of Analytical Procedures |
| 3.2.P.5.4 | Batch Analyses |
| 3.2.P.5.5 | Characterization of Impurities |
| 3.2.P.5.6 | Justification of Specifications |
| 3.2.P.6 | Reference Standards or Materials |
| 3.2.P.7 | Container/Closure System |
| 3.2.P.8 | Stability |
| 3.2.P.8.1 | Stability Summary and Conclusions |
| 3.2.P.8.2 | Post-Approval Stability Protocol and Stability Commitments |
| 3.2.P.8.3 | Stability Data |
| 3.2.A | Appendices |
| 3.2.A.1 | Facilities and Equipment |
| 3.2.A.2 | Adventitious Agents Safety Evaluation |
| 3.2.A.3 | Excipients |
| 3.2.R | Regional Information |
| 3.3 | Literature References |

| Module 4 | Non-Clinical Study Reports |
|---|---|
| 4.1 | Table of Contents of Module 4 |
| 4.2 | Study Reports |
| 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 |
| 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 |
| 4.2.2.7 | Other Pharmacokinetic Studies |
| 4.2.3 | Toxicology |
| 4.2.3.1 | Single-Dose Toxicity |
| 4.2.3.2 | Repeat-Dose Toxicity |
| 4.2.3.3 | Genotoxicity |
| 4.2.3.3.1 | In vitro Studies |
| 4.2.3.3.2 | In vivo Studies |
| 4.2.3.4 | Carcinogenicity |
| 4.2.3.4.1 | Long Term Studies |
| 4.2.3.4.2 | Short or medium term studies |
| 4.2.3.4.3 | Other studies |
| 4.2.3.5 | Reproductive and Development Toxicity |
| 4.2.3.5.1 | Fertility and Embryonic Development |
| 4.2.3.5.2 | Embryo-Fetal Development |
| 4.2.3.5.3 | Pre- and Post-natal Development & Maternal Function |
| 4.2.3.5.4 | Offspring, Juvenile, Second & Third-Generation Studies |
| 4.2.3.6 | Local Tolerance |
| 4.2.3.7 | Other Toxicity Studies |
| 4.2.3.7.1 | Antigenicity |
| 4.2.3.7.2 | Immunogenicity |
| 4.2.3.7.3 | Mechanistic Studies (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 |
| 4.3 | Literature References |

| Module 5 | Clinical Study Reports |
|---|---|
| 5.1 | Table of Contents of Module 5 |
| 5.2 | Tabular Listing of All Clinical Studies |
| 5.3 | Clinical Study Reports |
| 5.3.1 | Reports of Biopharmaceutic Studies |
| 5.3.1.1 | Bioavailability (BA) Study Reports |
| 5.3.1.2 | Comparative BA & BE Study Reports |
| 5.3.1.3 | In vitro/In vivo Correlation (IV/IVC) study reports |
| 5.3.1.4 | Reports of Bioanalytical and Analytical Methods for Human studies |
| 5.3.2 | Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials |
| 5.3.2.1 | Plasma Protein Binding Study Reports |
| 5.3.2.2 | Reports of Hepatic Metabolism and Drug Interactions studies |
| 5.3.2.3 | Reports of Studies Using other Human Biomaterials |
| 5.3.3 | Reports of Human Pharmacokinetic Studies |
| 5.3.3.1 | Healthy Subject PK and Tolerability |
| 5.3.3.2 | Patient PK and Initial Tolerability |
| 5.3.3.3 | Intrinsic Factor PK Study Reports |
| 5.3.3.4 | Extrinsic Factor PK Study Reports |
| 5.3.3.5 | Population PK Study Reports |
| 5.3.4 | Reports of Human Pharmacodynamic (PD) Studies |
| 5.3.4.1 | Healthy Subject PD and PK/PD Study Reports |
| 5.3.4.2 | Patient PD and PK/PD Study Reports |
| 5.3.5 | Reports of Efficacy and Safety Studies |
| 5.3.5.1 | Study reports of Controlled Clinical Studies pertinent to the claimed Indication |
| 5.3.5.2 | Study reports of Uncontrolled Clinical Studies |
| 5.3.5.3 | Reports of Analyses of Data from More than One Study |
| 5.3.5.4 | Other Study Reports |
| 5.3.6 | Reports of Post-Marketing Experience |
| 5.3.7 | Case Report Forms and Individual Patient Listings |
| 5.4 | Literature References |

# MODULE 1 REGIONAL ADMINISTRATIVE INFORMATION

## 1. Cover letter

The applicant shall include a cover letter for each submission outlines the product's worldwide registration status.

A template is provided in the *SFDA Guidance for Submission.*

## 1.2. Application Form

The completed application form printed out from the Saudi Drug Registration (SDR) system (https://esdr.sfda.gov.sa) should be presented in this section.

## 1.3. Product Information

This section contains the Summary of Product Characteristics (SPC), Labeling, Patient Information Leaflet (PIL) in Arabic and English, Artwork and the Samples.

### *1.3.1. Summary of Product Characteristics (SPC)*

The SPC should include the name of the product, strength, pharmaceutical form, quantity of active ingredients, posology, method of administration, indications, contraindications, excipients, shelf-life and any special warnings and precautions for use … etc.

*Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information.*

### *1.3.2. Labeling*

The labeling forms part of the authorization of the product and must therefore be approved by the SFDA. The text of the labeling must be in compliance with the SPC.

*Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information.*

### *1.3.3. Patient Information Leaflet (PIL)*

1.3.3.1. Arabic leaflet

1.3.3.2. English leaflet

The Patient Information Leaflet (PIL) forms part of the authorization of the product and must therefore be approved by the SFDA. The text of the PIL must be in compliance with the SPC. The application for a marketing authorization must include a draft for the PIL.

*Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information.*

### *1.3.4. Artwork (Mock-ups)*

*A mock-up* is a flat artwork design in full color, presented so that, following cutting and folding, where necessary, it provides a full size replica of both the outer and immediate packaging so that the two dimensional presentation of the label text is clear.

The application for a marketing authorization must include 4 *mock-ups* as following:

1. The non-contrast photo of flat outer pack.

2. The on shelf photo of outer pack.

3. The photo of internal product.

4. The photo of dosage form.

*Refer to the GCC Guidance for Presenting the SPC, PIL and Labeling Information.*

### *1.3.5. Samples*

A number of samples should be provided in order to perform complete testing. The required quantities of samples is further described in *the SFDA Guidance for Submission* .The submitted samples must represent the final finished product to be marketed in Saudi Arabia.

## 1.4. Information on the experts

### *1.4.1. Quality*

### *1.4.2. Non-Clinical*

### *1.4.3. Clinical*

It is important to emphasize that well prepared expert reports greatly facilitate the task of the SFDA in evaluating the dossier and contribute towards the speedy processing of applications.

Authors of expert reports must be chosen on the basis of their relevant qualifications and their recognized expertise in the field concerned. The experts should preferably not have been personally involved in the conduct of the tests included in the dossier.

Each expert report should consist of:

- An abbreviated product profile;
- A critical evaluation of the dossier;
- The opinion of the expert as to whether sufficient guarantees have been provided as to the suitability of the product for its proposed use;
- A summary of all the important data;
- The signature of the expert and the place and date of the report's issue;
- The expert's *curriculum vitae* and a declaration of the expert's professional relationship to the applicant.

It is essential to note that the expert reports must include a critical discussion of the properties of the product as demonstrated by the contents of the dossier. The expert is expected to take and defend a clear position on the final product, in the light of current scientific knowledge. A simple factual summary of the information contained in the application is not sufficient and the expert reports must not be a repetition of other parts of the dossier, although important data will need to be summarized in the expert report in some form. Both expert reports and summaries must contain precise references to the information contained in the main documentation. If experts wish to supplement their report by reference to additional literature, they must indicate clearly that the applicant has not included this information in the relevant part of the dossier.

### 1.5. Environmental Risk Assessment

#### 1.5.1. Non-Genetically Modified Organism (Non-GMO)

#### 1.5.2. GMO

The applicant shall include an evaluation for any potential risks of the product to the environment. This should include risks to the environment arising from use, storage and disposal of products and not for risks arising from the synthesis or manufacture of products.

### 1.6. Pharmacovigilance

#### 1.6.1. Pharmacovigilance System

A summary description of the pharmacovigilance system used by the marketing authorization holder and by the SFDA to fulfil the tasks and responsibilities listed in the published guideline on good pharmacovigilance practices which is designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance.

For further information, refer to Guideline on Good Pharmacovigilance Practices.

#### 1.6.2. Risk Management Plan

A detailed description of the risk management system.

To this end, it must identify or characterize the safety profile of the medicinal product(s) concerned, indicate how to characterize further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimize the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorization obligations that have been imposed as a condition of the marketing authorization.

For further information, refer to Guideline on Good Pharmacovigilance Practices.

## 1.7. Certificates and Documents

### 1.7.1. GMP Certificate

A valid GMP Certificate should be submitted.

### 1.7.2. CPP or Free-sales

It should be noted that CPP / free -sales submission is optional and no longer required for new Marketing Authorization applications (MAA) within all regulatory pathways. However, SFDA reserves the right to request the CPP at any time during the application process or post-authorization if deemed necessary.

