GUIDANCE DOCUMENT FOR SUBMISSION OF APPLICATION ON FORM 5-F (CTD) FOR REGISTRATION OF BIOLOGICAL DRUG PRODUCTS FOR HUMAN USE

Document No.: **BE&R/GL/AF**

Document History: **1st Edition**

Effective Date: **DD-MM-YYYY**

This draft guideline is uploaded on the official website of DRAP dated on 9th May, 2023, for seeking comments and suggestions from stakeholders on the draft document. Stakeholders can submit their comments and suggestions within 15 days of uploading this document using prescribed format, (further information on comments submission can access on this link. Comments and suggestions can be forwarded via email to a ahmad.ansari@dra.gov.pk copying at ahsan.hafiz@dra.gov.pk , or can be posted at mailing address, Director, Biological Drugs, Drug Regulatory Authority of Pakistan, 4th floor TF Complex, 7th Mauve Area, G-9/4, Islamabad.

Drug Regulatory Authority of Pakistan
Islamabad - Pakistan.

1. HISTORY

This is the first edition of these guidelines after the introduction of Form-5F (CTD).

2. APPLICATION[1] - Guidance for Industry.

This document is applicable to the Biological products (BP) manufacturer and importers who intend to apply for registration / Marketing Authorization for import or local manufacture intended for human use.

3. SCOPE

The scope of this Guideline is limited to application on Form-5F (CTD) for registration of biological drug products for human use.

4. BACKGROUND

Section 7 (c) (ii, viii, ix) of DRAP Act 2012, mandated the registration of therapeutic goods, implementation of internationally recognized GLP, cGMP etc and systematic implementation of internationally recognized standards of World Health Organization, International Conference on Harmonization (ICH), and Food and Drug Administration guidelines etc.

These guidelines conform and shall be read in consistence to DRAP Act, 2012 and Drugs Act 1976 and Rules framed there under.

[1] **The Guidance document is prepared by Drug Regulatory Authority of Pakistan for better illustration of data requirements of the Form 5-F (CTD). However, content of guidance document only reflects the current thinking perspective of the Authority on the subject and does not create or confer any rights for or on any person and does not operate to bind the Authority or the public.**

Contents

GLOSSARY

ACRONYMS

API	Active Pharmaceutical Ingredient
BAN	British Approved Name
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CAS	Chemical Abstract Service
CEP	Certificate of Suitability
CoA	Certificate of Analysis
CPP	Critical Process Parameters
CQA	Critical Quality Attribute
CTD	Common Technical Document
DML	Drug Manufacturing License
DRAP	Drug Regulatory Authority of Pakistan
EPAR	European Public Assessment Report
FDA	Food & Drug Administration of United States
GCP	Good Clinical Practices
GLP	Good laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
INN	International nonproprietary name
IR	Infrared
JP	Japanese Pharmacopoeia
LR&A	Licensing, Registering & Advertising
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
OSD	Oral Solid Dosage form
PAR	Public Assessment Report
Ph.Eur	European Pharmacopoeia
Ph.Int	International Pharmacopoeia
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
RRA	Reference Regulatory Authority
SAE	Serious Adverse Events
TSE	Transmissible Spongiform Encephalopathies
USAN	United States Adopted Name
USP	United States Pharmacopoeia
UV	Ultraviolet-Visible
WHO	World Health Organization

1. INTRODUCTION

This guidance is developed to assist manufacturers and importers in developing their applications for registration of human biological drug products. Drug Regulatory Authority of Pakistan (DRAP) has adapted CTD format for registration of all such drugs vide SRO-713(l)/2018 dated 8th June 2018. The detailed guidance regarding the data requirement for CTD format has been provided in ICH M-4 guidelines. Since the DRAP is introducing the CTD in a progressive manner, therefore, initial guidance to applicants would be helpful for harmonization and appropriate data submission to achieve consistency and uniformity of application.

This guidance document is developed on the basis of best available knowledge and scientific data / evidence.

2. LEGAL PROVISIONS

Rule 26 of the Drugs (Licensing, Registering and Advertising) Rules, 1976, as amended vide S.R.O 713(I)/2018 dated 8th June, 2018, under 26(1) section provides the standard formats and requirements for submission of registration application dossier on Form 5F (Common Technical Documents) for registration of Human drugs.

3. GENERAL GUIDANCE FOR APPLICANTS

For submitting applications on CTD format, applicant needs to follow the following general instructions/guidance to ensure proper submission.

