إدارة تسجيل ورقابة الأدوية والمنتجات الطبية
Medicines & Medical Products Registration
& Regulatory Administration

وزارة الصحة
Ministry of Health
State of Kuwait | دولـــة الكويت

MINISTERIAL DECREE FOR REGISTRATION OF PHARMACEUTICAL MEDICINAL PRODUCTS

ملحق القرار الوزاري رقم (341) لسنة 2025

بشأن تنظيم تسجيل الأدوية البشرية وتداولها

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Definitions and Abbreviations

Authorized Representative: also referred to as the Local Agent or scientific office or local approved affiliates, is a legal entity established in the State of Kuwait, officially appointed by the Marketing Authorization Holder (MAH) to act on their behalf before the Medicine and Medical Products Registration and Regulatory Administration in all matters related to the registration, importation, pricing, post-marketing surveillance, and communication of medicinal products.

Bioavailability Studies (BA) Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action.

Bioequivalence Studies (BE): Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits

Central Medical Store (CMS): Kuwait entity for drug procurement for the public sector.

Common Technical Document (CTD): The CTD is a standardized format developed by the International Council for Harmonization (ICH) for submitting applications for the registration of medicines. It organizes data into five well-defined modules (module 1-5) covering administrative information, quality, non-clinical, and clinical information.

Country of Origin: The country in which the product is manufactured and first registered.

Drug: Any substance or combination of substances intended to be used in the diagnosis, treatment, mitigation or prevention of disease in man or to restore, correct or modify physiological functions

Electronic Common Technical Document (eCTD): The eCTD is the electronic version of the Common Technical Document. It retains the same modular structure but allows digital submission lifecycle management, and electronic navigation of documents.

Emergency Use Authorization (EUA): Emergency Use Authorization (EUA) is a regulatory mechanism that allows the use of unapproved medical products or unapproved uses of approved products during a declared public health emergency.

Exclusivity rights: refer to regulatory protections granted by a drug regulatory authority that restrict the approval of competing generic, hybrid, or biosimilar applications for a defined period, regardless of patent status.

Generic Medicinal Product: is a medicinal product that contains the same active substance(s) as a Reference Medicinal Product (RMP), in the same strength, pharmaceutical form, and route of administration, and is intended to be used at the same dosage regimen for the same indications.

Good Manufacturing Practice (GMP): A system of quality assurance that ensures medicinal products are consistently produced and controlled according to quality standards appropriate for their intended use, as required by the marketing authorization and relevant regulatory guidelines. GMP compliance is mandatory for all manufacturers of medicinal products and is verified through regular inspections by competent authorities.

Gulf Health Council (GHC): The Gulf Health Council (GHC) is a specialized health organization established under the umbrella of the Gulf Cooperation Council (GCC). It operates as a regional regulatory and coordination body for health-related initiatives among member states, which include Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman.

Innovative Drug Product (Innovator): is a medicinal product that contains a new active substance (new chemical entity or new biological entity) not previously authorized in any form

within the country, and for which the applicant has generated original data demonstrating quality, safety, and efficacy. It may also refer to a product that introduces a novel mechanism of action, new therapeutic indication, new route of administration, or distinct formulation with clinically meaningful improvement over existing therapies.

Manufacturer: The manufacturer is responsible for all operations involved in the manufacture, quality control, batch release, storage, and distribution of medicinal products.

Marketing Authorization Holder (MAH): A legal entity that holds the marketing authorization for a medicinal product, granting it the right to place the product on the market and assume full responsibility for its quality, safety, and efficacy throughout its lifecycle.

Ministry of Health (MOH) – Kuwait: The Ministry of Health is the central governmental authority responsible for regulating, planning, and overseeing healthcare services in the State of Kuwait.

Patent: is a legal right granted by a national or regional patent authority that gives the patent holder the exclusive right to prevent others from making, using, selling, or importing an invention—such as a new chemical entity, formulation, or manufacturing process—for a limited period, typically 20 years from the filing date. Patent protection is granted independently of marketing authorization and must be enforced through national intellectual property systems.

Qualified Person (QP): A QP or responsible person is a pharmacist responsible for certifying that each batch of medicinal product has been manufactured, tested, and released in compliance with the marketing authorization, EU Good Manufacturing Practice (GMP), and applicable regulatory requirements before it is placed on the market or imported.

Quality by Design (QbD): QbD is an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology

Reference Medicinal Product (RMP) - RMP is a medicinal product that has been granted marketing authorization in Kuwait, or in a country with a stringent regulatory authority, based on a complete dossier, including comprehensive quality, non-clinical, and clinical data as

required under standard registration pathways. The RMP serves as the scientific and regulatory comparator for the evaluation of: Generic products, to establish bioequivalence; Hybrid products, to support abridged applications with additional data; and Biosimilar products, to demonstrate bio similarity through a stepwise comparability exercise.

Stringent Regulatory Authority (SRA): SRAs include USFDA, EMA, Health Canada, MHRA, PMDA, Swiss medic, TGA and other regulatory authorities that are recognized by the World Health Organization (WHO) as operating at Maturity Level 4 or is a WHO listed Authority (WLA). These authorities typically demonstrate advanced regulatory capacity and are often involved in mutual recognition agreements.

Introduction

This guidance document outlines the requirements for the preparation and submission of pharmaceutical registration dossiers in electronic Common Technical Document (eCTD) or CTD format to Kuwait's Drug Regulatory Authority (Medicine and Medical Products Registration and Regulatory Administration), Pharmaceutical and Herbal Medicines Registration and Control Administration. It is based on the harmonized structure established by the International Council for Harmonization (ICH) M4 (M4Q, M4S,& M4E) and incorporates regional specifications aligned with regulatory standards set by the Gulf Health Council (GHC), as well as reference authorities such as the European Medicines Agency (EMA), US Food and Drug Administration (FDA), and others. The purpose of this guideline is to ensure completeness, consistency, and regulatory compliance in dossier content, thereby facilitating efficient review and decision-making for marketing authorization applications.

Scope

The document applies to all human medicinal products subject to registration in Kuwait, including chemical, biological, and advanced therapy products to be submitted to Medicine and Medical Products Registration and Regulatory Administration.

Types of products under the scope of this document

Chemically Synthesised Drugs

1. **New Drug Entities**

Pharmaceutical products containing new active substances of defined chemical composition, synthesized through conventional chemical processes. These include innovative drugs (new drug entities) or a drug that is the first to be introduced to Kuwait markets.

2. **Generic drugs**

Medicinal products that contain the same qualitative and quantitative composition in active substances and the same pharmaceutical form as a reference medicinal product, and whose bioequivalence with the reference product has been demonstrated through appropriate bioequivalence studies and marketed after the expiry of patent or other exclusivity rights.

Biological Products

Medicinal products that contain one or more active substances produced from or extracted from a biological source, and for which a combination of physicochemical and biological testing, together with process controls, is necessary for characterization and determination of quality.

1. **Vaccines**

Medicinal products containing antigens derived from biological sources—such as inactivated or attenuated pathogens, recombinant proteins, toxoids, or conjugates—administered to induce active immunity against specific infectious diseases.

2. **Monoclonal antibodies**

Immunoglobulins with defined specificity produced from a single clone of B lymphocytes or recombinant expression systems, often with immune effector functions (e.g., ADCC, CDC). Used therapeutically or diagnostically, their specificity and effector activity are critical quality attributes.

3. **Recombinant proteins**

Proteins engineered using recombinant DNA technology in living cells (e.g., bacterial, yeast, mammalian) that require characterization of structure, post-translational modifications, and biological activity to confirm identity and function.

4. **Blood and plasma-derived products**

Therapeutic substances derived from human or animal blood or plasma, such as clotting factors, immunoglobulins, and albumin, which undergo rigorous pathogen safety processing and quality testing.

5. **Biosimilars**

Biological medicinal products that are highly similar in terms of quality characteristics, biological activity, safety, and efficacy to an already authorised reference biological product, based on comprehensive comparability testing and marketed after the expiry of the patent or other exclusivity rights.

6. **Biopharmaceuticals**

Medicinal products whose active substances are proteins or peptides engineered using recombinant DNA techniques in living cells (e.g., bacterial, yeast, or mammalian systems). These products require thorough physicochemical, post-translational, and biological characterization to ensure identity, purity, potency, and consistency.

Hormonal Products

Pharmaceutical products containing natural or synthetic hormones that mimic or regulate endogenous endocrine functions. These products may be of biological origin (e.g., recombinant human insulin) or synthetically derived analogues and are used across various therapeutic areas including replacement therapy, contraception, and management of hormonal disorders.

1. **Peptide and Protein Hormones**

    - Includes recombinant or biosynthetic versions of:
        1. Insulin and insulin analogues
        2. Growth hormone (somatropin)
        3. Thyroid hormones (levothyroxine and liothyronine)

These are often classified as biopharmaceuticals and must comply with ICH Q6B and WHO guidelines for biological therapeutic proteins.