If needed, the CPP should be in accordance with WHO guidelines. If the CPP is not available, a marketing authorization (or free sales certificate) from the country of origin (COO) should be submitted, including the following:

1. Product trade name in the COO.
2. Number and date of marketing authorization in the COO.
3. Name of active and inactive substances with their concentrations.
4. A statement that certifies the product is marketed in the COO. If not, please specify the reasons and provide a marketing authorization showing that the product is marketed in one of the countries approved by SFDA (reference member state in EU, USA, Canada, Switzerland, Australia and Japan).
5. Provide official document demonstrating that the product has been registered for no less than one year in the COO.
6. Provide the Summary of Product Characteristics (SPC).
7. Provide a copy of the patient information leaflet (PIL).

### 1.7.3. Certificate of analysis – Drug Substance/Finished Product

- Certificates of analysis for more than one batch of the drug substance should be submitted from the supplier (drug substance manufacturer).
- Certificates of analysis for the drug substance should be submitted from the finished product manufacturer.
- Certificates of analysis for more than one batch of the finished product should be submitted.

**The information on drug substance batch analyses is recommended to be presented as follows:**

| Batch number | Batch size | Batch type | Site(s) of: | | Date(s) of: | |
|---|---|---|---|---|---|---|
| | | | Manufacturing | Analysis | Manufacturing | Analysis |
| | | | | | | |

**The information on finished product batch analyses is recommended to be presented as follows:**

| Batch number | Batch size | Batch type | Site(s) of: | | Date(s) of: | | API manufacturer |
|---|---|---|---|---|---|---|---|
| | | | Manufacturing | Analysis | Manufacturing | Analysis | |
| | | | | | | | |
| | | | | | | | |

### 1.7.4. Certificate of analysis – Excipients

– Certificates of analysis for more than one batch of the excipients may be submitted to support the application.

### 1.7.5. Alcohol-content declaration

This section should contain a declaration letter, in an official company letterhead, stating that the finished product is free from alcohol. In the case of alcohol come into existence in the finished product, a pre-approval from the authority is required along with the justification to make it possible for the authority to evaluate the request and send the respond to the applicant.

### 1.7.6. Pork-content declaration

This section should contain a declaration letter in an official company letterhead stating that the product is free from any materials of pork/porcine source.

### 1.7.7. Certificate of suitability for TSE

This section should contain a valid TSE Certificate of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), which conforms the compliance of a substance to the relevant monograph of the European Pharmacopoeia.

### 1.7.8. The diluents and coloring agents in the product formula

This section should contain a declaration letter in an official company letterhead stating the diluents and coloring agents used in the product formula.

### 1.7.9. Patent Information

This section should contain a declaration letter in an official company letterhead stating the patent status of the product.

For more information refer to "*Approach of Dealing with Patents when Register Generic Drugs in SFDA*".

### 1.7.10. Letter of access or acknowledgment to DMF

The DMF owner should specify which of the following options is chosen to present the drug substance information:

- Certificate of suitability (CEP); or
- Drug master file (DMF); or
- Complete information on the "3.2.S drug substance" sections.

A letter written by the DMF owner or authorized Agent permitting SFDA to reference information in the DMF on behalf of the Applicant.

**The letter of access should include the following information on DMF:**

- Name of the holder:
- **Applicant's part:**
  - DMF Version number:
  - DMF Date (yyyy-mm-dd):

- **Restricted part:**
  - DMF Version number:
  - DMF Date (yyyy-mm-dd):
- If no changes were made within the last five years, a letter indicating that the DMF remains current.
- In regards to the ***restricted part***, has it been submitted to the SFDA:

  ❍ Yes ❍ No

  If yes, please attach the confirmation email of DMF/ASMF submission.

**If the applicant has already a <u>Certificate of Suitability (CEP)</u>, the following should be submitted:**

- A valid Certificate of Suitability (CEP) (including any annexes) where the declaration of access for the CEP should be duly filled out by the CEP holder.
- A written assurance that no significant changes in the manufacturing method have taken place following the granting of certificate or its last revision.

For more information about the certificates that must be authenticated *refer to the SFDA Guidance for Submission.*

### 1.8. Pricing

The applicant shall include the price of the product in countries listed in the *SFDA Guidance for Submission.*

#### 1.8.1. Price List:

Price list (Form 16) containing of all marketed countries of the product as detailed in the pharmaceutical pricing rules

#### 1.8.2. Other documents related:

- Pricing Application Form (found in the pharmaceutical pricing rules)
- Clinical studies overview (including: approved indication, guidelines, and comparative safety and efficacy studies)

- Economic studies summaries

### 1.9. Responses to questions

The response document should follow the same presentation as the initial dossier.

The applicant should include in this section a document which lists the questions with the corresponding narrative text response for each question. This section will not be used for supporting technical documentation, which will be included to the relevant Modules. Each question should be followed by the name of section, page number and a hyperlink where the answer can be found in the concerned Module.

### Additional Data:

In this section the applicant/sponsor should submit the following:

- The Bioequivalence Study Summary Template[3].
- Excel file for the tabulated plasma concentrations for the test and reference products along with the randomization plan in the bioequivalence study.
- Addition documents related to abridge and verification, if applicable.
- Any SFDA exemption, advice, or prior communication.
- For advanced therapy medicinal products (ATMPs): Providing Out of Specification Release Protocol if applicable.

[3] The template can be found in *Guidelines for Bioequivalence* - Annex 1 and also available as a soft copy in the SFDA website *Forms Section.*

# MODULE 2 COMMON TECHNICAL DOCUMENT SUMMARIES

## Table of Contents of Module 2-5

The table of content should list all documents included in Modules 2 to 5.

## 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. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the eCTD. The QOS should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under module 4), including cross-referencing to volume and page number in other Modules, the following requirements should be submitted under this module if applicable:

## 2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product

Non-Proprietary Name of Drug Product

Non-Proprietary Name of Drug Substance

Company Name

Dosage Form

Strength(s)

Route of Administration

Proposed Indication(s)

## 2.3. S DRUG SUBSTANCE

- **2.3.S.1 General Information**

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

For Biologics:

Identity , physical prosperity and Biological activity.

- **2.3.S.2 Manufacture**

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

- **2.3.S.3 Characterization**

How was the drug substance structure elucidated and characterized?

How were potential impurities identified and characterized?

- **2.3.S.4 Control of Drug Substance**

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

- **2.3.S.5 Reference Standards**

How were the primary reference standards certified?

For biologics:

Brief on characterization and stability of the primary standard and protocol for generating working standards

- **2.3.S.6 Container Closure System**

What container closure system is used for packaging and storage of the drug substance?

- **2.3.S.7 Stability**

What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

## 2.3. P DRUG PRODUCT

### 2.3. P.1 Description and Composition

What are the components and composition of the final product? What is the function(s) of each excipient?

Does any excipient exceed the IIG limit for this route of administration?

Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

### 2.3.P.2 Pharmaceutical Development

#### 2.3.P.2.1 Components of the Product

##### 2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

##### 2.3.P.2.1.2 Excipients

What evidence supports compatibility between the excipients and the drug substance?

#### 2.3.P.2.2 Drug Product

What attributes should the drug product possess?

How was the drug product designed to have these attributes?

Were alternative formulations or mechanisms investigated?

How were the excipients and their grades selected?

How was the final formulation optimized?

### 2.3.P.2.3 Manufacturing Process Development

(If applicable for example: Non-Simple Dosage Form)

Why was the manufacturing process described in 2.3.P.3 selected for this drug product?

How are the manufacturing steps (unit operations) related to the drug product quality?

How were the critical process parameters identified, monitored, and/or controlled?

What is the scale-up experience with the unit operations in this process?

### 2.3.P.2.4 Container Closure System

What specific container closure attributes are necessary to ensure product performance?

### 2.3.P.3 Manufacture

(For All Products)

Who manufactures the drug product?

What are the unit operations in the drug product manufacturing process?

What is the reconciliation of the exhibit batch?

Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?

What are the in-process tests and controls that ensure each step is successful?

(If Product is Not a Solution)

What is the difference in size between commercial scale and exhibit batch? Does the equipment use the same design and operating principles?

(If the Product is a NTI Drug or a Non-Simple Dosage Form)

In the proposed scale-up plan what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

What evidence supports the plan to scale up the process to commercial scale?

### 2.3.P.4 Control of Excipients

What are the specifications for the inactive ingredients and are they suitable for their intended function?

For Biologics:

What is the function of each excipient?

### 2.3.P.5 Control of Drug Product

What is the drug product specification? Does it include all the critical drug product attributes?

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

### 2.3.P.6 Reference Standards and Materials

How were the primary reference standards certified?

### 2.3.P.7 Container Closure System

What container closure system(s) is proposed for packaging and storage of the drug product? Has the container closure system been qualified as safe for use with this dosage form?

### 2.3.P.8 Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

What drug product stability studies support the proposed shelf life and storage conditions?

What is the post-approval stability protocol?

This 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). The use of tables to summarize the information is encouraged, where possible.