1. Module 1 (Administrative part) shall be prepared as provided in Form-5F without deleting any component. Applicant shall mention "Not applicable" with proper justification for those parts which are not related to any particular application.
2. Quality Overall Summary (QOS) in module 2 shall be prepared using WHO QOS-PD template or template provided hereinafter without deleting any component / table of the template.

   Applicant shall mention "Not applicable" with proper justification for those parts which are not related to any particular application.
3. The Quality overall Summary (QOS) prepared as per WHO QOS-PD template or template provided hereinafter needs to be submitted as "MS Word document" in CD / USB as well.
4. Application shall be submitted along with complete data as per the module 3.
5. Each section / sub section of CTD application shall be properly segregated using page separators.

MODULE 1: (ADMINISTRATIVE PART)

1.1 Covering Letter and Fee Deposit Slip

a) Covering letter on the Applicant company / manufacturer / importer letter head in context to the application for the registration of the Pharmaceutical Drug Product shall be submitted, which shall be dully signed by owner/ authorized person on behalf of company/ manufacturer/ importer as per below mentioned format:

"I / We ……..... of ……hereby apply for registration of the drug, namely ……details of which are enclosed."

b) An original cash deposit slip of prescribed fee as per Notification No. F. 7-11/2012-B&A/DRAP dated 13-07-2021, for specified category shall be attached therewith.

1.2 Table of Contents (From Module 1 to Module 5)

a) A comprehensive Table of Contents shall contain Module and sub module heading with page number on the pharmaceutical dossier. The contents of all the Module from 1 to 5 shall be covered. Comprehensive Table of Contents is different form individual table of contents in the beginning of each Module.

b) Also, a complete list of all documents provided in the registration dossier by Module, Section and sub-section shall be included.

1.3 Applicant Information

1.3.1. Name, address and contact details of Applicant / Marketing Authorization Holder:

a) In this section, administrative information related to the applicant is required.

b) It is necessary to provide the complete particulars of the applicant, which shall contain:

i. Name of Licensed Pharmaceutical Manufacturer / Licensed Importer having Drug Sale License by respective licensing authority.

ii. Manufacturing Site Address of Pharmaceutical unit or address of the godown / warehouse in case the applicant is Drug Sale license Holder.

iii. Contact details, including postal address, telephone contact number, Fax number, website and email address.

1.3.2. Name, address and contact details of manufacturing site

There could be following three situations:

a) **The applicant is manufacturer**
Provide the details including name, DML number and complete address of the manufacturing site of the applicant (manufacturer).

b) **Contract Manufacturing (The applicant is not manufacturer for the applied product)**
Provide the details including name, DML number and complete address of the manufacturing site of the manufacturer.

c) **Import (The applicant is importer for the applied product)**
Provide the details including name and complete address of the manufacturing site and name of marketing authorization Holder/ Product License Holder for the applied product. In case multiple manufacturing sites are involved, provide details for each.

1.3.3. Specify whether the Applicant is:

a. Manufacturer
b. Importer
c. Is involved in none of the above (contract giver)

This point requires the status of applicant for the instant product. The applicant must select one of the above-mentioned options.

- A manufacturer will provide all the requisite information as per Registration procedure of Pakistan, subsequently mentioned in 1.3.4-1.3.5.
- An importer shall provide Certificate of Pharmaceutical Product (CoPP) / Free Sale certificate and GMP certificate of the Manufacturer issued by relevant regulatory authority in the country of origin and name of exporting country.
- "c" is for Contract Manufacturing as per Rule 20-A of Drugs (Licensing, Registering and Advertising) Rules, 1976.

1.3.4. Valid Drug Manufacturing License (DML) of manufacturer / Applicant or Drug Sale License, whichever is applicable.

a) For drug to be locally manufactured, copy of valid Drug Manufacturing License (DML) issued by Licensing Division, DRAP.
b) For drugs to be imported, copy of valid Drug Sale License (DSL) issued by relevant licensing authority. The address of applicant mentioned on Drug Sale License (DSL) shall match with the information provided in sub-section 4.3.1 and sole agency agreement / letter of authorization between applicant and marketing authorization holder (abroad).

1.3.5. Evidence of approval of manufacturing facility / Approved Section from Licensing Authority

a) To be provided if option **a** or **c** is selected in sub-section 1.3.3
b) Approval letter of the section (Dosage form) in which manufacturing of the applied product is to be carried out needs to be submitted or panel inspection report conducted for renewal of DML or grant of GMP certificate. In case of contract manufacturing, the same documents from the contract manufacturer shall be submitted.
c) GMP inspection report/ GMP certificate of the manufacturing unit issued within the last three years shall be submitted.