2. **Steroid Hormones**

Includes synthetic and semi-synthetic derivatives of:

- Estrogens, progestogens, and androgens used in:
    1. Hormonal contraceptives (oral, injectable, implants, etc.)
    2. Hormone Replacement Therapy (HRT) (e.g., menopause, hypogonadism)
    3. Glucocorticoids and mineralocorticoids used for anti-inflammatory and metabolic purposes

These are often chemically synthesized and regulated under small molecule guidelines (ICH Q6A), but their dosage form, systemic effects, and long-term use require careful evaluation of efficacy, safety, and risk–benefit balance. Hormonal contraceptives and HRT are evaluated for endocrine activity, carcinogenicity, and reproductive toxicity under ICH M3 and S5 guidelines.

Advanced Therapy Medicinal Products (ATMPs)

Advanced Therapy Medicinal Products are a class of complex biological medicinal products that are based on genes, cells, or engineered tissues, intended to repair, regenerate, or replace human cells or tissues, or to treat or cure disease at the molecular level. They include gene therapy products, somatic cell therapy products, and tissue-engineered products.

1. **Somatic cell therapy products**

Contain cells or tissues that have been substantially manipulated or are not intended for the same essential function in the recipient. Used to treat, prevent, or diagnose disease through biological activity.
Examples: Allogeneic T-cell therapies, chondrocyte implantation for cartilage repair.

2. **Tissue-engineered products**

Contain engineered cells or tissues that may be combined with scaffolds or matrices to repair, regenerate, or replace human tissue.
Examples: Cultured epithelial autografts, bioengineered skin, cartilage, or bone substitutes.

3. **Gene therapy products**

Contain or consist of recombinant nucleic acids used to regulate, repair, replace, or introduce genetic sequences for therapeutic purposes. These products can involve viral or non-viral vectors and may target somatic or germline cells (germline therapies are not authorized in most jurisdictions).
Examples: AAV-based therapies for genetic diseases, CAR-T therapies (which also fall under cell therapies).

Combination Products

Combination products are therapeutic or diagnostic products that combine a drug (or biological product) with a medical device, where the constituents are either physically or chemically integrated or are packaged together and intended for combined use to achieve a specific therapeutic effect. The components may have independent regulatory classifications, but their integration requires a unified regulatory assessment to ensure safety, efficacy, and quality.

- Prefilled Syringes and Auto-injectors - The drug is filled into a syringe or auto-injection device to enable sterile administration.
- Metered-Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs) - Deliver a fixed dose of drug via an integrated inhalation device.
- Transdermal Patches with Active Pharmaceutical Ingredients (APIs) - Integrate drug and delivery mechanism into one patch for controlled absorption.

Vitamins and Minerals (When Intended for Therapeutic Use)

These are pharmaceutical preparations containing one or more vitamins or mineral substances administered in doses that exceed accepted limits set out in the Health Product departement of Medicine and Medical Products Registration and Regulatory Administration, intended for treatment or prevention of clinically diagnosed deficiencies, or as adjuncts in the treatment of specific disease conditions.

Such products are distinct from food supplements or health products and are regulated as medicinal products under the same quality, safety, and efficacy standards as other pharmaceuticals. Dosage, indication, and pharmacological action determine their classification.

Radiopharmaceuticals

Radiopharmaceuticals are medicinal products containing radionuclides (radioactive isotopes) used in diagnostic imaging, therapy, or theranostics. Their regulation encompasses radioactive safety, pharmaceutical quality, and clinical utility, and they are subject to specific GMP, labeling, and handling requirements.

1. **Diagnostic Radiopharmaceuticals**
   Used to visualize, characterize, or measure physiological functions in vivo via imaging techniques like PET or SPECT.
   Example: Technetium-99m compounds, fluorodeoxyglucose (FDG).
2. **Therapeutic Radiopharmaceuticals**
   Deliver targeted radiation to specific tissues or tumors for therapeutic effect.
   Example: Iodine-131 for hyperthyroidism or thyroid cancer, Lutetium-177 for neuroendocrine tumors.
3. **Theranostic Radiopharmaceuticals**
   Combine diagnostic and therapeutic capabilities in one agent or paired agents to enable personalized treatment.
   Example: Ga-68/177Lu DOTATATE pairing for neuroendocrine tumors.

Review Types

Medicine and Medical Products Registration and Regulatory Administration accepts several types of submissions, as outlined in the Regulatory Framework. The following submission types are typically applicable:

Standard Pathway

The standard submission pathway involves a comprehensive evaluation of the product based on a complete Common Technical Document (CTD/eCTD). This route requires a full scientific assessment by the authority.

Fast Track Pathway

The fast track review process aims to expedite the registration of innovative drug products, to ensure fast and timely access to patients with minimal delays. Request for fast track along with supportive documents must be submitted by the authorised represenative on behalf of the marketing authorization holder.

This review pathway may follow a simplified pathway for pharmaceutical products that are approved by a Stringent Regulatory Authority (SRA).

Priority Pathway

A priority review may be granted for requests submitted by Central Medical Store (CMS) for drugs intended for the treatment of serious or life-threatening conditions, or those that address unmet medical needs and without any available registered alternative.

Document submission requirements:

1. A formal request must be submitted by CMS.
2. Certificate of a Pharmaceutical Product (CPP) from Health Authority in Country of origin.
3. Letter of appointment from the Marketing Authorization Holder stating the authorised represenatative in Kuwait.
4. A valid Manufacturing License (ML), Good Manufacturing Practice (GMP) certificate, and Site Master File (SMF) must be submitted (in case the site is not registered).
5. Certificate of Analysis (COA) of the finished product.
6. Finished product specification with method of analysis.
7. Confirmation of the active substance manufacturer, along with a valid Good ManufacturingPractice (GMP) certificate for the respective site.
8. Outer pack, label & Patient Information Leaflet (PIL).

9. Long term stability data conducted in accordance with ICH guidelines for Kuwait's climatic zone (Zone IV).
10. Accelerated stability studies, conducted for 6 months in accordance with ICH guidelines.
11. Confirmation regarding primary packaging material, pack size, shelflife and storage condition intended for Kuwait market.
12. Clinical & non-clinical studies for innovator products.
13. Bioequivalence studies for generic products (If applicable), Comparative quality , non clinical and clinical studies for biosimilars.
14. Confirmation regarding the Marketing Authorization Holder (MAH), manufacturer, primary& secondary packager and batch releaser for Kuwait market.
15. Commitment letter to complete all the CTD/eCTD file registration requirements within one year.

Expedited Pathway

This expedited review process is designed to accelerate the evaluation of drugs intended for the treatment of serious or life-threatening conditions, or those that address unmet medical needs where no alternative is currently available in Kuwait market.

Locally based MAH or manufacturers may also utilize this pathway to contribute to the development of the national pharmaceutical sector. This expedited designation does not compromise the scientific standards or the level of evidence required for product approval.

Biosimilars Pathway

This review pathway is intended for biosimilar products that demonstrate high comparability to a reference (originator) biological product that is already approved by a recognized SRA. The goal is to provide a streamlined evaluation process for biosimilars that meet established international standards. The biosimilar must have obtained approval from a recognized SRA or GHC

Emergency Use Pathway

The Emergency Use Review is a regulatory pathway designed to rapidly evaluate and authorize the use of medical products during a declared public health emergency (i.e., pandemic, outbreak, bioterrorism event). It allows the temporary use of such products when no adequate, approved, and available alternatives exist. To qualify for the Emergency Use pathway, the product must have obtained prior approval from a recognized SRA.

Rolling Pathway

A rolling review is a regulatory pathway that allows for the submission and evaluation of data in stages (as they become available) instead of waiting for a complete data package at once. This process speeds up the assessment timeline, especially useful in emergencies or for high-priority medicines. The product must be justified as eligible for rolling review based on its designation as a breakthrough therapy or equivalent accelerated development status.

GHC Approved Drug Pathway

This pathway is designated for pharmaceutical products that have already received approval from the Gulf Health Council (GHC) under the centralized registration procedure. It aims to streamline national registration by leveraging the scientific assessment and approval conducted at the GCC level, while ensuring full compliance with local regulatory requirements.

Types of Approvals

Standard Approval

Standard registration is the primary regulatory pathway for placing a pharmaceutical product on the local market. It applies to products with a complete data package that demonstrates their quality, safety, and efficacy. Registration must be submitted by a Authorised representative (Local Agent or scientific office or their local affiliates) acting on behalf of the MAH.

Conditional Approval

Conditional approval is a regulatory mechanism that allows for the early market authorization of promising pharmaceutical products intended to address serious or life-threatening conditions, where comprehensive clinical data are not yet complete (early-phase efficacy data Phase II trials), but there is sufficient evidence to suggest a positive benefit-risk balance.

Approval is granted under the condition that the applicant will complete ongoing or post-authorization studies to confirm the product's efficacy and safety.

Emergency Use Authorization (EUA)

EUA is a regulatory mechanism that allows the temporary approval of pharmaceutical products, including vaccines or treatments, during a declared public health emergency. The EUA pathway enables early access to products that may prevent or treat serious or life-threatening conditions when no adequate, approved alternatives are available, based on preliminary evidence supporting their safety and potential benefit.

Overview of CTD/eCTD Submission Structure

Introduction to the CTD Format

Typically, an eCTD/CTD application will cover all dosage forms and strengths of a product. Applicants should carefully consider what an eCTD application should cover before submitting the first sequence, as the choice could have implications for the workload for the entire lifespan of the product.