### Non-Clinical Overview

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

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/active substance and product should be included along with what is known of their potential pharmacological and toxicological effects. This assessment should form part of the justification for proposed impurity limits in the drug substance/active 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/medicinal product includes a novel excipient, an assessment of the information regarding its safety should be provided.

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.

## Clinical Overview

The clinical overview should include:

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

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will 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 summarization of the clinical information in the eCTD, 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 should:

1. Present the strengths and limitations of the development program and study results,
2. Analyze the benefits and risks of the medicinal product in its intended use, and
3. 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 good clinical practice (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 optimize 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.

## Non-Clinical Written and Tabulated Summaries

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 Nonclinical Written Summaries will facilitate their review. A table for converting units might also be useful.

When available, *in vitro* studies should precede *in vivo* studies. Where multiple studies of the same type are summarized 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.
- Nonhuman primate.
- Other nonrodent mammal.
- Nonmammals.

***Routes of administration should be ordered as follows:***

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

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.

## Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarization 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 eCTD 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.

# MODULE 3 QUALITY

## 3.1 Table of Contents of Module 3

The table of content should list all documents included in Module 3.

## 3.2 Body of data

### 3.2.S Drug Substance

The number of Active Pharmaceutical Ingredients (API) suppliers must not exceed **two sources** for each API, unless reasonably justified.

The drug substance information can be submitted in one of the following options:

1. Certificate of suitability (CEP); or
2. Drug master file (DMF) / For products containing viral vectors: Submission of a Viral Master File (VMF)/Regulatory Support File as applicable; or
3. Complete information on the *"3.2.S drug substance"* sections.

The drug substance information submitted should include the following for each of the options used.

***1. Certificate of Suitability (CEP)***

The applicant should submit:

- A valid Certificate of Suitability (CEP) (including any annexes) where the declaration of access for the CEP should be duly filled out by the CEP holder.
- A written assurance that no significant changes in the manufacturing method have taken place following the granting of certificate or its last revision.

A complete copy of the CEP (including any annexes) should be provided in *Module 1* (section 1.7.10). Along with the CEP, the applicant should submit the following:

*a) 3.2.S.1.3 General properties*

Discussions on any additional applicable physicochemical and other relevant drug substance properties that are not controlled by the CEP and Ph. Eur. monograph, e.g. solubilities and polymorphs.

b) *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.

c) *3.2.S.4.1 Specification*

The specifications of the finished product manufacturer including all tests and limits of the CEP and Ph. Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph. Eur. monograph, such as polymorphs and/or particle size distribution.

d) *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.

e) *3.2.S.4.4 Batch analysis*

Results from three batches of at least pilot scale, demonstrating compliance with the finished product manufacturer's API specifications.

f) *3.2.S.5 Reference standards or materials*

Information on the finished product manufacturer's reference standards.

g) *3.2.S.6 Container closure system*

The specifications including descriptions and identification of primary packaging components should be included in this section, except where the CEP specifies a re-test period.

h) *3.2.S.7 Stability*

The stability should be included in this section, except 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.

In the case of sterile drug substances, data on the ***sterilization process*** of the drug substance, including ***validation*** data, should be included in the dossier.

### *2. Drug Master File (DMF)*

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the drug substance may be submitted as DMF. In such cases, the *Open part* needs to be included *in its entirety* in the dossier as an annex to 3.2.S. In addition, the applicant/finished product manufacturer should complete the following sections:

*a) General information 3.2.S.1.1 through 3.2.S.1.3*

*b) Manufacture 3.2.S.2*

- *Manufacturer(s) 3.2.S.2.1*
- *Description of manufacturing process and process controls 3.2.S.2.2*[4]
- *Controls of critical steps and intermediates 3.2.S.2.4*[5]

*c) Elucidation of structure and other characteristics 3.2.S.3.1*

*d) Impurities 3.2.S.3.2*

*e) Control of the API 3.2.S.4.1 through 3.2.S.4.5*

*f) Reference standards or materials 3.2.S.5*

*g) Container closure system 3.2.S.6*

*h) Stability 3.2.S.7.1 through 3.2.S.7.3*

It is the responsibility of the applicant to ensure that the complete DMF *(i.e. both the applicant's **Open part** and the API manufacturer's **Restricted part**)* is supplied to SFDA directly by the API manufacturer and that the applicant has access to the relevant information in the DMF concerning the current manufacture of the drug substance.

DMF submissions and correspondence should be submitted as per the SFDA Drug Master File (DMF) Guidance for Submission.

[4] Flow chart and short description is regarded as sufficient, if the detailed information is presented in the Restricted Part.

[5] As far as the information is also relevant for the Applicant/MA holder.

A copy of the letter of access should be provided in *Module 1 (Section 1.7.10).* **The letter should include the following information on DMF:**

- Name of the holder:
- **Applicant's part:**
  - DMF Version number:
  - DMF Date (yyyy-mm-dd):
- **Restricted part:**
  - DMF Version number:
  - DMF Date (yyyy-mm-dd):
- If no changes were made within the last five years, a letter indicating that the DMF remains current.
- In regards to the ***restricted part***, has it been submitted to the SFDA:

  ❍ Yes ❍ No

  If yes, please attach the confirmation email of DMF/ASMF submission.

### *3. Complete Information on the "3.2.S Drug Substance" Sections*

Information on the *3.2.S Drug Substance* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the drug substance, should be submitted in the dossier as outlined in the subsequent sections of this guideline.

### 3.2.S.1 General Information

#### 3.2.S.1.1 Nomenclature

Information on the nomenclature of the drug substance(s) 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), British Approved Name (BAN),* and
- Chemical Abstracts Service (CAS) registry number.

### 3.2.S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. For drug substance(s) existing as salts, the molecular mass of the free base or acid should be provided.

***For Biotech:***

In addition to the above, a schematic representation of the plasmid/vector structure or amino acid sequence should be provided, as appropriate. This should include details such as gene insertion sites, glycosylation sites, other post-translational modifications, and the relative molecular mass.

### 3.2.S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance. This includes:

a) Physical description (e.g., appearance, color, physical state).
b) Physical form (e.g., polymorphic form, solvate, hydrate).
c) Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile).
d) pH and pKa values.
e) Other (e.g., partition coefficients, melting or boiling points, optical rotation, refractive index (for a liquid), hygroscopicity, UV absorption maxima and molar absorptivity).

***For Biotech:***

In addition to the above, the biological activity should be provided.

## 3.2.S.2 Manufacture

### 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. In addition, a valid manufacturing authorization for the production of drug substance(s) and a

certificate of GMP compliance should be provided.

This section should also include all the proposed QC testing site(s) intended to be approved in Saudi Arabia (along with required method transfer reports).

### 3.2.S.2.2 Description of 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:

- Individual unit operations and their sequence in the manufacturing process
- For levels/details of Established Conditions (ECs) for inputs (process parameters and material attributes) and outputs of individual unit operations *(ICH Q12 chapter : Identification of ECs for the Manufacturing Processes)*
- 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.
- Detailed information on the starting material(s) including the name of the manufacturer(s)/supplier(s), route of synthesis and specifications which should be justified by supporting data.
- 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… etc).*
- Alternate processes should be explained and described with the same level of detail as the primary process. Justification should be provided for the alternate manufacturing processes.
- If applicable, 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.

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

***For Biotech:***

In addition to the above, 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.

The size of a batch produced by continuous manufacturing (CM) can be defined in terms of one of the following:

- Quantity of output material
- Quantity of input material
- Run time at a defined mass flow rate
- Other approaches to define batch size can also be considered, if scientifically justified based on the characteristics of the CM process.
- A batch size can also be defined as a range. For example, a batch size range can be established by defining a minimum and maximum run time

– *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.

***For CM:***

- Commercial manufacturing process description, including flow diagram and equipment scheme
- Process controls and limits (e.g., input rates/mass flow rates, feeder control limits)
- Critical process parameters
- Active controls (e.g., feedforward or feedback control) and process models, if these elements are part of the control strategy
- Criteria for product collection, including control limits and strategy for segregation and diversion to waste.
- Description of equipment and system integration critical to the output material quality
- Overview of high-impact process models, if used.

### 3.2.S.2.3 Control of Materials

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. For each starting material, the name, manufacturing site, and the address of each manufacturer should be indicated. Information on the quality and control of these materials should be provided *(including the route of synthesis, specifications, impurity profile, scientific justification/rationale for selecting starting material(s) and certificate of analysis from each supplier).* 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 characterization *(details in 3.2.A.2)*.

A letter should be provided confirming that the drug substance, starting materials and reagents used to manufacture the drug substance are without risk of transmitting agents of Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE). When available, a CEP demonstrating TSE-compliance should be submitted. A complete copy of the CEP (including any annexes) should be provided in Module 1 (Section 1.7.7).