1.3.6. List of already approved registered drugs in this section

The submission against this point is optional

1.3.7. Identification of Signature(s) of authorized persons, Incharge Production, Quality Control and Incharge Quality Assurance

The submission against this point is optional**.**

1.3.8. Manufacturer's Site Master File and Credential (for importer)

The submission against this point is optional.

1.4 Type of Application

1.4.1. Application is for the registration of:

- **New Drug Product (NDP)**
- **Similar Biotherapeutic Product (SBP)**

a) New Drug Product (*Product not already registered in Pakistan*) includes New Molecule/ New strength / New Formulation.
b) It is important to specify here whether the applicant has submitted the CTD for a New Drug Product Registration or a similar Biotherapeutic Product.
c) It is important to mention here if the Biological Product is a vaccine manufactured under relevant WHO TRS or is a new vaccine for which WHO TRS is not yet developed.
d) It is to be noted that established vaccines are not Biosimilar Biologicals, each vaccine is unique in its own right but are similar due to absence of difference in the parameter of interest.

1.4.1 Biological product is intended for:

- **Domestic sale**
- **Export sale**
- **Domestic and Export sales**

a) Applicant needs to clarify whether the applied product (drug product) is intended for sale in domestic market or both for domestic and export market.
b) For Export only registrations application on Form 5F (CTD) is already exempted by the Authority vide its Circular No. F.1-21/2019-Add: Dir. (PE&R) dated 06-02-2019.

1.4.2. For imported products, please specify one of following:

- □ **Finished Pharmaceutical Product Import**
- □ **Bulk Import and local repacking (specify status of bulk)**
- □ **Bulk Import Local Repacking for Export purpose only**

This point only pertains to registration applications of drug products for import.
The applicant / importer needs to specify whether the import is of finished pharmaceutical product or of bulk product. In case of bulk import local repack, the applicant also needs to provide following documents:

a) Evidence and GMP status of packing facility for the bulk imported drug to be repacked and batch release.
b) Agreement between the importer and the firm responsible for local repacking in Pakistan.

1.4.3. Contract Manufacturing as per Rule 20-A of Drugs (Licensing, Registering and Advertising) Rules, 1976.

□ Domestic Manufacturing

□ Export Purpose Only

a) Provide notarized copy of Contract manufacturing agreement.
b) Provide documents confirming number of approved sections of the applicant (DML holder).
c) Provide details of already registered drug products of contract giver on contract manufacturing.

1.5 Detailed Information of Drug, Dosage From & Labeling Claims

1.5.1. Generic name with chemical name & synonyms of the applied drug.

The following necessary information shall be provided in this sub-section:

a) (Recommended) International Non-proprietary name (INN):
b) Compendia name, if relevant:
c) Chemical name(s):
d) Chemical Abstracts Service (CAS) registry number: (where applicable)

The submission of following is **optional**

a) Company or laboratory code
b) Other non-proprietary name(s) (e.g. national name, USAN, BAN):

1.5.2. Strength / concentration of drug of Active Pharmaceutical ingredient (API) per unit

a) Strength of Active ingredient shall be stated clearly.
For example, each tablet contains, each ml contains in case of Injectable. However, description like each ampoule / vial contains shall be avoided.

1.5.3 The proposed proprietary name / brand name under which the drug is intended to be sold with trade mark certification / clearance.

a) The proposed brand name shall be justified keeping in view the LASA (Look alike and Sound alike) with specific emphasis on prefix, mid-name and suffix.
b) An undertaking in this regard that the applicant shall be responsible to change the name in case the name resembles with already approved / registered names.

1.5.4 Proposed Pack size and Proposed unit price of drug e.g., per tablet / capsule. Maximum Retail Price (MRP) per pack shall also be mentioned.

a) The applicant needs to submit the proposed pack size as well as demanded price for each pack size.

1.5.5 Pharmacotherapeutic Group of Active Pharmaceutical Ingredient (API)

a) Indicate Pharmacological class of the API (drug substance) with proper reference.
b) Also, state the WHO ATC code for each distinct therapeutic indication.