Table 1: Overview of CTD modules (full outline of modules available in appendices)

CTD Modules:	**Description**
Module 1:	Regional Administrative Information; This module includes the regional required information specific to Kuwait Pharmaceutical &Herbal Medicines Registration And Control Administration, such as administrative information and certificates.
Module 2:	Common Technical Document Summaries; Must reflect the information provided in modules 3, 4 and 5.
Module 3:	Quality
Module 4:	Non-Clinical Study Reports
Module 5:	Clinical Study Reports

Electronic Format and Technical Specifications (eCTD v3.2.2 and v4.0)

- Refer to the eCTD submission guideline

Lifecycle Management and Submission

- Refer to the eCTD submission guideline

General Requirements for Submissions

Submission Types and Pathways

The requirements may vary depending on the product type. For New Drug Entities, Biologicals and Biosimilars all eCTD Modules are mandatory, while in case of generic products certain modules or sections of the eCTD may not be applicable; however, these sections must be clearly marked as “Not Applicable” and should not to be deleted (refer to eCTD submission guidance)

In specific cases, a customized set of registration requirements may apply. These will be determined by Medicine and Medical Products Registration and Regulatory Administration and communicated to authorised representatives via official memos.

For technology transferred products, documents such as product development report, master formula record, comparative dissolution, when applicable, needed stability, BE if needed, quality assurance documents, technology transfer plan, protocol and quality agreement/contract detailing role of each party must be submitted.

Responsibilities of MAH and Authorised Representative

In accordance with Pharmacy Law in the State of Kuwait, a pharmaceutical product can only be introduced to the local market if it has been officially registered with the Pharmaceutical and Herbal Medicines Registration and Control Administration, Kuwait’s Drug Regulatory Authority (Medicine and Medical Products Registration and Regulatory Administration).

MAHs must be represented by a local pharmaceutical company, referred to as the Authorised Reprasentative (Local Agent or scientific office or their local approved affiliates.)

Authorised representative is responsible for submitting the necessary documents, as specified in this ministerial decree to complete the registration process for the pharmaceutical product and its MAH and manufacturing site/s.

All Documents submitted for the registration of pharmaceutical product must comply with eCTD structure. Applicants are not permitted to alter the content of the eCTD as outlined in this ministerial decree.

Authorized Representative Registration

If the authorised representative is a new local pharmaceutical company, the following must be submitted:

1. Valid license issued by the Ministry of Commerce in which the company activity includes the sale of medicines.
2. Valid agency license issued by Drug Inspection Administration.
3. Valid store license issued by Drug Inspection Administration.
4. Copy of authorized signatories from public authority of manpower.
5. Copy of authorized personal legalized from Kuwait chamber of commerce
6. Any other documents set by the administration in accordance with other MD’s or memos issued.

Marketing Authorization Holder (MAH) Registration:

1. A legalized letter of appointment from the MAH, confirming that the local agent or scientific office or their local approved affiliates is the authorized representative in the State of Kuwait.
2. A legalized Manufacturing License for each manufacturing site, issued by Health Authority in the country of origin.
3. A legalized “Good Manufacturing Practice” (GMP) certificate issued by the Health Authority in country of origin.
4. Site master file or company profile should include comprehensive details covering the following aspects:
    I. General information and history of the company.
    II. Capital investment and annual turnover for the past three years.
    III. Layout and diagrams of manufacturing facilities.
    IV. Quality control unit and quality management.
    V. Personnel details including number of employees per department their qualification & Qualified person (QP) details.
    VI. Information on premises and equipment, including manufacturing sites owned by the company, production lines, and machinery.
    VII. List of products manufactured and countries to which they are exported.
    VIII. Records of distribution issues, complaints, product defects and recalls from any global regulatory authority.
    IX. Details of any contract manufacturing arrangements.
    X. Pharmacovigilance Master File.
    XI. Recognized international regulatory approvals such as USFDA, EMA, MHRA, GHC. (If applicable)

Manufacturing site registration

Application for manufacturing sites will be assessed and upon completion of the requirements, a Registration Certificate will be issued valid for 5 years. Medicine and Medical Products Registration and Regulatory Administration may request a GMP inspection visit for any manufacturing site to be registered following a risk based approach.

Local Pharmaceutical Manufacturers

For Locally manufactured pharmaceutical products or when the marketing authorization holder is a local pharmaceutical company, Medicine and Medical Products Registration and Regulatory Administration is the competent authority to issue CPP, Manufacturing License, Good Manufacturing Practice (GMP) certificate and any other certificate related to pharmaceutical product registration.

Document Legalization and Certification

Legalization of Certificates issued by Health Authorities such as the CPP, GMP Certificate, Manufacturing License, and any other certificates issued by the Health Authority in the country of origin must be Original, legalized by the Embassy or Consulate of the State of Kuwait in the country of origin.

In cases where this is not possible, legalization may be done by an authorized GCC Embassy or Consulate in the country of origin.

Other Official Documents such as the Letter of Appointment, Pricing Certificate, and similar administrative documents must be legalized by the Embassy or Consulate of the State of Kuwait in the country of origin (or an authorized GCC Embassy/Consulate if not available), and The Chamber of Commerce in the country of origin.

Electronic Certificates and Verification

Valid Electronic certifictaes are acceptable provided that an approved verification tool is available for the authentication and verification of the electroic certificates.

For Electronic certificates legalisation is not required.

Eletronic legalization is acceptable provide that an approved verification tool is available for the authenticity of legalisation.

eCTD certificate submission

Applicants are required to include scanned copies of all valid, legally authenticated documents within their respective sections of the eCTD submission to facilitate regulatory assessment. The Regulatory Authority reserves the right to request submission of the original hard copies of these documents at any stage of the review process, should further verification be deemed necessary.

Notwithstanding the above, legalization shall not be required for specific documents—namely the Good Manufacturing Practice (GMP) certificate, Manufacturing License (ML), and Certificate of Pharmaceutical Product (CPP)—provided that these documents are issued by a recognized authority and are subject to electronic verification through officially accessible platforms. In such cases, the applicant must ensure that verifiable links or access credentials are provided as part of the submission.

Throughout this document legalisation and validity of the listed documents outlined here must be adhered as specified.

Detailed Requirements of the eCTD submission

Module 1: Regional Administrative Information

1.0 Cover Letter

A template of the cover letter with the required basic information is provided in the appendices.

1.1 Comprehensive Table of Contents

Central navigation index for Modules 1–5. Ensure any Kuwait-specific national appendices (e.g., legalized documents or Arabic translations) are indexed here.

1.2 Application Form

Application form will be filled out through the portal to generate an electronic application form, accurate information is required as this information will be reflected in the approval certificate.

1.3 Product Information

This section contains the Summary of Product Characteristics (SPC), Labeling, Patient Information Leaflet (PIL) in Arabic and/or English, Artwork and the Samples (if applicable). Product information should be supplied as PDF files within the eCTD.

1.3.1 Summary of Product Characteristics (SPC)

The SPC must 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.

SPC must be submitted as per the GCC Guidance for Presenting the SPC, PIL and Labeling Information.

1.3.2 Labelling

The labeling content must be in compliance with the SPC and must be submitted as per the GCC Guidance for Presenting the SPC, PIL and Labeling Information.

1.3.3 Patient Information Leaflet (Arabic/English)

The PIL content must be in compliance with the SPC. PIL must be submitted as per the GCC Guidance for presenting the SPC, PIL and Labeling Information.

1.3.4 Artwork and 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 one or more mock-ups of the outer packaging and of the immediate packaging of the product. Artworks must be submitted as per the GCC Guidance for Presenting the SPC, PIL and Labeling Information.

1.3.5 Samples

Medicine and Medical Products Registration and Regulatory Administration reserves the right to request whenever needed sample/s for review or to perform complete analysis. The submitted samples must represent the final finished product to be marketed in Kuwait.

1.4 Information on Experts (CV, independence, critical review)

1.4.1 Quality

1.4.2 Non-Clinical

1.4.3 Clinical

This section provides a formal declaration from the qualified experts responsible for the scientific content submitted in Modules 3 (Quality), 4 (Nonclinical), and 5 (Clinical). It is a regulatory requirement intended to demonstrate that appropriately credentialed professionals have reviewed and endorsed the information presented in the dossier. Each expert must prepare and sign a Declaration of the Expert**,** confirming that the respective module (Quality, Nonclinical, or Clinical) is an accurate and comprehensive representation of the data. These declarations should also state that the expert has prepared or reviewed the module in accordance with applicable regulatory guidelines, including ICH and other SRA standards, and that the data are truthful, complete, and scientifically justified.

In addition to the signed declarations, the curriculum vitae (CV) of each expert must be submitted. The CV should clearly outline the expert's academic background, professional experience, relevant publications, regulatory experience, and areas of expertise. The objective is to provide evidence of the expert's qualifications and competence to evaluate the information within their domain.

1.5 Environmental Risk Assessment (GMO and Non-GMO)

This section should contain a summary statement regarding the Environmental Risk Assessment (ERA) status of the medicinal product, including confirmation of whether an ERA has been conducted or a justification for its exemption. The need for an ERA is determined based on the product type, usage pattern, and potential environmental exposure. In general, an ERA is mandatory for products containing new active substances, products expected to be widely distributed, or those with novel indications or formulations. Products falling under generic, well-established use, or hospital-onlycategories may be exempt, provided a scientifically justified waiver is included.