***For Biotech:*** "In addition to the above"

- Information on the development genetics including origin of the gene, description of the gene construction, rationale behind the gene construct, genetic stability (specify state of the recombinant gene and copy number).
- Description of the producer strain /cell line (type, origin), history of establishment and identification. Highlight any issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin).
- Cell banks: Establishment of the MCB/WCB, adequacy of tests performed, cell bank stability, phenotypic and genotypic characterisation, protocol for the establishment of future WCB. (as described in Q5B and Q5D).
- For of biological materials (e.g. monoclonal antibody purification columns, blood/plasma derivatives) used in the manufacture of the drug substance, the assessment of the source, manufacture, characterisation and control should be provided. For biological materials (e.g. blood/plasma derivatives such as human albumin) used in the manufacture of the drug substance, the assessment of the source, manufacture, characterisation and control should be provided.
- Specifications of culture media and other additives.
- Other 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 with information on the quality and control of these materials.

- Information related to materials such as membranes and chromatography resins
- For plasma products such as human albumin that whenever it is used in the manufacture of medicinal products, it should comply with the note for guidance and should have the same documentation, including the origin of donations, the same quality and specifications as that of albumin for therapeutic use.
- Summaries of viral safety information for biologically-sourced materials should be provided (details in 3.2.A.2.).

### 3.2. S.2.4 Control 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.

***For Biotech:***

- List critical process steps and critical process parameters, intermediate specifications, and in-process control acceptance criteria
- End of production / cultivation criteria if applicable
- Proposed intervals of set-point specifications and limits of In Process Control specifications in relation to the results of process validation.
- Description of storage conditions/shelf life of intermediates.
- Highlight any specific step aimed/validated for virus removal/inactivation (e.g. low pH treatment).

- Stability data supporting storage conditions and holding time between steps of manufacturing should be provided.

### 3.2. S.2.5 Process Validation and/or Evaluation

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

**The information on process validation and/or evaluation studies for STERILE drug substance is recommended to be presented as follows:**

| | | |
|---|---|---|
| **Number of batches** | | |
| **Batch number** | | |
| **Batch type** | | |
| **Batch size** | | |
| **Are the submitted batches consecutive?** | ❍ Yes | ❍ No |
| **Is the process validation protocol submitted?** | ❍ Yes | ❍ No |
| **Are the process validation results submitted?** | ❍ Yes | ❍ No |

***For 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 (protocol) 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.

For continuous process, the use of a continuous process verification approach should be justified based on the product and process understanding, system design, and overall control strategy. When continuous process verification is used, the CM system performance and material quality should be continuously monitored, such that the real-time data collected demonstrate the maintenance of a state of control and production of output material with the desired quality for the run time duration. The dossier should contain justifications to support the adequacy of a proposed control strategy for continuous process verification.

### 3.2.S.2.6 Manufacturing Process Development

The developmental history of the manufacturing process, *as described in 3.2.S.2.2*, should be provided. In addition, 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.

***For 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.

**For continuous manufacturing (CM)**

- Summary of the overall process development, including all relevant control strategy elements (with links to the eCTD sections that contain detailed information), for example:
  - Description and justification of the system start-up, shutdown and pauses
  - Description and justification of the material diversion and collection strategy
  - Description of feedforward and feedback controls
- Development and justification of process models, if used
- Summary of disturbance management

### 3.2.S.3 Characterization

#### 3.2.S.3.1 Elucidation of Structure and Other Characteristics

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. This should include 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 drug substance.

- For non-pharmacopoeial drug substance(s), these studies normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray diffraction (XRD) and differential scanning calorimetry (DSC).
- For pharmacopoeial drug substance(s), it is generally sufficient to provide copies of the IR spectrum of the drug substance run concomitantly with a reference standard.

Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

In addition, studies performed to identify the particle size distribution of the drug substance should be included.

***For Biotech:***

In addition to the above, Characterization to justify classification as CQA (cross reference to nonclinical/clinical sections if relevant) details (for the desired product and product-related substances) should be provided on primary, secondary and higher-order structure, post-translational forms *(e.g., glycoforms)*, biological activity, purity, and immunochemical properties, when relevant.

### 3.2.S.3.2 Impurities

Information on impurities should be provided, including a discussion on the potential and actual impurities arising from the synthesis, manufacture, or degradation of the drug substance. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins.

In addition, a specific discussion should be provided with regard to impurities with potential genotoxicity *(Refer to ICH M7 guideline: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk).*

Details on the principles for the control of process-related impurities & degradation products *(e.g. reporting, identification and qualification*), solvents and elemental impurities are outlined in the ICH Q3A, Q3B, Q3C and Q3D impurity guidelines.

In addition, a comprehensive risk assessment to address possible formation of N-nitrosamine impurities in substances for human use. If a risk is identified, a suitable control strategy should be introduced. The risk evaluation should not only address risks related to the manufacturing process, but also those deriving from the introduction of materials used in the manufacturing process and other potential sources of contamination (e.g. starting materials, reagents, solvents, recovery of materials, equipment, degradation).

**The information on impurities is recommended to be presented as follows:**

| Drug-related Impurity (chemical name) | Structure | Origin | Acceptance Criteria | Reference |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |

It should be known that some solvents (e.g. acetone, toluene, ethanol, methanol, isopropanol, xylene, hexane, petroleum ether, chloroform and dichloromethane (methylene chloride)) may be contaminated with Class 1 solvents (e.g. benzene, carbon tetrachloride). Therefore, when these solvents are used in the manufacturing process of the final substance, and in particular in the purification steps, potential residues of their contaminant in an intermediate or in the final substance should be addressed *(refer to CPMP/QWP/450/03 Rev. 1, Annex I, B: Class 1 Solvents Present as an Impurity).*

According to the European "*Note for Guidance on Specifications for Class 1 and Class 2 residual solvents in active substances, annex to the CPMP/ICH/283/95 Impurities: Guideline for Residual Solvents*, three options may be used that support the absence of routine testing of the contaminant in the final substance. When one of the three options is met and demonstrated in the application, a routine test for Class I solvent in a suitable intermediate or in the final active substance is not required.

### 3.2.S.4 Control of Drug Substance

#### 3.2.S.4.1 Specifications

Copies of the drug substance specifications, dated and signed by the concerned individual(s) should be provided, including specifications from each drug substance manufacturer as well as

those of the finished product manufacturer.

### 3.2.S.4.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided. Copies of the non-compendial analytical procedures used to generate testing results provided in the dossier, as well as those proposed for routine testing of the drug substance by the finished product manufacturer, should be provided. Unless modified, it is not necessary to provide copies of the compendial analytical procedures.

Chromatographic methods (e.g., HPLC & GC) are normally considered the method of choice for determining API-related impurities and assay. The analytical procedure submitted should be described in sufficient detail including: Preparation of mobile phase, Chromatographic condition (Column: packing type (e.g., C18 or C8), dimension (length, inner diameter), particle size (10 µm, 5 µm), Detector (wavelength), Injection volume, Column Temperature, Flow rate), elution procedure (isocratic or gradient elution), preparation of standards and samples solution, type of reagent & materials used, operation procedure (sequence of injections), system suitability testing (SST) and criteria and calculations formulas.

It is essential that the applicant has to provide a detailed documentation of the formula and the method of calculation used to calculate the content of the drug substance or impurities, with numerical values using actual raw data to demonstrate how the final results were obtained. All mathematical transformations, along with a scientific justification for any correction factors used must be presented.

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the satisfactory performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution.

**The information on analytical procedures is recommended to be presented as follows:**

| | |
|---|---|
| **Tested parameter** | *e.g. assay, related substances, … (one separate table for each tested parameter).* |
| **Reference** | *e.g. USP, BP, in-house method, …* |

| **Chromatographic Conditions:** | |
|---|---|
| – Column | |
| – Flow rate | |
| – Wavelength | |
| – Injection volume | |
| – Temperature | |
| – Run time | |
| – Retention time | |
| **Solutions preparation:** | |
| – Mobile phase | |
| – Buffer | |
| – Gradient programs *(if applicable)* | |
| – Stock standard solution | |
| – Standard solution | |
| – Test solution | |

| | |
|---|---|
| – System suitability solution | |
| **Acceptance criteria for system suitability test:** | |
| – % RSD | |
| – Tailing factor | |
| – No. of theoretical plates (N) | |
| – Resolution | |

**GC for Residual Solvents:**

| **Chromatographic Conditions:** | |
|---|---|
| – Column | |
| – Column flow | |
| – Carrier | |
| – Air flow | |
| – $H_2$ flow | |
| – Split | |
| – Detector temperature | |
| – Load | |
| – Injector temperature | |
| – Makeup flow | |
| **Solutions preparation:** | |

| | |
|---|---|
| – Stock solution(s) | |
| – Standard preparation | |
| – Sample Preparation | |
| – System suitability | |
| **Acceptance criteria for system suitability test:** | |
| – % RSD | |
| – Tailing factor | |
| – Resolution | |

### 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 *(in accordance with ICH Q2 (R1) and Q6A)*. Copies of the validation reports for the analytical procedures used to generate testing results provided in the dossier, as well as those proposed for routine testing of the drug substance by the finished product manufacturer, should be provided. For in-house methods full validation are required.

Verification of compendial methods is necessary, since the compendial methods as published are typically validated based on an API originating from a specific manufacturer. Different sources of the same API can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated as suitable to control the impurity profile of the API from the intended source(s). For the verification of compendial API assay methods, specificity should be demonstrated.