1.5.6 Pharmacopoeial reference / Status of applied formulation

Mention the reference specifications of the finished product (drug product) from the following list

- USP
- BP

- Int. Ph.
- JP
- Pharmacopoeia of any Reference Regulatory Authority
- Manufacturer's specifications.
- Specifications as per Innovator's product
- Any other (specify exact reference)
- Any other pharmacopoeia as mentioned in Drug specification rules. (Specify the exact reference).

1.5.7 Route of administration

The applicant needs to specify the exact route of administration for the applied drug product. In case of multiple route of administration, specify all routes of administration.

1.5.8 For Biosimilar Drug Product, reference of other similar approved medicines with information pertaining to Manufacturer name, brand name, strength, composition, registration number & dosage form, Pack size and Price.

If the applicant has selected Biosimilar Drug Product (GDP) in sub-section 1.4.1, the reference of already registered product including the following details needs to be submitted.

- Brand name
- Manufacturer/Registration holder
- Registration number

If the applicant has selected New Drug Product (NDP) in sub-section 1.4.1 "Not applicable since this is a new drug" needs to be mentioned against this point.

1.5.9 The registration status of applied drug in same molecule and salt, strength, dosage form, container closure system, indications and route of administration etc. in other countries. The status in reference regulatory authorities is mandatory to mention.

Evidence of approval / registration / marketing status of the applied formulation in the same composition, salt form and dosage form in one of the reference regulatory authority specified by Registration Board. The name of the reference authority shall be mentioned as adopted by Board currently.
Mention the name of innovator product in case of non-pharmacopoeial product.

1.5.10 Dosage form of applied drug

- Dosage form of applied drug shall be mentioned clearly.

1.5.11 Proposed label [outer (secondary) & inner (primary)] & colour scheme in accordance with Drug (Labelling & Packing) Rules, 1986 along with specimens

The submission against this point is optional.

1.5.12 Description of Batch numbering system

The submission against this point is optional.

1.5.13 Training evidence of technical staff with respect of manufacturing of applied drug (mandatory in case of specially designed pharmaceutical product / Novel Dosage Form).

The submission against this point is optional.

1.5.14 Summary of Product Characteristics (SmPC) including Prescribing Information (PI) along with Patient information Leaflet (PIL) of the Finished Pharmaceuticals Product (FPP).
The submission against this point is optional.

1.5.15 – 1.5.20 Commitments
I/ we hereby undertake that:

1.5.15 After registration of applied drug, the Pharmacovigilance department of the applicant / manufacture is liable to impose similar restrictions, addition of any clinical information (like in Indications, Contra-indications, Side effects, Precautions, Dosage & Adverse Drug Reactions etc. in Summary of Product Characteristics (SmPC), Labelling & Promotional material) or withdraw the drug from market in Pakistan within fourteen days after knowing that such information (which was not available or approved by the DRAP at the time of registration) / actions taken (for safety reasons) by any reference / stringent drug regulatory agency / authority & also inform the DRAP (Drug Regulatory Authority of Pakistan) for further action in this regard.

1.5.16 We shall recall the defective Finished Pharmaceutical Products (FPP) and notify the compliance to the authority along with detail of actions taken by him as soon as possible but not more than ten days. The level of recall shall also be defined.

1.5.17 In case of any false claim / concealing of information, the DRAP has the right to reject the application at any time, before and even after approval or registration of the product in case if proved so.

1.5.18 We will follow the official pharmacopoeia specifications for product / substance as published in the latest edition & shall update its specification as per latest editions of the same. In case, the specifications of product / substance not present in any official pharmacopoeia the firm shall establish the specifications. In both cases, the validation of specifications shall be done by the applicant. *(For drug products to be imported, this commitment must be submitted by manufacturer abroad as well).*

1.5.19 In case of any post approval change, the applicant shall ensure that the product with both approvals shall not be available in the market at the same time. And the product with new approvals shall be marketed only after consumption / withdrawal of stock with previous approvals. The company shall be liable to inform the same regarding marketing status of product to the DRAP after getting such post-registration approvals.

1.5.20 We will perform process validation and stability studies till the assigned shelf life for the first three consecutive batches of commercial scale, stability study of at least one batch every year in accordance with the protocols and continue real time stability study till assigned shelf life of the applied product.

1.5.20 a) We will be responsible to change the brand name in case the name resembles with already approved / registered names.

b) We will be responsible to change the label design if it resembles with any of the previously registered drug.

I / We hereby undertake that the above given information is true and correct to the best of my / our knowledge and belief.

1.5.21 Protocols along with the commitment to follow Good Laboratory Practices (GLP) by the Manufacturer.
The submission against this point is optional.