1.5.1 Non-Genetically Modified Organism (Non-GMO)

For non-GMO products, a standard ERA (or waiver with justification) is generally sufficient. The applicant should also indicate whether any raw materials, cell lines, or excipients used in the product are derived from GMOs, even if the final product does not contain genetically modified sequences. This transparency allows the regulatory authority to evaluate any residual environmental or biosafety concerns.

1.5.2 Genetically Modified Organism (GMO)

Where applicable, the applicant must clearly state whether the product contains or is derived from genetically modified organisms (GMOs). Products that are classified as GMOs, such as certain advanced therapy medicinal products (ATMPs), gene therapies, or live recombinant vaccines, require a comprehensive GMO Environmental Risk Assessment.

1.6 Pharmacovigilance System and Risk Management Plan

1.6.1 Pharmacovigilance System

This section provides essential administrative details regarding the applicant's pharmacovigilance system. It must include the name and contact details of the Qualified Person for Pharmacovigilance (QPPV) responsible for the product within the region, along with the location of the Pharmacovigilance System Master File (PSMF). A summary of the pharmacovigilance system should be submitted, confirming that it meets the requirements of Good Pharmacovigilance Practices (GVP).

1.6.2 Risk Management Plan

Where applicable, a Risk Management Plan (RMP) should also be included or cross-referenced to Module 2.4 or 2.7.4. The RMP 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. A detailed description of the risk management system which the applicant will introduce must be provided, where appropriate.

1.7 Certificates and Official Documents

1.7.1 GMP Certificate

A valid Good Manufacturing Practice (GMP) certificate must be provided for each manufacturing site involved in the production, packaging, testing, or batch release of the medicinal product.

To be accepted for regulatory review in Kuwait, the GMP certificate must be legalized by the Embassy of the State of Kuwait in the issuing country or authenticated through another officially recognized legalization process. The legalized certificate should be current (not older than 3 years unless otherwise justified) and must clearly indicate the approved activities, dosage forms, and site address.

In cases where an official GMP certificate is not issued such as with the U.S. FDA, & Canada, confirmation of GMP compliance from the authority's official database is acceptable, provided the site is clearly listed and identifiable as GMP-compliant.

1.7.2 Certificate of Pharmaceutical Product (CPP)

A valid original Certificate of Pharmaceutical Product (CPP) must be submitted to demonstrate that the product is authorized and marketed in the country of origin. The CPP should be issued in accordance with the format recommended by the World Health Organization (WHO Certification Scheme) and must include key product information such as the product name, dosage form, strength, registration status, composition and manufacturing site(s) details. To be accepted for use in Kuwait, the CPP must be issued by the national competent authority of the exporting country and must be legalized by the Embassy of the State of Kuwait or through another officially recognized authentication process. The CPP must be current or as per the validity mentioned in the CPP.

If the product is not marketed in the country of origin, clear justification is required along with list of countries where the product is registerd and marketed which is

subject to review and approval by Medicine and Medical Products Registration and Regulatory Administration.

1.7.3 Certificate of analysis – Drug Substance/Finished Product

Certificates of Analysis (CoAs) must be provided for more than one batch of the drug substance. These CoAs must be issued by the drug substance manufacturer and, the finished product manufacturer. Each CoA should include results for all specified tests in accordance with the proposed specifications outlined in Module 3.2.S.4.1

The CoAs must be signed by an authorized quality control representative, clearly indicate the batch number and date of analysis, and be representative of commercial-scale production.

Certificates of Analysis must also be submitted for more than one batch of the finished pharmaceutical product. These CoAs must be issued by the finished product manufacturer and should demonstrate compliance with the release specifications detailed in Module 3.2.P.5.1. Each certificate must include results for key quality attributes. The CoAs must be signed by the responsible quality control personnel, stating the batch numbers, API supplier and manufacturing site.

1.7.4 Certificate of analysis – Excipients

Certificates of Analysis (CoAs) for all **excipients** used in the formulation should be submitted to support the quality evaluation of the finished product. These CoAs must be issued by the **excipient manufacturer** and by the **finished product manufacturer** upon receipt and testing of incoming materials. It is recommended that **CoAs must be in** compliance with the proposed specifications outlined in Module 3.2.P.4.1. Each certificate should include test results for relevant parameters. All CoAs must be signed by an authorized quality control representative and include the batch number, date of testing, and reference to the analytical methods used. For excipients of human or animal origin, additional safety and compliance documentation may be required.

1.7.5 Alcohol-free declaration

This section must include a formal declaration letter on the company's official letterhead confirming that the medicinal product is free from alcohol (ethanol). The declaration should be signed and dated by an authorized representative of the applicant or manufacturer. If the product contains alcohol, a clear justification must be provided, along with the exact concentration and purpose of its inclusion. The justification must comply with the Guidelines for Importing and Handling Ethyl Alcohol Containing products/substances, and must align with the requirements outlined in the relevant Ministerial Decree issued by the Ministry of Health. Supporting documents such as product composition, formulation rationale, and applicable certificates may be requested to substantiate the justification.

1.7.6 Pork-free declaration

This section must include a formal declaration letter on the company's official letterhead confirming that the medicinal product is free from any materials of pork or porcine origin. The declaration must be signed and dated by an authorized representative of the applicant or manufacturer. In the event that the product contains any materials derived from pork or porcine sources, a clear justification must be provided, including the specific component used, its function in the formulation, and whether any alternatives were considered and state or extent of denaturation or hydrolysis of the pork content. The justification should be scientifically supported and must comply with the applicable ethical, religious, and regulatory considerations in the State of Kuwait.

1.7.7. Certificate of suitability (CEP) for Transmissible Spongiform Encephalopathies (TSE)

This section must contain a Certificate of Suitability for TSE.

The CEP must be issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) and should cover all materials of human or animal origin used in the manufacture of the active substance, excipients, or finished product. In cases where a CEP is not available, the applicant must submit a comprehensive TSE risk assessment, regardless of the country of origin. This assessment must detail the source species, tissue origin, country of origin, age of the animals, and processing methods including inactivation/removal steps validated for TSE risk mitigation. The justification must align with the principles outlined by the WHO Guidelines on Tissue Infectivity Distribution and the ICH Q5A, Q5D) regarding biological safety of materials of animal origin.

1.7.8 The diluents and coloring agents in the product formula

This section must include a declaration letter on the company's official letterhead, signed by an authorized representative, clearly listing all diluents and coloring agents used in the finished product formulation. The declaration should specify the name, function, and concentration of each excipient classified as a diluent or coloring agent, including synthetic dyes, natural colorants, or pigments.

The selection and use of these substances must comply with internationally recognized safety and quality standards, taking into account relevant guidelines issued by the ICH Q3A, Q3B, and Q3C on impurities and excipients, the EMA including its Reflection Paper on the Use of Colouring Agents in Medicinal Products (EMA/CHMP/SWP/617239/2013), and applicable regulations by the U.S. FDA under 21 CFR Part 73 and 74, which specify color additives approved for use in pharmaceuticals.

Any coloring agent used must be permitted for pharmaceutical use in the country of origin and must not exceed the limits established by applicable pharmacopeial or regulatory standards. If the product is intended for oral or pediatric use, special consideration must be given to the potential for hypersensitivity, allergic reactions, or toxicity associated with specific dyes or diluents. Where applicable, justification should be provided for the use of agents that are subject to regulatory concern or restricted use in certain populations (e.g., tartrazine, sunset yellow, or benzyl alcohol).

Additionally, excipients of recognised SRA raised precautions must be provided for example Glycerin, Propylene Glycol, Manitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol.

All information submitted in this section must align with the formulation data presented in Module 3.2.P.1 and 3.2.P.4, and must be consistent across all modules and labeling. The declaration may be subject to review in accordance with Kuwait Ministry of Health policies, including restrictions on certain coloring agents for ethical, safety, or religious considerations.

1.7.9 Patent Information

This section must include a declaration letter on the company's official letterhead, signed and dated by an authorized representative, clearly stating the patent status of the drug substance (active ingredient) in the State of Kuwait and/or the Gulf Cooperation Council (GCC) Patent Office. The declaration must confirm whether the active pharmaceutical ingredient (API) is currently under patent protection or if no relevant patent exists. Patent information is only applicable to the drug molecule (i.e., the active substance) and indication/s does not extend to excipients, manufacturing processes, formulations, packaging, unless specifically required under local legislation.

The declaration must be accompanied by an official letter from the Kuwait Patent Office or the GCC Patent Office, confirming the registration or non-registration status

of the patent rights .If the product is still under patent, documentation should identify the patent number**,** expiry date**,** patent holder, and territorial coverage. Any claim of waiver, license, or authorization to market a patented product must be supported with legal documentation.

1.7.10 Letter of access or acknowledgment to DMF

This section must include a formal Letter of Access or Acknowledgment issued by the Drug Master File (DMF) owner or their authorized agent, granting the Kuwait Ministry of Health permission to refer to and review the confidential information contained in the DMF. The letter must be issued on the DMF holder's official letterhead, clearly identify the product and applicant, and authorize the Ministry to access specific parts of the DMF in support of the current application.