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

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

Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the approved specifications. Analytical methods used to test pharmaceutical products, should be implemented at the testing laboratory. The analytical methods transfer protocol should include a description of the objective, scope and responsibilities of the SU and the RU; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any).

**The information on validation of analytical procedures is recommended to be presented as follows:**

| | |
|---|---|
| **Tested parameter** | *e.g. assay, related substances, … (one separate table for each tested parameter).* |

| | | |
|---|---|---|
| **Specificity** | | |
| – Brief summary on how it was performed: | | |
| – Representative chromatogram(s) | *The chromatogram(s) can be found in page No…* | |
| **Linearity** | | |
| – No. of concentrations | | |
| – Specified ranges | | |
| – Parameters: | **Acceptance criteria** | **Results** |
| • *Correlation coefficient* | | |
| • *y-intercept* | | |
| • *Residual sum of squares* | | |
| **Accuracy** | | |
| – Brief summary on how it was performed: | | |
| – Parameters: | **Acceptance criteria** | **Results** |

| | | |
|---|---|---|
| • *% Recovery* | | |
| • *% RSD* | | |
| • *CI* | | |
| **Precision (repeatability and intermediate precision)** | | |
| – Brief summary on how it was performed: | | |
| – Parameter: | **Acceptance criteria** | **Results** |
| • *% RSD* | | |
| **LOQ/LOD** | | |
| – Brief summary on how it was performed: | | |
| – LOD | | |
| – LOQ | | |
| **Robustness** | | |
| – Brief summary on how it was performed: | | |
| **Systems suitability** | | |
| – Parameters: | **Acceptance criteria** | **Results** |
| • *% RDS* | | |
| • *Tailing factor* | | |

| | | |
|---|---|---|
| • *No. of theoretical plates* | | |
| • *Resolution* | | |

**Method transfer *(if applicable)*:**

| **Protocol:** | | |
|---|---|---|
| – **Tested Parameters:** | **Acceptance criteria** | **Results** |
| • | | |
| • | | |

### 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 drug substance batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches.

**The information on drug substance batch analyses is recommended to be presented as follows:**

| **Batch number** | **Batch size** | **Batch type** | **Site(s) of:** | | **Date(s) of:** | |
|---|---|---|---|---|---|---|
| | | | **Manufacturing** | **Analysis** | **Manufacturing** | **Analysis** |
| | | | | | | |
| | | | | | | |

Copies of the certificates of analysis from both the API manufacturer(s) and the FPP manufacturer should be provided.

Analytical results should be provided from at least two batches of at least pilot scale from each proposed manufacturing site of the drug substance 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.

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. assay test, individual and total impurity tests)*, it should be ensured that actual numerical results are provided rather than vague statements such as *"within limits"* or *"conforms"*.

### 3.2.S.4.5 Justification of Specification

Justification for the drug substance specification should be provided. This should include a discussion on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, etc. If the 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)* and does not need to be repeated here, although a cross-reference to their location should be provided.

### 3.2.S.5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should include the following:

1. The source of reference standards or reference materials *(e.g., House, USP, BP, Ph. Eur.).*
2. Certificate of analysis for reference standards or reference materials .
3. Characterization and evaluation of non-official *(e.g., non-compendial)* reference standards or reference materials *(e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard).*

**The information on reference standards/reference materials is recommended to be presented as follows:**

| | |
|---|---|
| **Type of reference standards** | ❍ Primary reference standard<br>❍ Working or secondary reference standard<br>❍ Manufacturer reference standard |
| **Information on potency** | ……. % |
| **Information on calibration of working standard with primary reference standard** | |

### 3.2.S.6 Container/Closure Systems

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 GCC guidelines for *"Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)"* should be followed for recommendations on the

stability data required for the drug substance(s).

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include information on storage conditions, batch number, batch size, batch type, batch manufacturing date, container closure system and testing intervals (completed and proposed), results, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

**The information on stability studies is recommended to be presented as follows:**

| | **Accelerated stability studies** | **Long term stability studies** |
|---|---|---|
| **Storage conditions (°C, % RH)** | | |
| **Batch number** | | |
| **Batch type** | | |
| **Batch size** | | |
| **Completed (and proposed) testing intervals** | | |
| **Container closure system** | | |
| **Manufacturing site** | | |
| **Manufacturing date** | | |
| **Stability start date** | | |
| **Storage conditions and the proposed retest date or shelf-life** | | |

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as *"all tests meet specifications"*.

Where the methods used in the stability studies are different from those described in 3.2.S.4.2, descriptions and validation of the methodology used in stability studies should be provided.

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

The post-approval stability protocol and if applicable stability commitment should be provided. When the available long-term stability data on primary batches do not cover the proposed re-test period granted at the time of assessment of the dossier, a commitment should be made to continue the stability studies in order to firmly establish the re-test period. A written commitment (signed and dated) to continue long-term testing over the re-test period should be included in the dossier.

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. Otherwise one of the following commitments should be made:

- **If the submission includes data from stability studies on three production batches,** a written commitment (signed and dated) should be made to continue these studies through the proposed re-test period.
- **If the submission includes data from stability studies on less than three production batches,** a written commitment (signed and dated) should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, in long-term stability studies through the proposed re-test period.
- **If the submission does not include stability data on production batches,** a written commitment (signed and dated) should be made to place the first three production batches on long term stability studies through the proposed re-test period.

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

- Number of batch(s) 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; and
- Other applicable parameters specific to the drug substance.

The stability of the drug substance should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue *(e.g. changes in levels of degradation products)*. For this purpose, the ongoing stability programme should include at least one production batch per year of drug substance *(unless none is produced during that year)*. In certain situations, additional batches should be included. Therefore, a written commitment *(signed and dated)* for ongoing stability studies should be included in the dossier.

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.

### 3.2.S.7.3 Stability Data

Results of the stability studies should be presented in a tabular format. The results of all testing parameters related to each batch for the entire testing period should be presented in one table *(i.e. presenting the results of one parameter of all batches in one table is not acceptable)*.

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"*.

Information on the analytical procedures used to generate the data and validation of these procedures should be included.

## 3.2.P Drug Product

### 3.2.P.1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information

provided should include, for example:

- Description of the dosage form;
- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards *(e.g., compendial monographs or manufacturer's specifications)*;
- Description of accompanying reconstitution diluent(s); and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

### 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.

#### 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 combination products, the compatibility of drug substances with each other should be discussed.

In general, drug substance-excipient compatibility is not required to be established for specific excipients when evidence is provided *(e.g. SPC or PIL)* 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.

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. Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies. Where relevant, the antimicrobial preservatives should be discussed in 3.2.P.2.5.

- For vaccines:

  It is important to note that the use of thiomersal is not permitted in pediatric vaccines intended for children under one year of age.

## 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 in the formulations for the batches used the in the *in vivo* studies *(e.g., pivotal clinical, comparative bioequivalence)* and the formulation *(i.e. composition)* described in 2.3.P.1 should be discussed.

Summary of the results from comparative *in vitro* studies *(e.g., dissolution)* or comparative *in vivo* studies *(e.g., bioequivalence)* should be discussed when appropriate, including the description of batches (e.g., batch number, strength, type of the study … etc) used in the these studies.

The discussion should include the results of studies justifying the choice of *in vitro* dissolution or drug release conditions *(e.g. apparatus, rotation speed, medium)*. Furthermore, the submitted data should 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.

***Scored Tablets***

In order to ensure that the patient will receive the intended dose, the efficacy of the break-mark(s) must be assessed during the development of the product, in respect of uniformity of mass of the subdivided parts.

If the proposed finished product is a scored tablet or the applicant indicates that it may be divided into equal doses, the following should be submitted:

- A justification/rationale for the tablet scoring, and
- The tablet description in the FPP specification and in the product information (e.g. SPC, labelling or package leaflet) should reflect the presence or the absence of a score line (please refer to Templates for Labeling information, SPC and PIL).
- Results of the appropriate compendial tests demonstrating equivalence in characteristics/correct dosing (*i.e. results demonstrating that the proposed tablet breaks evenly)*. The submitted data should be conducted on at least one batch of each strength and include a description of the splitting (breaking) method, test method, number of tablets, individual values, mean and relative standard deviation (RSD) of the results.

### 3.2.P.2.2.2 Overages

In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged. Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product.

**Information should be provided on the:**

- ***Amount*** of overage,
- ***Reason*** for the overage *(e.g., to compensate for expected and documented manufacturing losses),* and
- ***Justification*** for the amount of overage. The 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 (comparative data showing the differences in the assay test results before and after adding the overage).

The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2).

### 3.2.P.2.2.3 Physiochemical and Biological Properties

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

### 3.2.P.2.3 Manufacturing Process Development

The scientific rationale for the selection and optimization and scale-up of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained.

Where relevant, the method of sterilization should be explained and justified. The justification for selecting aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing process(s) used to produce pivotal clinical batches/ comparative bioavailability 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

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product 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),* and performance *(such as reproducibility of the dose delivery from the device when presented as part of the drug product)*. In case of using new packaging materials, the discussion should include the safety of those materials, in addition to the above mentioned requirements.

For a device accompanying a multidose container, the discussion should provide the results that demonstrate the reproducibility of the device (*e.g. consistent delivery of the intended volume)*, generally at the lowest intended dose.