1.5.22 Protocols to implement Good Pharmacovigilance Practice by the Pharmacovigilance department/section of the Manufacturer / Company.
The submission against this point is optional.

1.6 Miscellaneous Information
1.6.1 Information on Prior-related Applications
The submission against this point is optional.

1.6.2 Appendix

1.6.3 Electronic Review Package
The applicant shall submit electronic review package in CD / USB including Quality Overall Summary.

1.6.4 QIS (Quality Information Summary)
The submission against this point is optional

1.6.5 Drug Substance related Document including following:
a. Name and address of API manufacturer.
b. Approval of manufacturing facility of API by regulatory body of country and validity.
For applications of locally manufactured drug product(s), the one of the following documents shall be submitted.

i. Valid Drug Manufacturing License issued by the relevant regulatory authority of country of origin.
ii. Valid Good Manufacturing Practice (GMP) certificate of the Drug Substance manufacturer issued by relevant regulatory authority of country of origin.

For applications of imported drug product(s), the submission against this point is not required.

MODULE 2: (OVERVIEWS AND SUMMARIES)

2.3 Quality Overall Summary (QOS)

- The QOS as per ICH template for consideration by the Registration Board.

INTRODUCTION

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

2.3.S. DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (name, manufacturer)

Information from 3.2.S.1 should be included. 2.3.S.2 Manufacture (name, manufacturer) Information from 3.2.S.2 should be included:

- Information on the manufacturer
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- A flow diagram, as provided in 3.2.S.2.2;
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that 1 The Common Technical Document - Quality used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterization (name, manufacturer)

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

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

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

2.3.S.4 Control of Drug Substance (name, manufacturer)

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

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided. 2.3.S.5 Reference Standards or Materials (name, manufacturer) Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.5 Reference Standards or Materials

a) CoA of primary / secondary reference standard including source and lot number

<For testing of Pharmacopeial Drug Substance, the use of primary reference standard is recommended,

however for non-pharmacopeial Drug Substance, a secondary reference standard provided by the Drug Substance manufacturer is acceptable>

2.3.S.6 Container Closure System (name, manufacturer)
A brief description and discussion of the information, from 3.2.S.6 should be included.
2.3.S.7 Stability (name, manufacturer)
This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.
The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

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

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)
Information from 3.2.P.1 should be provided.
Composition from 3.2.P.1 should be provided.

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

A discussion of the information and data from 3.2.P.2 should be presented.
A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, dosage form)
Information from 3.2.P.3 should include;

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

2.3.P.4 Control of Excipients (name, dosage form)
A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (name, dosage form)
A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.
Specification(s) from 3.2.P.5.1 should be provided.
A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (name, dosage form)
Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

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

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

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

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

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

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

2.3.A Appendices

2.3.A.1 Facilities and Equipment

<Provide a list of manufacturing and testing facilities / equipment available with reference to the applied drug product>

2.3.A.2 Adventitious Agents Safety Evaluation

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

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

2.3.A.3 Excipients

<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, with cross references to supporting safety (nonclinical and/or clinical) data shall be provided>

2.3.R Regional Information

2.3.R.1 Production Documentation

2.3.R.1.1 Executed Production Documents

<Provide copy of Batch Manufacturing Record (BMR) for all the batches of drug product for which stability studies data is provided in Module 3 section 3.2.P.8.3>

2.3.R.1.2 Comparability Protocols

This point is only for Biosimilar Drugs. The applicant shall submit summary of quality comparison of their product with Innovator product.

2.4 NONCLINICAL OVERVIEW

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

The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate. Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation.

Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

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

2.5 CLINICAL OVERVIEW

The Clinical Overview should present the strengths and limitations of the development program and study results, analyze the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives, the Clinical Overview should:

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions.
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance.
- provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy).
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will 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). 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.

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
    2.5.6.1 Therapeutic Context
        2.5.6.1.1 Disease or Condition
        2.5.6.1.2 Current Therapies
        2.5.6.2 Benefits
        2.5.6.3 Risks
        2.5.6.4 Benefit-Risk Assessment
        2.5.6.5 Appendix
    2.5.7 Literature References

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Order of Presentation of Information within Sections
When available, in vitro studies should precede in vivo studies.
Where multiple studies of the same type need to be 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
- Non-human primate
- Other non-rodent mammal
- Non-mammals

Routes of administration should be ordered as follows:

- The intended route for human use
- Oral

- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

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

2.7 Clinical Summary

The Clinical Summary includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations.