The DMF owner must also specify which of the following three options has been chosen to present the drug substance information:

- A valid Certificate of Suitability (CEP) issued by the EDQM,
- A Drug Master File (DMF) submitted directly to the Kuwait Ministry of Health or through the applicant, or
- A complete set of information provided in Module 3.2.S of the Common Technical Document (CTD).

The letter should include the DMF number, version and revision date, and the scope of information being referenced (e.g., manufacturing process, specifications, stability data). It must also include the contact details of the DMF holder for verification or further correspondence.

1.8 Pricing

1.8.1 Pricing

This section must include a valid and updated price certificate for the product, submitted by the authorised representitve in accordance with the relevant Ministerial Decree regulating drug pricing in the State of Kuwait.

1.8.2 Price List

The local repeesntative must submit a completed International Price List in the form stated in the Ministerial decree regulating pricing of medicinal products in Kuwait,

1.8.3 Registration Status

This section must include a list of all countries where the product is currently registered, along with valid copies of the official registration certificates issued by the respective national regulatory authorities.

1.9 Responses to questions

This section must include a clearly structured response document addressing all questions or deficiencies raised by the Medicine and Medical Products Registration and Regulatory Administration during the evaluation of the application. The format of the response document must follow the same structure and presentation style as the original dossier, ensuring consistency and traceability.

The document must list each question verbatim, followed by the applicant's corresponding response. For each response, the applicant must identify the relevant CTD module, section title, page number, and provide a hyperlink or electronic reference that directs the reviewer to the exact location of the updated or supporting content within the resubmitted dossier.

This section is intended solely for the narrative responses to regulatory questions. Any revised or supporting technical documentation (e.g., updated SmPC, stability data, or analytical reports) must be submitted in the appropriate CTD Modules (e.g., Modules 2–5), not within Module 1.9. Medicine and Medical Products Registration and Regulatory Administration reserves the right to reject responses that lack clarity, traceability, or adequate referencing.

Module 2: Common Technical Document Summaries

Module 2 of the Common Technical Document (CTD) serves as a bridge between the detailed data presented in Modules 3 (Quality), 4 (Nonclinical), and 5 (Clinical) and the overall evaluation required by regulatory authorities. It contains structured summaries and expert overviews that present the scientific data in a concise, integrated format to facilitate regulatory review.

2.1 Table of Contents for Modules 2-5

This section includes the comprehensive table of contents for Modules 2 through 5, structured according to the Common Technical Document format. The table of contents must provide a clear and organized index of all sections and subsections, including headings, document titles, and file paths, as applicable.

2.2 Introduction

This section provides a brief but informative introduction to the application, giving regulators an immediate understanding of the product's nature and regulatory context. The applicant must clearly state the proprietary name, non-proprietary (INN or USAN) name, dosage form, strength(s), route(s) of administration, and indications for which marketing authorization is sought. The introduction should also identify the type of application being submitted (e.g., full dossier, generic, hybrid, biosimilar, fixed-dose combination etc.).

2.3 Quality Overall Summary

The Quality Overall Summary (QOS) provides a structured, high-level synopsis of the quality (CMC) information submitted in Module 3 for both the drug substance (active ingredient) and drug product (finished product). It is a critical component of the CTD that facilitates the regulatory review by summarizing key data, justifications, and critical quality attributes (CQAs). The QOS must be prepared in accordance with ICH M4Q guidance and must reflect the same numbering and structure as Module 3. It should be written in clear, concise language and must not merely repeat the full data but highlight and interpret critical points such as control strategies, specifications, manufacturing processes, stability, and risk-based justifications.

The summary is divided into two main sections:

2.3.S – Drug Substance: Includes general information (nomenclature, structure), manufacturer(s), description of the manufacturing process and process controls, control of materials, specifications, analytical methods and validations, reference standards, container closure systems, and stability data.

2.3.P – Drug Product: Covers product composition, pharmaceutical development, manufacturing process and validation, control of critical steps and intermediates, specifications, analytical procedures and validation, packaging, and product stability.

Applicants must ensure consistency between this summary and the full data provided in Module 3, and any critical issues such as atypical impurities, novel excipients, or complex formulations must be adequately addressed. The QOS should also highlight any comparability, bridging data, or regulatory justifications (e.g., shelf-life extrapolation, real-time stability commitments) relevant to the product's approval.

2.4 Non-Clinical Overview

The Nonclinical Overview is a critical, expert-authored summary of the pharmacological, pharmacokinetic, and toxicological data presented in Module 4,

prepared in accordance with ICH M4S(R2). It provides an integrated and interpretive assessment of the nonclinical studies conducted to evaluate the safety of the drug substance and drug product. The overview should address all key areas, including primary and secondary pharmacodynamics, safety pharmacology, absorption, distribution, metabolism, and excretion (ADME), as well as single-dose and repeated-dose toxicity, genotoxicity, carcinogenicity (if required), reproductive and developmental toxicity, local tolerance, and any other relevant toxicological studies.

The overview must provide a scientific justification for the overall nonclinical strategy, identifying no-observed-adverse-effect levels (NOAELs), relevant safety margins, and the translational relevance of animal data to humans. Particular attention must be paid to commenting on the GLP (Good Laboratory Practice) compliance status of each study. Studies supporting safety evaluation must clearly indicate whether they were conducted in compliance with GLP standards, and if not, a justification for their acceptability must be provided.

The overview should also identify and explain any omitted studies, with justification based on relevant ICH guidelines. A discussion of the species selection, dosing regimens, and toxicokinetic support should be included, along with any residual safety concerns or proposed risk mitigation strategies. The summary must be authored and signed by a qualified expert in nonclinical safety, with the expert's declaration and CV submitted in Module 1.4. The narrative should conclude with an integrated assessment of how the nonclinical data support the proposed clinical use, dosage, route of administration, and duration of treatment.

2.5 Clinical Overview

The Clinical Overview is a critical, expert-authored document intended to provide a succinct interpretation and evaluation of all clinical data presented in Module 5. Unlike the Clinical Summary (Module 2.7), which offers a factual and comprehensive tabulation of study data, the Clinical Overview must present the conclusions,

implications, and clinical relevance of that data. It should highlight key findings, strengths and limitations of the clinical program, unresolved issues, and how the overall evidence supports the proposed indication and prescribing information.

The Clinical Overview must:

- Present the strengths and limitations of the clinical development program and study results;
- Analyze the benefits and risks of the medicinal product in its intended use;
- Describe how study results support critical elements of the prescribing information.

The document must be concise (typically no more than 30 pages, unless complexity warrants more), clearly written, and well-structured. The use of tables, graphs, and cross-references is strongly encouraged to enhance clarity and avoid redundancy. Material already fully presented in the Clinical Summary or Module 5 should not be repeated.

2.5.1 Product Development Rationale

This section should describe the overall approach to clinical development, including the regulatory, scientific, and clinical rationale for the choice of indication, patient population, dosage form, dosing regimen, and route of administration. It must explain any critical study design decisions, including deviations from standard approaches (e.g., bridging studies, extrapolation strategies, or reliance on foreign data). If the application is based on literature, a hybrid or generic basis, or a biosimilar route, this must be clearly stated and justified.

2.5.2 Overview of Biopharmaceutics

This section should summarize and interpret the biopharmaceutic studies, such as in vivo bioavailability/bioequivalence studies and in vitro dissolution testing. Applicants should describe the impact of formulation, food, and administration route on drug

absorption and justify any biowaivers in accordance with ICH M9 and regional (EMA/FDA) guidance. Cross-references to detailed data in Module 2.7.1 and Module 5 should be provided. Key findings should be evaluated in terms of their relevance to the clinical efficacy and safety profile.

2.5.3 Overview of Clinical Pharmacology

This section must provide an analytical summary of the product's pharmacokinetics (PK) and pharmacodynamics (PD)in humans. The applicant should assess the reliability of the study designs, and summarize ADME properties, dose linearity, PK/PD relationships, and results in special populations (e.g., renal/hepatic impairment, pediatric, elderly). Any drug–drug interaction potential, genetic polymorphism, or ethnic sensitivity should be evaluated. Applicants must confirm GCP compliance of the clinical pharmacology studies and reference specific Module 5 reports and Module 2.7.2.

2.5.4 Overview of Efficacy

This section must present an evaluative summary of the efficacy data, based on pivotal and supportive clinical studies. The focus should be on how the clinical trial design, patient populations, endpoints, statistical analyses, and results support the proposed indication(s). Limitations must be acknowledged, such as lack of head-to-head data with relevant innovator, absence of key subgroups, or limited endpoint coverage. The use of graphs and summary tables is encouraged. Where appropriate, efficacy in special populations, subgroup analyses, or use in combination therapy should be critically discussed. Cross-reference must be made to Module 2.7.3 and individual study reports in Module 5.

2.5.5 Overview of Safety

This section must interpret the safety profile of the product as observed across the clinical program. It should summarize and critically discuss adverse events (AEs), serious adverse events (SAEs), deaths, laboratory abnormalities, and

any clinically significant safety findings. The analysis should highlight data from different populations (e.g., by age, sex, comorbidities) and exposure durations, and evaluate identified and potential risks, including emerging signals. If any risk minimization strategies are proposed (e.g., RMP or labeling restrictions), they should be discussed here. All conclusions should be based on data in Module 2.7.4 and Module 5, with appropriate referencing.