### 3.2.P.2.5 Microbiological Attributes

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, the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. A single primary stability batch of the finished product 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.

For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

### 3.2.P.2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage device(s) (*e.g., precipitation of drug substance in solution, sorption on injection vessels, stability)* should be addressed to provide appropriate and supportive information for the labeling.

Where sterile reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling. These studies should preferably be conducted on aged samples. Where the labeling does not specify the type of containers, compatibility (with respect to parameters such as *appearance, pH, assay, levels of individual and total degradation products, sub-visible particulate matters 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 labeling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Where the labeling specifies co-administration with other finished products, compatibility should be demonstrated with respect to the principal finished product as well as the co-administered finished product *(i.e. in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co-administered finished product 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.

A valid manufacturing authorization and marketing authorization should be submitted. A GMP certificate should be submitted for each manufacturing site where the major production step(s) are carried out, when applicable.

This section should also include all the proposed QC testing site(s) intended to be approved in Saudi Arabia.

#### 3.2.P.3.2 Batch Formula

A batch formula for all proposed individual batch sizes should be provided that includes a list of all components of the dosage form to be used in the manufacturing process *(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])*, and their amounts on a per batch basis, including overages. The components used in the manufacturing process should be declared by their proper or common names and a reference to their quality standards *(e.g. BP, USP)*.

In addition, an official letter indicating the expected production size range and confirming that this range will not be changed before getting the SFDA approval.

#### 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)* 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.

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

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

Detailed information on Biotech facilities and equipment should be provided in 3.2.A.1.

### 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.

**The following are examples for applicable in-process controls:**

– ***Granulations:***

  Moisture (limits expressed as a range), blend uniformity *(e.g. low dose tablets)*, bulk and tapped densities, particle size distribution, …etc.

– ***Solid oral products:***

  Average weight, weight variation, hardness, thickness, friability, and disintegration checked

periodically throughout compression, weight gain during coating, …etc.

- ***Semi-solids:***

  Viscosity, homogeneity, pH, …etc.

- ***Transdermal dosage forms:***

  Assay of drug substance-adhesive mixture, weight per area of coated patch without backing, …etc.

- ***Metered dose inhalers:***

  Fill weight/volume, leak testing, valve delivery, …etc.

- ***Dry powder inhalers:***

  Assay of drug substance-excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters, …etc.

- ***Liquids:***

  Specific gravity, pH, clarity of solutions, …etc.

- ***Parenterals:***

  Appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, …etc.

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

The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control *(ICH Q10).*

**The following information should be provided:**

***For non-sterile products:***

1. A copy of the process validation protocol, specific to this finished product, that identifies the critical equipment and process parameters that can affect the quality of the finished product and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
2. A letter of commitment to conduct prospective validation on three consecutive production-scale batches (Section 3.2.P.3.5) and to report immediately any out of specification (OOS) results to the SFDA.

***For sterile products:***

1. Process validation on three consecutive validation batches including the sterilization process (Section 3.2.P.3.5).
2. A letter of commitment to conduct prospective validation on three consecutive production batches including the sterilization process (Section 3.2.P.3.5) and to report immediately any out of specification (OOS) results to the SFDA.

**The information on process validation and/or evaluation studies for STERILE product is recommended to be presented as follows:**

| | | |
|---|---|---|
| **Number of batches** | | |
| **Batch number** | | |
| **Batch type** | | |
| **Batch size** | | |
| **Are the submitted batches consecutive?** | ❍ Yes | ❍ No |
| **Is the process validation protocol submitted?** | ❍ Yes | ❍ No |
| **Are the process validation results submitted?** | ❍ Yes | ❍ No |

### 3.2.P.4 Control of Excipients

#### 3.2.P.4.1 Specifications

The specifications 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 finished product *(e.g. solvents)* and any others used in the manufacturing process *(e.g. nitrogen, silicon for stoppers)*.

For excipients of natural origin, microbial limit testing should be included in the specifications. For oils of plant origin (e.g. soy bean oil, peanut oil) the absence of aflatoxins or biocides should be demonstrated.

The colors permitted for use are limited to those listed in the EU "List of permitted food colors" and the US FDA "Inactive ingredient guide". For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the finished product manufacturer's specifications for the product including identification testing.

#### 3.2.P.4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided. Copies of the non-compendial analytical procedures used to generate testing results should be provided. Unless modified, it is not necessary to provide copies of the compendial analytical procedures.

#### 3.2.P.4.3 Validation of Analytical Procedures

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

#### 3.2.P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate. This should include a discussion on the tests that are supplementary to those appearing in the compendial monograph.

#### 3.2.P.4.5 Excipients of Human or Animal Origin

List of excipients that are of human or animal origin (including country of origin). Summary of the information *(e.g., sources, specifications, description of the testing performed, viral safety data)* regarding adventitious agents for excipients of human or animal origin (details should be

located in 3.2.A.2).

For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents *(e.g., ruminant origin)*, a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. When available, a CEP demonstrating TSE-compliance should be submitted. A complete copy of the CEP (including any annexes) should be provided in Module 1 (Section 1.7.7).

### 3.2.P.4.6 Novel Excipients

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls (Specification and each Quality Attribute on the specification, test Method, acceptance Criteria) with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format (details in 3.2.A.3).

## 3.2.P.5 Control of Drug Product

### 3.2.P.5.1 Specifications

A copy of the finished product specification(s) (**release** and **shelf-life** specifications) dated and signed by authorized personnel *(i.e. the person in charge of the quality control or quality assurance department)*, should be provided.

Generally, stability indicating parameters in specifications should have tighter release limits than shelf life.

The specification(s) sheet should include, but not be limited to, the following:

- The tests;
- Acceptance criteria;
- The standard declared by the applicant *(e.g. compendial or in-house standard)*;
- The specification reference number and version *(e.g. revision number and/or date)*;
- Analytical procedures, including their type *(e.g. visual, IR, HPLC ...)*, source *(e.g. Ph. Eur.,*

*BP, USP, in-house)* and version *(e.g. code number/version/date).*

Specifications should include, at minimum, tests for appearance, identification, assay, purity, pharmaceutical tests *(e.g. dissolution),* physical tests *(e.g. loss on drying, hardness, friability, particle size, apparent density),* uniformity of dosage units, identification of coloring materials, identification and assay of antimicrobial or chemical preservatives *(e.g. antioxidants)* and microbial limit tests *(refer to ICH Q6A).*

### 3.2.P.5.2 Analytical Procedures

The analytical procedures used for testing the drug product should be provided. Copies of the non-compendial analytical procedures used during pharmaceutical development (if used to generate testing results provided in the dossier) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of the compendial analytical procedures.

Chromatographic methods (e.g., HPLC & GC) are normally considered the method of choice for determining impurities and assay. The analytical procedure submitted should be described in sufficient detail including: Preparation of mobile phase, Chromatographic condition (Column: packing type (e.g., C18 or C8), dimension (length, inner diameter), particle size (10 µm, 5 µm), Detector (wavelength), Injection volume, Column Temperature, Flow rate), elution procedure (isocratic or gradient elution), preparation of standards and samples solution, type of reagent & materials used, operation procedure (sequence of injections), system suitability testing (SST) and criteria and calculations formulas

It is essential that the applicant has to provide a detailed documentation of the formula and the method of calculation used to calculate the content of the drug product or impurities, with numerical values using actual raw data to demonstrate how the final results were obtained. All mathematical transformations, along with a scientific justification for any correction factors used must be presented. The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the satisfactory performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. HPLC assay methods should include SSTs for repeatability and in addition either peak asymmetry, theoretical plates or resolution.

**The information on analytical procedures is recommended to be presented as follows:**

| | |
|---|---|
| **Tested parameter** | *e.g. assay, related substances, … (one separate table for each tested parameter).* |
| **Reference** | *e.g. USP, BP, in-house method, …* |

| **Chromatographic Conditions:** | |
|---|---|
| – Column | |
| – Flow rate | |
| – Wavelength | |
| – Injection volume | |
| – Temperature | |
| – Run time | |
| – Retention time | |
| **Solutions preparation:** | |
| – Mobile phase | |
| – Buffer | |
| – Gradient programs *(if applicable)* | |
| – Stock standard solution | |
| – Standard solution | |

| | |
|---|---|
| – Test solution | |
| – System suitability solution | |
| **Acceptance criteria for system suitability test:** | |
| – % RSD | |
| – Tailing factor | |
| – No. of theoretical plates (N) | |
| – Resolution | |

### 3.2.P.5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided *(in accordance with ICH Q2(R1) and Q6A)*.

Copies of the validation reports (including the acceptance criteria and representative chromatograms) for the non-compendial 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. For in-house methods full validation are required.

Verification of compendial methods can be necessary. The compendial methods, as published, are typically validated based on a drug substance or a finished product originating from a specific manufacturer. Different sources of the same drug substance or finished product can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed finished product.

For compendial assay methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If a 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 a compendial standard is claimed and an in-house method is used in lieu of the compendial method *(e.g. for assay or related substance)*, 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 substance methods, the sample analyzed should be the placebo spiked with related substances at concentrations equivalent to their specification limits.