In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium. The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

Table of Contents:

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

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

2.7.2 Summary of Clinical Pharmacology Studies

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

2.7.3 Summary of Clinical Efficacy

2.7.3.1 Background and Overview of Clinical Efficacy
2.7.3.2 Summary of Results of Individual Studies

2.7.3.3 Comparison and Analyses of Results Across Studies
2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations
2.7.3.5 Persistence of Efficacy and/or Tolerance Effects
2.7.3.6 Appendix

2.7.4 Summary of Clinical Safety

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

2.7.5 Literature References

2.7.6 Synopses of Individual Studies

5. MODULE 3: (QUALITY / CMC)

3.1. TABLE OF CONTENTS OF MODULE 3

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

3.2. BODY OF DATA

3.2.S DRUG SUBSTANCE* (NAME, MANUFACTURER)

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

3.2.S.1.1 Nomenclature (name, manufacturer)

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

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

For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.

3.2.S.1.2 Structure (name, manufacturer)

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

3.2.S.1.3 General Properties (name, manufacturer)

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

Reference ICH Guidelines: Q6A and Q6B

3.2.S.2 Manufacture (name, manufacturer)

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

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

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

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:

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.

<u>Batch(es) and scale definition</u>

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

<u>Cell culture and harvest</u>

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 inprocess tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in 3.2.S.2.4.)

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

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

Filling, storage and transportation (shipping)

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

Reference ICH Guidelines: Q5A, Q5B, and Q6B

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

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (e.g., media components, monoclonal antibodies, enzymes etc.) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate.

Reference ICH Guidelines: Q6A and Q6B

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information should be provided. (Details in 3.2.A.2.)

Source, history, and generation of the cell substrate

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

Cell banking system, characterization, and testing

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

Reference ICH Guidelines: Q5A, Q5B, Q5C and Q5D

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

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

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

Reference ICH Guidelines: Q6A and Q6B

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

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

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

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

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

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

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

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

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

Reference ICH Guideline: Q6B

3.2.S.3 Characterization (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

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

Reference ICH Guideline: Q6B

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q5C, Q6A, and Q6B

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specification for the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B

3.2.S.4.2 Analytical Procedures (name, manufacturer)

The analytical procedures used for testing the drug substance should be provided.

Reference ICH Guidelines: Q2A and Q6B

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

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

Reference ICH Guidelines: Q2A, Q2B, and Q6B

3.2.S.4.4 Batch Analyses (name, manufacturer)

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

Reference ICH Guidelines: Q3A, Q3C, Q6A, and Q6B

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A and Q6B

3.2.S.5 Reference Standards or Materials (name, manufacturer)

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

Reference ICH Guidelines: Q6A and Q6B

3.2.S.6 Container Closure System (name, manufacturer)

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification.

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 (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

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

Reference ICH Guidelines: Q1A, Q1B, and Q5C

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

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

Reference ICH Guidelines: Q1A and Q5C

3.2.S.7.3 Stability Data (name, manufacturer)

Results of the stability studies (Real time & Accelerated) should be presented in an appropriate format.

3.2.P Drug Product

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

a) Description of the dosage form

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

Reference ICH Guidelines: Q6A and Q6B

b) Composition

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). * *Overages are not acceptable unless fully justified*

If the Drug product is formulated using an active moiety, then the composition for the active ingredient shall be clearly indicated.

c) Description of accompanying reconstitution diluent(s)

Provide information including type of diluent, its composition, quantity or volume, specifications (as applicable) and regulatory status in Pakistan (as applicable) for the diluent which is to be provided along with the applied drug.

d) Type of Container Closure:
The container-closure used for the Drug Product (and accompanying reconstitution diluent, if applicable) shall be briefly described, with further details provided under 3.2.P.7 Container-closure system

3.2.P.2 Pharmaceutical Development
A brief information on the pharmaceutical development shall be included. This information specifies the justification of formulation and method of manufacturing. It is also important that critical quality attributes (CQAs) and Critical Process Parameters (CPP) shall be discussed.

3.2.P.2.1 Components of the Drug Product

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.

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.

3.2.P.2.2 Formulation Development
A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.
Any overages in the formulation(s) described in 3.2.P.1 should be justified.
Parameters relevant to the performance of the drug product, such as pH, reconstitution, particle size biological activity or potency, and/or immunological activity, should be addressed.