2.5.6 Benefits and Risks Conclusions

This section provides an integrated benefit–risk assessment based on the clinical evidence. The applicant should justify how the efficacy outweighs any potential risks for the intended patient population and indication. The narrative must demonstrate how study findings support the proposed prescribing information, including dosing, precautions, and contraindications. Any unresolved safety concerns should be addressed, with plans for post-approval monitoring or risk mitigation outlined. Applicants should also justify any unusual claims or deviations from established standards in the label.

2.5.7 Literature References

This section must list all scientific publications and guidelines cited throughout the Clinical Overview. References should be relevant, peer-reviewed, and formatted consistently (e.g., Vancouver style). Inclusion of regulatory guidelines, expert consensus statements, and authoritative reviews is encouraged, especially where used to support development decisions or justify omissions.

2.6 Non-Clinical Written and Tabulated Summaries

This section provides structured, detailed summaries of all nonclinical pharmacology, pharmacokinetics, and toxicology studies submitted in **Module 4**, following the format and expectations of **ICH M4S(R2)**. The objective is to present data in a **clear, logical,**

and consistent manner to facilitate regulatory review, with narrative summaries supported by tabulated data where appropriate.

The nonclinical summaries are divided into three main components:

2.6.1 Pharmacology (primary, secondary, safety pharmacology)

2.6.2 Pharmacokinetics (ADME, in vitro/in vivo metabolism, drug interaction potential)

2.6.3 Toxicology (single and repeated dose, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, etc.)

In vitro studies must be presented before in vivo studies, and findings must be summarized in a consistent sequence: first by species, then by route of administration, and finally by duration (from shortest to longest). The following species ordering must be followed: mouse, rat, hamster, other rodent, rabbit, dog, non-human primate, other non-rodent mammal, and non-mammals. Routes of administration must be presented in the following order: the intended route for human use, followed by oral, intravenous, intramuscular, intraperitoneal, subcutaneous, inhalation, topical, and other routes.

Whenever applicable, the summaries must include discussion of age- and gender-related effects, as well as findings related to stereoisomers, metabolites, or degradation products if these are clinically relevant. The consistent use of SI units throughout the summaries is required. Differences in pharmacological or toxicological response between animal species should be analyzed and, where necessary, linked to clinical relevance.

Each subsection must be clearly organized and traceable to the original study reports in Module 4. Tabulated summaries should be used to present key data (e.g., NOAELs, exposure margins, clinical observations) and must align with the narrative interpretation. The level of detail included should be sufficient to support regulatory decision-making without repeating the full study data.

2.7 Clinical Summary

The Clinical Summary is intended to provide a comprehensive, factual, and structured presentation of all clinical data submitted in support of the application. It complements but does not replace the Clinical Overview (Module 2.5). While the Clinical Overview provides expert interpretation and benefit–risk evaluation, the Clinical Summary must focus solely on objective and detailed summarization of clinical study results and supporting data.

The Clinical Summary must include detailed summaries of:

- Individual ICH E3 clinical study reports;
- Integrated summaries of efficacy and safety across studies;
- Biopharmaceutic data, including bioavailability and bioequivalence;
- Clinical pharmacology data, including PK/PD, dose-response, and metabolism studies;

Any available meta-analyses, pooled data analyses, or post-marketing experience (if applicable), provided the full reports are included in Module 5.

This section should present data in a structured and logical sequence, using consistent terminology and units. Tables, graphs, and statistical summaries are encouraged to enhance clarity and facilitate comparison across studies. The emphasis must remain on factual reporting, with minimal interpretation or subjective discussion. When applicable, post-marketing experience from other regions may be included to support long-term safety, special population exposure, or real-world effectiveness.

The structure of Module 2.7 includes the following subsections:

2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods

2.7.2 Summary of Clinical Pharmacology Studies

2.7.3 Summary of Clinical Efficacy

2.7.4 Summary of Clinical Safety

2.7.5 Synopses of Individual Clinical Study Reports

Each subsection should align closely with the format and content of the underlying study reports provided in Module 5. Any cross-study comparisons must focus on factual observations (e.g., response rates, adverse event incidence) and avoid interpretive commentary, which belongs in the Clinical Overview.

The Clinical Summary must be prepared with the level of detail necessary for regulatory reviewers to understand the totality of the clinical evidence. Cross-referencing to Module 5 is essential to ensure traceability and transparency. Data inconsistencies, missing data, or protocol deviations should be clearly presented but not interpreted.

Module 3: Quality (Drug Substance and Drug Product)

This section provides a brief overview of the quality documentation for both the drug substance and drug product included in the application. It should summarize the type of product (e.g., small molecule, biologic, sterile, modified-release), the dosage form, and route of administration, and highlight any notable features or complexities in the manufacturing or formulation process. If applicable, the introduction should identify whether the product is a generic, biosimilar, fixed-dose combination, or a new drug entity .It should also mention whether a Drug Master File (DMF), Certificate of Suitability (CEP), or any regional documentation is referenced in the dossier.

The introduction must clearly state if any novel excipients, complex delivery systems, site transfers, or atypical manufacturing processes are included, and should flag any bridging data, comparability studies, or post-approval changes proposed for evaluation. This section does not replace the detailed data in subsequent sections, but serves as a brief orientation for the assessor.

3.1 Table of Contents

For drug products containing multiple active substances, a separate and complete Section 3.2.S must be submitted for each drug substance. These should be arranged consecutively, with one 3.2.S section per substance. Likewise, if a single drug substance is sourced from multiple manufacturers, a full Section 3.2.S must be provided for each manufacturer. Each version must contain manufacturer-specific information and controls. The Table of Contents must reflect this structure clearly to facilitate navigation and review.

In electronic submissions, the Table of Contents is typically system-generated within the eCTD framework. However, the applicant is responsible for ensuring accuracy, completeness, and alignment with the content actually submitted. All headings and document titles must be correctly labeled and cross-referenced throughout the dossier to support efficient review and compliance with ICH M4Q formatting expectations.

3.2 Body of data

3.2.S Drug Substance

3.2.S.1 General Information

This section must include a clear and complete description of the drug substance (active pharmaceutical ingredient – API), including its identity, nomenclature, structural features, and key physicochemical characteristics. The API must be described in a manner that enables full traceability throughout the manufacturing and quality sections of the dossier.

Each API may be sourced from no more than two manufacturers, unless otherwise scientifically and regulatorily justified. A separate Section 3.2.S must be submitted for each API source. Additionally, information on the drug substance may be submitted using one of the following three options:

1) A valid Certificate of Suitability (CEP) issued by EDQM;
2) A Drug Master File (DMF) submitted to the Kuwait Ministry of Health with an accompanying Letter of Access;
3) A complete dossier using Sections 3.2.S.1 through 3.2.S.7 as per ICH M4Q(R1).

For chemically synthesized APIs, the following information must be provided:

- Nonproprietary name(s) (e.g., INN, USAN), chemical name(s), synonyms, CAS number, and internal code (if applicable).
- Molecular formula, molecular weight, and structural formula, including stereochemistry, salt or solvate form, and polymorphic form, where relevant.
- Physicochemical properties such as:
    - Appearance
    - Solubility (including aqueous solubility across pH values and in organic solvents)
    - Partition coefficient (log P or log D)
    - pKa
    - Melting point or range
    - Optical rotation (if applicable)

If the drug substance is a chiral compound or exists in multiple forms (e.g., salts, polymorphs), the specific form used in the product must be stated and justified.

For biologic or biotechnologically derived APIs, the general information must additionally include:

- Source of the biological material, including cell line, host organism, tissue, or plasma.
- Description of the expression system and vector used (if recombinant).
- Structural and molecular characterization, including:
    - Amino acid sequence
    - Molecular weight or size heterogeneity
    - Glycosylation profile and post-translational modifications
- Description of isoforms, variants, and degradation products (if relevant).
- Overview of biological activity, binding properties, or mechanism of action.
- Summary of structural characterization techniques used (e.g., SDS-PAGE, HPLC, mass spectrometry, western blot, peptide mapping).

Additional data may be required depending on the nature and complexity of the substance. Applicants should refer to the relevant ICH guidelines specific to the product type.

3.2.S.2 Manufacture

This section must provide detailed information on the manufacturing process and control of the drug substance. The objective is to demonstrate that the active substance is consistently produced and controlled to meet quality standards suitable for its intended use.

3.2.S.2.1 Manufacturer(s)

Include the name, address, and responsibility of each manufacturer involved in the production, testing, or packaging of the drug substance. This includes:

- Manufacturing site(s) where synthesis or fermentation takes place
- Intermediate or final purification facilities
- Contract testing laboratories (if applicable)
- Packaging and labeling sites

All listed manufacturers must operate in accordance with Good Manufacturing Practice (GMP). Valid GMP certificates or evidence of GMP compliance may be requested by the regulatory authority and should be available upon request or included in Module 1.13.

3.2.S.2.2 Description of Process and Process Controls

This section must include a detailed narrative description and a flow diagram of the drug substance manufacturing process. The information provided must demonstrate that the process is appropriately designed, controlled, and reproducible to consistently yield an active substance that meets quality and purity standards.