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

Transfer of analytical methods should accommodate all the analytical testing required to demonstrate compliance of the product to be transferred with the approved specifications. Analytical methods used to test pharmaceutical products, should be implemented at the testing laboratory. The analytical methods transfer protocol should include a description of the objective, scope and responsibilities of the sending unit (SU) and receiving unit (RU); a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any).

**The information on validation of analytical procedures is recommended to be presented as follows:**

| | |
|---|---|
| **Tested parameter** | *e.g. assay, related substances, … (one separate table for each tested parameter).* |

| | | |
|---|---|---|
| **Specificity** | | |
| – Brief summary on how it was performed: | | |
| – Representative chromatogram(s) | *The chromatogram(s) can be found in page No…* | |
| **Linearity** | | |
| – No. of concentrations | | |
| – Specified ranges | | |
| – Parameters: | **Acceptance criteria** | **Results** |
| • *Correlation coefficient* | | |
| • *y-intercept* | | |
| • *Residual sum of squares* | | |
| **Accuracy** | | |
| – Brief summary on how it was performed: | | |
| – Parameters: | **Acceptance criteria** | **Results** |
| • *% Recovery* | | |
| • *% RSD* | | |

| | | |
|---|---|---|
| • *CI* | | |
| **Precision (repeatability and intermediate precision)** | | |
| – Brief summary on how it was performed: | | |
| – Parameter: | **Acceptance criteria** | **Results** |
| • *% RSD* | | |
| **LOQ/LOD** | | |
| – Brief summary on how it was performed: | | |
| – LOD | | |
| – LOQ | | |
| **Robustness** | | |
| – Brief summary on how it was performed: | | |
| **Systems suitability** | | |
| – Parameters: | **Acceptance criteria** | **Results** |
| • *% RDS* | | |
| • *Tailing factor* | | |
| • *No. of theoretical plates* | | |
| • *Resolution* | | |

**Method transfer *(if applicable)*:**

| Protocol: | | |
|---|---|---|
| – Tested Parameters: | **Acceptance criteria** | **Results** |
| • | | |
| • | | |

### 3.2.P.5.4 Batch Analyses

A description of batches and results of batch analyses should be provided. The information provided should include strength, batch number, batch size, batch type, date and site of production and API manufacturer.

**The information on finished product batch analyses is recommended to be presented as follows:**

| **Batch number** | **Batch size** | **Batch type** | **Site(s) of:** | | **Date(s) of:** | | **API manufacturer** |
|---|---|---|---|---|---|---|---|
| | | | **Manufacturing** | **Analysis** | **Manufacturing** | **Analysis** | |
| | | | | | | | |
| | | | | | | | |

Analytical results tested by the company responsible for the batch release of the finished product should be provided for not less than two batches of at least pilot scale batches. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

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 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.

A discussion and justification should be provided for any incomplete analyses *(e.g. results not*

*tested according to the proposed specification).*

### 3.2.P.5.5 Characterization of Impurities

Information on the characterization of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities". The discussion should be provided for all impurities that are potential degradation products and finished product process-related impurities.

A risk assessment report should be conducted to determine the materials that contribute to the potential inclusion of nitrosamines in the drug product. All potential sources for the introduction of nitrosamines should be considered in the risk assessment including, for example, the drug substance, excipients, water (including a discussion of the nitrosamine impurities that may be present in water during the purification and disinfection process), solvents, the manufacturing process, packaging components (e.g. aluminum foil, elastomers…etc.), and formation on stability**.**

### 3.2.P.5.6 Justification of Specifications

Justification for the proposed drug product specification(s) should be provided. The discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the compendial standard(s), …etc. If the 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)* 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.

### 3.2.P.6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should include the following, if not previously provided in "3.2.S.5 Reference Standards or Materials":

1. The source of reference standards or reference materials *(e.g., House, USP, BP, Ph. Eur.).*
2. Certificate of analysis for reference standards or reference materials .

3. Characterization and evaluation of non-official *(e.g., non-compendial)* reference standards or reference materials *(e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard).*

**The information on reference standards/reference materials is recommended to be presented as follows:**

| | |
|---|---|
| **Type of reference standards** | ❍ Primary reference standard<br>❍ Working or secondary reference standard<br>❍ Manufacturer reference standard |
| **Information on potency** | …… *%* |
| **Information on calibration of working standard with primary reference standard** | |

### 3.2.P.7 Container/Closure System

A description of the container closure systems should be provided, including unit count or fill size, container size or volume, the identity of materials of construction of each primary packaging component, its specification and the supplier's name and address.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight. Non-compendial methods (with validation) should be included where appropriate.

The discussion should include copies of certificate of analysis for all primary packaging components in which the specifications are in compliance with the pharmacopoeia.

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.

The suitability of the container closure system used for the storage, transportation (shipping) and

use of the drug product should be located in 3.2.P.2.4. Information to establish the suitability *(e.g. qualification)* of the container closure system should be discussed in Section 3.2.P.2.4. Comparative studies may be provided for certain changes in packaging components *(e.g. comparative delivery study "droplet size" for a change in manufacturer of dropper tips)*.

### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusions

The GCC guidelines for *"Stability Testing of Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)"* should be followed for recommendations on the stability data required for the finished product(s).

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include information on storage conditions, strength, batch number *(including the drug substance batch number(s) and manufacturer(s))*, batch size, batch type, batch manufacturing date, container closure system *(including where applicable the orientation e.g. inverted)* and completed (and proposed) testing intervals, results, as well as conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

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 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.

Where the methods used in the stability studies are different from those described in 3.2.P.5.2, descriptions and validation of the methodology used in stability studies should be provided.

**A summary of stability study information is recommended to be presented as follows:**

| | Accelerated stability studies | Long term stability studies |
|---|---|---|
| **Storage conditions (°C, % RH)** | | |
| **FPP batch number** | | |
| **Batch type** | | |
| **Batch size** | | |
| • ***Drug substance batch number(s)*** | | |
| • ***Drug substance manufacturer(s)*** | | |
| **Completed testing intervals** | | |
| **Proposed testing intervals** | | |
| **Container closure system** | | |
| **Manufacturing site** | | |
| **Manufacturing date** | | |
| **Stability starting date** | | |
| **Conclusions with respect to storage conditions and proposed shelf-life** | | |
| **Conclusions with respect to in-use storage conditions and shelf-life, if applicable** | | |

**In-use stability studies should be conducted in accordance with the GCC Guidelines for Stability Testing on at least two batches taking into consideration the following requirements:**

- Stability protocol to be submitted including: number of batch(s), size of batch(s), tested parameters, manufacturing date and the starting date of the in-use stability study.
- The study design simulates the use of the product in practice.
- **ONE** of the batches should be chosen towards the **END** of its shelf-life (if available).

  ***If such results are not available:***

  - **ONE** of the batches should be tested at the **FINAL POINT** of the submitted stability studies with
  - A **commitment** to conduct in-use stability study at the **END** of shelf-life and to report immediately any out of specifications to the SFDA.

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 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.

Where the methods used in the stability studies are different from those described in 3.2.P.5.2, descriptions and validation of the methodology used in stability studies should be provided.

**The information on the in-use stability study is recommended to be presented as follows:**

| | |
|---|---|
| **Number of batches** | |
| **Batch numbers** | |
| **Batch type** | |
| **Batch size** | |
| **Manufacturing date** | |
| **Starting date of the study** | |

| | |
|---|---|
| **Tested parameters** | |
| **Is the study protocol submitted?** | ❍ Yes ❍ No |

**The information on the compatibility study is recommended to be presented as follows:**

| | |
|---|---|
| **Number of batches** | |
| **Batch numbers** | |
| **Batch type** | |
| **Batch size** | |
| **Manufacturing date** | |
| **Starting date of the study** | |
| **Tested parameters** | |
| **Reconstitution diluent(s)** | |
| **Is the study protocol submitted?** | ❍ Yes ❍ No |

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitments

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

Where the submission includes long-term stability data on three production batches covering the proposed shelf-life period, 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 three production batches,** a written commitment (signed and dated) should be made to continue these studies through the proposed shelf-life period.

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

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; and
- Description of the conditions of storage.

The stability of the drug product should be monitored over its shelf-life to determine that the product remains within its specifications and to detect any stability issue *(e.g. changes in levels of degradation products)*. For this purpose, the ongoing stability programme should include at least one production batch per year of product manufactured in every strength and every container closure system *(unless none is produced during that year)*. Therefore, a written commitment *(signed and dated)* for ongoing stability studies should be included in the dossier.
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.

### 3.2.P.8.3 Stability Data

Results of the stability studies should be presented in a tabular format. The results of all testing parameters related to each batch for the entire testing period should be presented in one table *(i.e. presenting the results of one parameter of all batches in one table is not acceptable).*

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.

Information on the analytical procedures used to generate the data and validation of these procedures should be included. Information on characterization of impurities is located in 3.2.P.5.5.

## 3.2.A Appendices

### 3.2.A.1 Facilities and Equipment

***For 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, 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

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.

***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 *(refer to Q5A(R1), Q5D, and Q6B).*

***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 ICH Q5A(R1) and Q6B, results for viral testing of unprocessed bulk should be included.