3.2.P.2.3 Manufacturing Process Development
The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.
Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

3.2.P.2.4 Container Closure System

The submission against this point is optional.

3.2.P.2.5 Microbiological Attributes

The submission against this point is optional.

3.2.P.2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (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.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer

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

3.2.P.3.2 Batch formula

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

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 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.

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.

Reference ICH Guidelines: Q2A, Q2B, Q6A, and Q6B

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).

3.2.P.4 Control of Excipients Specifications
3.2.P.4.1 Specifications
3.2.P.4.2 Analytical procedures
3.2.P.4.3 Validation of analytical procedures
Validation information for the analytical procedures for in-house standard excipients shall be submitted.
<Copies of analytical procedures of non-compendial excipient shall be submitted>

3.2.P.4.4 Justification of specifications
Justification of the specifications for the analytical procedures for in-house standard excipients shall be provided.

3.2.P.4.5 Excipients of Human or Animal Origin
For excipients of human or animal origin, a certificate shall be provided, confirming that the excipient(s) are free from BSE and TSE.

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 specification and testing method shall be provided.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)
A copy of the drug product specification(s) including tests, acceptance criteria and reference to analytical procedure shall be provided. Specifications shall also include the details of impurities (as applicable).

3.2.P.5.2 Analytical procedures
Detailed analytical procedures used for testing the drug product shall be provided.

3.2.P.5.3 Validation of analytical procedures
For in-house methods, analytical method validation shall be performed.
All the officially recognized compendial methods for assay, impurities etc. (as applicable) are required to be verified and verification shall include a demonstration of specificity, repeatability (method precision) and accuracy.

3.2.P.5.4 Batch analysis
The copies of complete analysis of at least two batches shall be provided.

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".

3.2.P.5.6 Justification of specifications

The justification of specification(s) for non-pharmacopeial products must be provided. Justification of specification of non-pharmacopeial product shall be based on batch analysis results.

3.2.P.6 Reference Standards or Materials

For testing of Pharmacopeial Drug Product(s), the use of primary reference standard is recommended, however for non-pharmacopeial Drug Product(s), a secondary reference standard is acceptable. COA of primary / secondary reference standard including source and lot number shall be provided.

3.2.P.7 Container Closure System

A detail of the container closure systems, description of the primary container closure systems, including materials of construction, unit count or fill size, container size or volume shall be provided.

3.2.P.8 Stability

For the pre-market authorization stability studies for a period of 6 months accelerated and real time in proposed container closure system is required in accordance with the Zone IVa conditions. Based on the satisfactory results, a two years shelf life will be granted. For selection of number and size of batches applicant may follow, any of the following options:

a) ICH/WHO guidelines.

b) At least 2 batches having the following minimum batch size considering the scientific reliability
- OSDs: 5000 Units
- Oral Liquids: 2000
- Injectable: 2000

c) At least 3 batches having scientifically rational batch size, sufficient enough to perform complete testing till the claimed shelf life.

3.2.P.8.1 Stability summary and conclusion (Finished Product):

Summary of stability batches with details of storage conditions, batch numbers, batch size, testing intervals and container closure system along with proposed storage statement and shelf-life shall be provided.

Summary of additional stability studies (if applicable) e.g. in-use studies for drug products which are to be reconstituted before use, along with proposed in-use storage statement and in-use shelf-life shall be provided.

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

For applications of locally manufactured drug product(s), stability protocol for commitment batches (e.g. storage conditions, batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s) shall be provided. A written commitment (signed and dated) to continue long-term testing over the shelf-life shall be included in Module-1.

For applications of imported drug product(s) where stability study data till complete shelf life is submitted, post-approval stability protocols and commitment is not required.

3.2.P.8.3 Stability Data:

Results of the stability studies shall be presented in an appropriate format (provided below).

The actual stability results and reports used to support the proposed shelf-life shall be provided. For quantitative tests (e.g. individual and total degradation product tests and assay tests), actual numerical

results shall be provided rather than vague statements such as "within limits" or "conforms". Conduction of stability study data shall be scientifically justified.

Storage Conditions: a)
General case
The general case applies if the drug product is not specifically covered by any other storage condition in the subsequent sections.