The manufacturing process description must:

- Clearly outline all reaction steps, purification, crystallization, filtration, drying, and milling stages (as applicable).
- Identify and describe the use of all starting materials, reagents, solvents, catalysts, and processing aids.
- Include key operational parameters, such as temperature, pH, pressure, duration, and mixing speeds, where these impact product quality.
- Indicate expected yields at each stage (expressed as ranges) and describe reprocessing steps, if any, with justification.
- Identify critical process steps and clearly specify the associated in-process controls (IPCs) and their acceptance criteria.

The flow diagram should provide a visual summary of the synthesis, showing:

- All major manufacturing steps, including intermediate isolations and purifications
- The flow of materials and solvents
- Points of IPCs and sample collection
- Process steps carried out at different manufacturing sites, where applicable

For multistep synthesis, include intermediate structures, identify the designated starting material, and justify its selection per ICH Q11.

For biological products (e.g., monoclonal antibodies, recombinant proteins, vaccines), additional and specific requirements apply due to the complexity and variability of the production system. The process must be described in two main stages: upstream processing and downstream processing**.**

1. **Upstream Processing:**

   ⇒ Description of the cell culture or fermentation process, including the cell line or microbial strain used.

   ⇒ Source, history, and characterization of the Master Cell Bank (MCB) and Working Cell Bank (WCB).

   ⇒ Culture conditions, including media composition (with animal- or human-derived components clearly identified), feeding strategy, bioreactor parameters, and harvest process.

2. **Downstream Processing:**

   ⇒ Full description of purification steps**,** including filtration, centrifugation, chromatography (e.g., Protein A, ion exchange), and viral inactivation/removal steps.

   ⇒ Details of buffers used in each step, concentration/diafiltration processes, and bulk formulation steps.

   ⇒ Demonstration of robustness and clearance capacity for process-related impurities (e.g., host cell proteins, DNA, leachables, endotoxins).

In-process controls (IPCs) for biological APIs must be clearly defined at each stage, particularly for:

- Cell growth, viability, and productivity
- Harvest and purification yields
- Viral clearance parameters (referencing ICH Q5A and relevant EMA viral safety guidance)
- Final bulk identity, purity, and potency testing

If any reprocessing or rework steps are included in the process, they must be clearly described, scientifically justified, and supported by process validation data.

Additional Considerations:

- For continuous manufacturing processes, provide sufficient detail to demonstrate process control strategy and batch definition.
- For sterile APIs, describe sterilization steps (e.g., filtration, aseptic handling, terminal sterilization) and link to 3.2.S.2.5 for validation.
- For synthetic peptides, oligonucleotides, or highly potent APIs, describe any handling controls, containment strategies, or equipment cleaning procedures used to mitigate cross-contamination.

All manufacturing information must be consistent with the data presented in Module 2.3 (QOS), batch records, and validation reports.

3.2.S.2.3 Control of Materials

This section must provide detailed information on the quality and suitability of all materials used in the manufacture of the drug substance. This includes starting materials, reagents, solvents, catalysts, processing aids, and any other raw materials used in the synthesis, fermentation, or purification process.

Starting Materials (for chemically synthesized APIs)

- The identity and specifications of each starting material must be clearly provided, along with the name and address of its supplier(s).
- Justification for the selection of the starting material must be included in accordance with the principles outlined in ICH Q11.
- For each starting material, the applicant must provide:
  - Certificate of analysis (CoA)
  - Acceptance criteria and test methods
  - Summary of impurity profile, including carryover and fate through synthesis

- Where multiple suppliers are used, comparability and control strategies should be addressed.

Reagents, Solvents, Catalysts, and Other Process Materials

- These materials must be listed along with the specifications used to control their quality.
- The potential impact of impurities from these materials on the final drug substance should be assessed.
- Residual levels of **class 1, 2, or 3 solvents** should comply with **ICH Q3C**.
- Recycled solvents and recovered materials must be controlled to ensure no impact on product quality.

Materials of Animal or Human Origin

- Any material derived from animal or human sources must be fully characterized, and its TSE risk must be assessed.
- Documentation such as a Certificate of Suitability for TSE risk (Ph. Eur.) or equivalent must be provided or referenced (linked to Module 3.2.A.2).
- Materials used in early synthesis steps should still be assessed for residual risk if they are not removed entirely in downstream processing.

For biological APIs, the following specific material controls apply:

- Detailed characterization of cell banks (Master and Working Cell Bank) must be included in Section 3.2.S.2.1 but referenced here as part of raw material control.
- Culture media components, growth factors, and serum (if used) must be fully specified and controlled.
- The source, quality, and testing of any animal- or human-derived material used in the culture media (e.g., serum albumin, trypsin) must be clearly documented.

- A risk assessment of adventitious agents and viral safety control strategies must be included (cross-referenced with Section 3.2.A.2 and applicable to ICH Q5A and Q5D).

All specifications must be appropriately justified and should demonstrate control over the quality and consistency of input materials used in the manufacture of the drug substance. Where necessary, additional documentation such as vendor qualification procedures, material change control, and material testing frequency may be requested by the authority.

3.2.S.2.4 Controls of Critical Steps and Intermediates

This section must describe the control strategy applied to critical manufacturing steps and any isolated intermediatesused in the drug substance manufacturing process. The goal is to demonstrate that the manufacturing process is controlled in a manner that ensures the drug substance consistently meets its intended quality profile.

Critical Steps

Identify and describe all critical manufacturing steps—defined as those that directly impact the quality, safety, or efficacy of the final API.
For each critical step, provide:

- The in-process control (IPC) tests performed
- The acceptance criteria
- The scientific rationale for their selection and limits
- The sampling points, frequency, and test methods

Examples of critical steps may include: Reaction endpoints, Purification steps (e.g., crystallization, extraction), Solvent removal, Drying parameters, pH or temperature adjustments

The applicant should justify how IPCs contribute to controlling critical quality attributes (CQAs) and minimizing the risk of batch failure or product variability.

Intermediates

Where intermediates are isolated and stored, their specifications and storage conditions must be provided.

- ⇒ Justify the control strategy used to ensure that these intermediates do not introduce impurities or variability into the final API.
- ⇒ If an intermediate is carried over across multiple steps, its control should be shown to prevent accumulation of degradants or by-products.

Additional Considerations for Biological and Biotechnological Substances

For biologically derived APIs, in-process controls are typically more extensive due to the inherent variability of living systems. Applicants must include:

- IPCs for cell growth, viability, metabolite levels, product titre, and contamination checks (e.g., mycoplasma, bioburden).
- Real-time monitoring or batch data for culture duration, bioreactor conditions (temperature, pH, dissolved oxygen), and harvest criteria.
- Controls for downstream purification steps (e.g., column integrity, breakthrough limits, pool purity).
- Description and justification of viral inactivation or removal steps, and the corresponding IPCs to verify effectiveness (as outlined in ICH Q5A(R1)).
- Acceptance criteria for critical intermediates, such as partially purified bulk material, should include identity, purity, and bioburden (where applicable).

All IPCs and intermediate controls must be clearly traceable to the overall control strategy described in the Quality Overall Summary (Module 2.3) and consistent with the validated manufacturing process.

3.2.S.2.5 Process Validation and/or Evaluation

This section must provide a summary of the process validation or evaluation studies performed to demonstrate that the drug substance manufacturing process is capable of consistently delivering material that meets predefined quality attributes.

Applicants should include:

- A summary of process validation or process verification activities for at least three consecutive commercial-scale batches, or alternatively pilot-scale batches if justified (e.g., for early-phase submissions).
- The scale of manufacture, location, batch size, and equipment used should be specified and aligned with the proposed commercial process.
- Results should confirm that critical process parameters (CPPs) remain within controlled limits and produce drug substance that meets all critical quality attributes (CQAs).
- Validation of reprocessing or rework procedures, if part of the approved process, must also be summarized with supporting rationale and batch data.

If a full process validation package is not yet complete (e.g., for conditional or rolling submissions), a process validation protocol and commitment to submit data post-approval must be included.

For APIs Produced Using Continuous Manufacturing

- Provide a description of the continuous process control strategy, including batch definition and real-time release testing (if applicable).
- Describe how process monitoring, PAT tools, and data analysis are used to ensure control over CPPs and CQAs.

For Biotechnological/Biological APIs

For biological substances, process validation is a critical requirement and must follow the expectations outlined in ICH Q5C and Q5A (for viral safety).

Applicants must include:

- A detailed summary of process validation studies performed on full-scale batches using the proposed commercial cell line, media, and equipment.
- Validation of both upstream (e.g., cell culture, fermentation) and downstream (e.g., purification, concentration, filtration) processes, including batch consistency and impurity clearance (e.g., host cell proteins, DNA).
- For viral inactivation and removal steps, include data demonstrating robustness, effectiveness, and safety margins, referencing guidelines in ICH Q5A(R1) and relevant EMA viral safety guidance.
- Where applicable, validation of media fills, cleaning validation, and environmental monitoring procedures must be referenced or summarized, especially for sterile APIs.

If process changes occurred during development (e.g., scale-up or site transfer), include a comparability assessment(referencing ICH Q5E) to demonstrate product consistency across process versions.

All validation data should support the conclusion that the process is reliable, reproducible, and under control, and that it produces material meeting the specifications outlined in Section 3.2.S.4.