***Viral Clearance Studies***

In accordance with ICH Q5A(R1), 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).*

### 3.2.A.3 Excipients

### 3.2.R Regional Information

Any additional information should be provided in this section. The requirements for this section is being subjected to development and will be published soon.

- For biosimilars:

A comparative quality exercise between the reference product and the proposed biosimilar should be submitted in accordance with the SFDA Guideline on Quality Considerations for Development and Comparability Assessment of Biosimilars (Version 2.0).

- For advanced therapy medicinal products:

Providing shipping validation studies as applicable.

## 3.3 Literature References

A list and copies of all bibliographical references cited in support of this application should be provided. References that have not been provided should be available upon request.

# MODULE 4 NON-CLINICAL STUDY REPORTS

## 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 eCTD.

## 4.2 Study Reports

The study reports should be presented in the following order:

### 4.2.1 Pharmacology

This section should begin with a description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data *(e.g., lack of an animal model).*

#### 4.2.1.1 Primary Pharmacodynamics

Studies on primary pharmacodynamics should be provided and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data *(in terms of selectivity, safety, potency, … etc.)* on other drugs in the class.

#### 4.2.1.2 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics should be provided by organ system, where appropriate, and evaluated in this section.

#### 4.2.1.3 Safety Pharmacology

Safety pharmacology studies should be provided and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary pharmacodynamic studies should be considered along with safety pharmacology studies.

#### 4.2.1.4 Pharmacodynamic Drug Interactions

If they have been performed, pharmacodynamic drug interaction studies should be provided in this section.

### 4.2.2 Pharmacokinetics

#### 4.2.2.1 Analytical Methods and Validation Reports

This section should contain the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

#### 4.2.2.2 Absorption

The following data should be provided in this section:

- Absorption *(extent and rate of absorption, in vivo and in situ studies).*
- Kinetic parameters, bioequivalence and/or bioavailability *(serum/plasma/blood PK studies).*

#### 4.2.2.3 Distribution

The following data should be provided in this section:

- Tissue distribution studies.
- Protein binding and distribution in blood cells.
- Placental transfer studies.

#### 4.2.2.4 Metabolism

The following data should be provided in this section:

- Chemical structures and quantities of metabolites in biological samples.
- Possible metabolic pathways.
- Pre-systemic metabolism *(GI/hepatic first-pass effects).*
- *In vitro* metabolism including P450 studies.
- Enzyme induction and inhibition.

#### 4.2.2.5 Excretion

The following data should be provided in this section:

- Routes and extent of excretion.
- Excretion in milk.

#### 4.2.2.6 Pharmacokinetic Drug Interactions

If they have been performed, nonclinical pharmacokinetic drug-interaction studies *(in vitro and/or in vivo)* should be provided in this section.

#### 4.2.2.7 Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease *(e.g., renally impaired animals)*, they should be provided in this section.

### 4.2.3 Toxicology

#### 4.2.3.1 Single-Dose Toxicity

The single-dose data should be provided, in order by species, by route. In some cases, it may be helpful to provide the data in the form of a table.

#### 4.2.3.2 Repeat-Dose Toxicity

Studies should be provided in order by species, by route, and by duration, giving details of the methodology and highlighting important findings *(e.g., nature and severity of target organ toxicity, dose (exposure)/response relationships, no observed adverse effect levels, …etc)*.

#### 4.2.3.3 Genotoxicity

Studies should be provided in the following order:

- *In vitro* non-mammalian cell system.
- *In vitro* mammalian cell system.
- *In vivo* mammalian system *(including supportive toxicokinetics evaluation).*
- Other systems.

#### 4.2.3.4 Carcinogenicity

The choice of the studies and the basis for the high-dose selection should be explained. Individual studies should be provided in the following order:

##### 4.2.3.4.1 Long-term Studies

Long-term studies should be provided 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

Short- or medium-term studies should be provided 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 Development Toxicity

Studies should be provided in the following order, giving details of the methodology and important findings.

##### 4.2.3.5.1 Fertility and Embryonic Development

##### 4.2.3.5.2 Embryo-Fetal Development

##### 4.2.3.5.3 Pre- and Post-natal Development & Maternal Function

##### 4.2.3.5.4 Offspring, Juvenile, Second & Third-Generation Studies

If modified study designs are used, the sub-headings should be modified accordingly.

#### 4.2.3.6 Local Tolerance

If local tolerance studies have been performed, they should be provided in order by species, by route, and by duration, giving details of the methodology and important findings.

#### 4.2.3.7 Other Toxicity Studies

If other studies have been performed they should be provided in the following order, and where appropriate, the rationale for conducting the studies should be provided.

#### 4.2.3.7.1 Antigenicity

#### 4.2.3.7.2 Immunogenicity

#### 4.2.3.7.3 Mechanistic Studies (if not reported 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

### 4.3 Literature References

A list and copies of all bibliographical references cited in support of this application should be provided. References that have not been provided should be available upon request.

# MODULE 5 CLINICAL STUDY REPORTS

## 5.1 Table of Contents of Module 5

A Table of contents for the clinical study reports should be provided.

## 5.2 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. 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 5.3. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

## 5.3 Clinical Study Reports

### 5.3.1 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 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

#### 5.3.1.1 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.

## Table 5.1 Listing of Clinical Studies

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|
| *BA* | *001* | *Sec. No., page No.* | *Absolute BA IV vs Tablet* | *Cross-over* | *Tablet, 50mg single dose, oral, 10 mg IV* | *20* | *Healthy Subjects* | *Single dose* | *Complete; Abbreviated* |
| *BE* | *002* | *Sec. No., page No.* | *Compare clinical study and to-be-marketed formulation* | *Cross-over* | *Two tablet formulations, 50 mg, oral* | *32* | *Healthy Subjects* | *Single dose* | *Complete; Abbreviated* |
| *PK* | *1010* | *Sec. No., page No.* | *Define PK* | *Cross-over* | *Tablet, 50mg single dose, oral* | *50* | *Renal Insufficiency* | *Single dose* | *Complete; Full* |
| *PD* | *020* | *Sec. No., page No.* | *Bridging study between regions* | *Randomized placebo-controlled* | *Tablet, 50mg, multiple dose, oral, every 8 hrs* | *24 (12 drug, 12 placebo)* | *Patients with primary hypertension* | *2 weeks* | *Complete; Interim* |

### 5.3.1.2 Comparative BA & 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)*. Comparative Bioavailability (BA) or ***Bioequivalence (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.

***Biowaiver studies*** should be submitted in this section. For more information regarding the biowaiver studies, kindly refer to the SFDA Guidelines for Biowaiver.

### 5.3.1.3 In vitro/In vivo Correlation (IV/IVC) 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 submitted in this section.

*Comparative in vitro* dissolution profiles according to the GCC Guidelines for Bioequivalence should be submitted in this section.

*Reports* of *in vitro* dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the eCTD.

### 5.3.1.4 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 5.3.1.4 and referenced in the appropriate individual study reports.

### 5.3.2 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).

#### 5.3.2.1 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 5.3.3.

#### 5.3.2.2 Reports of Hepatic Metabolism and Drug Interactions studies

*Reports* of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be provided in this section.

#### 5.3.2.3 Reports of Studies Using other Human Biomaterials

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

### 5.3.3 Reports of Human Pharmacokinetic 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 5.3.3.1 and 5.3.3.2 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 5.3.3.1 to 5.3.3.2, as appropriate. These studies should characterize 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 5.3.3.1 and/or 5.3.3.2. 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 categorized 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 organized in Sections 5.3.3.3 and 5.3.3.4, 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 provided in Section 5.3.3.5.

#### 5.3.3.1 Healthy Subject PK and Tolerability

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

#### 5.3.3.2 Patient PK and Initial Tolerability

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

#### 5.3.3.3 Intrinsic Factor PK Study Reports

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

#### 5.3.3.4 Extrinsic Factor PK Study Reports

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

#### 5.3.3.5 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.

### 5.3.4 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 provided in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be provided in Section 5.3.5.

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 provided in Section 5.3.4.1, and the reports for those studies conducted in patients should be provided in Section 5.3.4.2.

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 5.3.5, not in Section 5.3.4.

### 5.3.4.1 Healthy Subject PD and PK/PD Study Reports

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

### 5.3.4.2 Patient PD and PK/PD Study Reports

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

### 5.3.5 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)*.

Within Section 5.3.5, 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 5.3.5 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 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5.3.5 and referenced as necessary in other Sections 5.3.5 *(e.g., Section 5.3.5A, Section 5.3.5B)*.

### 5.3.5.1 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 provided in this section.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be provided in this section. 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 this section. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in this section.

### 5.3.5.2 Study reports of Uncontrolled Clinical Studies

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

### 5.3.5.3 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 provided in this section. 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.

### 5.3.5.4 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 5.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in Section 5.3.5.1.
- Reports of ongoing studies.

### 5.3.6 Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be provided in this section.

### 5.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings that are described 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.

## 5.4 Literature References

Copies of referenced documents, *including important published articles, official meeting minutes*, or other regulatory guidance or advice should be provided here. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.