Study	Storage condition
Accelerated	40°C ± 2°C / 75% RH ± 5% RH
Long term	30°C ± 2°C / 65% RH ± 5% RH

b) Drug products packaged in semi-permeable containers
Aqueous-based products packaged in semi-permeable containers shall be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability.
Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition
Accelerated	40°C ± 2°C / NMT 25% RH
Long term	30°C ± 2°C / 35% RH ± 5% RH

c) Drug products intended for storage in a refrigerator

Study	Storage condition
Accelerated	25°C ± 2°C / 60% RH ± 5% RH
Long term	5°C ± 3°C

d) Drug products intended for storage in a freezer

Study	Storage condition
Accelerated	5°C ± 3°C or 25°C ± 2°C
Long term	- 20°C ± 5°C

Stability data submission:

- For applications of imported drug product(s), real time and accelerated stability data (summary sheets) as per ICH guidelines or till claimed shelf life as per the storage conditions mentioned above shall be provided.
- For applications of locally manufactured drug product(s), the stability study data shall be provided as per the below mentioned format.

Stability study data submission locally manufactured products for CTD:

<u>Stability Study Data Sheet</u>

Product details:

Product name	ABCD Injection		Batch No.	
Description of pack (container closure system)	Type I Glass Vial		Batch Size.	
Parameters and tests mentioned	As per Product Specifications		Mfg. Date	
Recommended storage conditions	Accelerated conditions		Exp Date	
	Real time conditions			
Date of initiation of stability studies			(API) lot no.	

Accelerated Stability study data:

Storage conditions				
Assessment frequency (Months)		Initial	3	6
Date of Testing				
Tests (as per specifications)	Acceptance Criteria			

Real time stability study data:

Storage conditions				
Assessment frequency (Months)		Initial	3	6
Date of Testing				
Tests (as per specifications)	Acceptance Criteria			

Documents / Data to be provided along with stability study data:

1.	Approval of API/ DML/GMP certificate of API manufacturer issued by concerned regulatory authority of country of origin.
3.	Data of stability batches will be supported by attested respective documents like chromatograms, Raw data sheets, COA, summary data sheets etc.
4.	Record of Digital data logger for temperature and humidity monitoring of stability chambers (real time and accelerated)

3.2.A Appendices

3.2.A.1 Facilities and equipment

A list of manufacturing and testing facilities / equipment available with reference to the applied drug product shall be provided.

3.2.A.2 Adventitious agent safety evaluation

For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

Reference ICH Guidelines: Q5A, Q5D, and Q6B

For viral adventitious agents:

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

Materials of Biological Origin

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

Testing at appropriate stages of production

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

Viral Testing of Unprocessed Bulk

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

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps

that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5). Reference ICH Guidelines: Q5A, Q5D, and Q6B

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, with cross references to supporting safety (non-clinical and/or clinical) data shall be provided.

3.2.R Regional Information

Comparability Protocols
For Biosimilar Drugs, the applicant shall submit complete quality comparison of their product with Innovator product in light of guidelines approved by Registration Board in its 297th meeting.

Module 4: (Non-clinical / Safety)

The table of contents for Module 4 should include all of the numerical items listed in the CTD guidance in order to identify all of the important components of the application and should continue down to at least the level of the study report. Thus, each study report should be identified in the table of contents.

The study reports should be presented in following order:

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

4.2.2 Pharmacokinetics
- 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4 2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology
- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
- 4.2.3.3.1 In vitro
- 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
- 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

Module 5: (Clinical / Efficacy)

The table of contents for Module 5 should include all of the numerical items listed in the CTD guidance in order to identify all of the important components of the application and should continue down to at least the level of the clinical study report. Thus, each clinical study report should be identified in the table of contents. The sections of a clinical study report (E3) could be identified in the Module 5 Table of Contents of the dossier or only in the table of contents of the individual clinical study report.

The study reports should be presented in following order:

Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

5.3.1.3 *In vitro-In vivo* Correlation 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 Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

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 Clinical Study Reports

REFERENCES

1. The DRAP Act, 2012.
2. The Drugs Act 1976.
3. The Drugs (Licensing, Registering and Advertising) Rules, 1976.
4. ICH -M4Q (R1) Guidelines.
5. ICH -SAFETY – M4S(R2)
6. ICH -EFFICACY - M4E(R2)
7. WHO GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)
8. WHO QUALITY OVERALL SUMMARY: PRODUCT DOSSIER (QOS-PD) TEMPLATE

DRUG REGULATORY AUTHORITY OF PAKISTAN
Telecom Foundation Complex, G-9/4, Islamabad, Pakistan
Email: addl-dir.pe.reg@dra.gov.pk Phone:92-51-9107416 www.dra.gov.pk
www.dra.gov.pk