3.2.S.2.6 Manufacturing Process Development

This section should provide a summary of the developmental history and rationale for the current manufacturing process of the drug substance. It should explain how the process was designed and optimized to ensure that the final API consistently meets predefined quality attributes, in accordance with the principles of Quality by Design (QbD) where applicable.

General Requirements (All APIs)

- ⇒ Describe the **evolution of the manufacturing process**, from laboratory scale through pilot and commercial scale.
- ⇒ Identify key decisions made during development, such as:
- ⇒ Selection of **starting materials**
- ⇒ Optimization of **reaction conditions**
- ⇒ Development of **purification strategies**
- ⇒ Control of **critical process parameters (CPPs)**
- ⇒ Justify how the current process ensures robust control over **critical quality attributes (CQAs)**.
- ⇒ Discuss the **linkage between process parameters and product quality**, referencing data from experimental work, development batches, or process characterization studies.
- ⇒ Highlight changes made during development and provide a brief **comparability assessment**, if applicable, especially in the context of scale-up, site transfer, or equipment change.

This section does not require full validation data (covered in 3.2.S.2.5), but it should show that process development was scientifically driven and adequately supports the final manufacturing strategy.

Additional Requirements for Biological and Biotechnological APIs

This section must include a more detailed narrative of the scientific rationale behind cell line selection, process design, and scale-up strategies.

Applicants should:

- Describe how the cell line or production organism was selected, including host/vector design and selection criteria.
- Summarize studies conducted to:
- Optimize culture conditions (media composition, feeding strategy, bioreactor parameters)
- Develop robust purification steps that ensure high yield and purity
- Define in-process controls critical to product quality
- Discuss strategies to control process-related impurities, including host cell proteins, DNA, and endotoxins.
- Reference data from early-stage lots, engineering runs, and consistency batches used to support process knowledge and refinement.
- If significant changes occurred during development (e.g., scale change, raw material source change, cell bank revision), provide a comparability justification, referring to ICH Q5E.

For complex or novel biological platforms (e.g., mRNA, gene therapy, or cell-based products), this section should briefly outline development considerations relevant to platform-specific challenges (e.g., LNP encapsulation, transduction efficiency, vector purity).

This section should demonstrate that the current process is based on sound scientific understanding and that development studies have informed the control strategy to ensure batch-to-batch consistency.

3.2.S.3 Characterization

This section must provide comprehensive data confirming the structure, physicochemical properties, and impurity profile of the drug substance.

The aim is to demonstrate that the identity and purity of the API have been thoroughly established using appropriate analytical techniques.

3.2.S.3.1 Elucidation of Structure and Other Characteristics

For all APIs (small molecule and biological):

- A full elucidation of the drug substance structure must be provided, supported by data from **appropriate spectroscopic and/or physicochemical methods**, such as:
    - Nuclear Magnetic Resonance (NMR)
    - Infrared Spectroscopy (IR)
    - Ultraviolet/Visible Spectroscopy (UV/Vis)
    - Mass Spectrometry (MS)
    - Elemental Analysis
    - **X-ray Diffraction** (if applicable, especially for polymorphic forms)
- Discuss the **physicochemical characteristics** of the substance, including:
    - Solubility
    - Polymorphism
    - Hygroscopicity
    - Optical rotation (if applicable)
    - Particle size (for low-solubility APIs)
- For **chirality**, provide data confirming stereochemical configuration and enantiomeric purity, along with the method of control.

Additional Requirements for Biological/ Biotechnological APIs:

For biological APIs, structure elucidation must be supported by a **panel of analytical techniques** suited to the complexity of the molecule. These should include:

- Amino acid composition and sequencing
- Peptide mapping
- Disulfide bond analysis
- Glycosylation profiling and site analysis

- Isoform pattern (e.g., charge variants)
- **Higher-order structure** (e.g., circular dichroism, FTIR, DSC)
- For monoclonal antibodies: heavy and light chain analysis, antigen binding assays

The **biological activity** of the API must be demonstrated through a **valid bioassay**, unless otherwise justified. The method must be adequately described and validated (see also Section 3.2.S.4.3).

The combination of methods must be sufficient to fully confirm the primary, secondary, and (as relevant) tertiary/quaternary structure of the API and its post-translational modifications.

3.2.S.3.2 Impurities

This section must include a thorough discussion of all known and potential **process- and product-related impurities**, including:

- Organic impurities (e.g., by-products, degradants)
- Inorganic impurities (e.g., reagents, catalysts, elemental impurities)
- Residual solvents (with classification per **ICH Q3C**)
- Genotoxic impurities (if applicable, in line with **ICH M7**)

For each impurity:

- State the origin and rationale for presence
- Provide structural identification (where known)
- Specify **qualifying limits** based on **ICH Q3A/Q3B** thresholds
- Include **analytical method(s)** used for detection and quantification
- Provide **impurity profile** from multiple batches and trend data (if available)

For biological APIs, also include:

- Process-related impurities, such as:
    - Host cell proteins (HCP)
    - Host cell DNA

    - Residual protein A (or other chromatography ligands)
    - Media components or additives
- Product-related impurities, such as:
    - Aggregates
    - Truncated or misfolded forms
    - Deamidated or oxidized variants
- The **control strategy** for detecting and limiting these impurities should be described and supported by **process validation or clearance data** (linked to 3.2.S.2.5 and 3.2.S.4).

All impurity assessments must align with the **drug substance specification (3.2.S.4.1)** and reflect both process capability and safety thresholds.

3.2.S.4 Control of Drug Substance

This section must describe the **specification** for the drug substance and the associated **analytical methods**, **validation**, **batch data**, and **justification of specifications**. The specification must ensure that the drug substance consistently meets its intended quality standards for identity, purity, potency (if applicable), and other critical attributes.

3.2.S.4.1 Specification

⇒ Provide the **drug substance specification** in tabular format, clearly listing:
- Test parameters
- Acceptance criteria
- Reference to the analytical procedures used

⇒ Specifications must include tests for:
- Identity (e.g., IR, HPLC retention time, peptide mapping for biologics)
- Appearance
- Assay (content or potency)
- Impurities (organic, inorganic, residual solvents)

- Physicochemical properties (e.g., pH, water content, particle size, polymorphism)
- Microbial limits (as applicable)

For biological APIs:

The specification must also address:

⇒ Biological activity (potency assay)
⇒ Purity and heterogeneity (e.g., aggregate levels, isoforms)
⇒ Residual host cell proteins and DNA
⇒ Product-related and process-related impurities
⇒ Glycosylation profile (for glycoproteins)
⇒ Endotoxin (for parenterals)
⇒ Sterility or bioburden, where applicable

Specifications for biological products must be developed in line with ICH Q6B and reflect batch consistency, clinical experience, and manufacturing capability.

3.2.S.4.2 Analytical Procedures

This section must provide a detailed description of each analytical procedure used to test the drug substance against the specification outlined in Section 3.2.S.4.1. The information must be sufficient to allow replication of the test methods by a regulatory laboratory or third-party testing facility, and must reflect the validated procedures used during routine batch release and stability testing.

Each analytical procedure should include:

⇒ The test parameter (e.g., identity, assay, purity, water content)
⇒ A full description of the method (e.g., HPLC, GC, UV, FTIR, NMR, titration)
⇒ The method type (compendial or in-house)
⇒ A description of the sample preparation procedure
⇒ The instrumentation and operating conditions
    - Column type and dimensions

- Mobile phase composition and flow rate
- Detection wavelength or mode
- Injection volume

⇒ The system suitability criteria

⇒ The reference standard used (see also 3.2.S.5)

For compendial methods (e.g., Ph. Eur., USP), the monograph reference must be provided. Any modifications made to compendial methods (e.g., chromatographic conditions, detection wavelength) must be clearly described and scientifically justified.

Additional Requirements for Biotechnological/Biological APIs:

Due to the complexity of biological molecules, a multi-parameter control strategy is often needed. Analytical methods used must be capable of detecting structural and functional integrity, impurities, and variants.

Typical analytical techniques for biological API may include:

⇒ Peptide Mapping: LC-MS or HPLC to verify primary structure

⇒ Glycan Profiling: HILIC or LC-MS for glycosylation patterns

⇒ Charge Variants: Isoelectric focusing or ion-exchange chromatography

⇒ Aggregate Detection: SEC-HPLC, DLS (dynamic light scattering)

⇒ Biological Activity (Potency): ELISA, cell-based bioassays, receptor binding

⇒ Host Cell Protein/DNA: ELISA and qPCR

⇒ Endotoxin Testing: LAL assay

Each analytical method must be:

⇒ Fit-for-purpose

⇒ Selective and specific for the attribute measured

⇒ Sensitive enough to detect and quantify process- or product-related impurities

If orthogonal methods (e.g., two or more techniques measuring the same attribute differently) are used for key quality attributes, the rationale must be presented.

Cross-reference to method validation reports in 3.2.S.4.3 and reference standard information in 3.2.S.5 must be included. All procedures should be consistent with the methods applied in batch release testing and stability studies (linked to 3.2.S.7).

3.2.S.4.3 Validation of Analytical Procedures

This section must provide validation data and summaries for each analytical procedure listed in Section 3.2.S.4.2, except for compendial methods that are used without modification other than minor changes to an approved test procedure (e.g. a change in column length or temperature, but not a different type of column or method, within pharmacopoeial changes). The objective is to demonstrate that all test methods are suitable for their intended purpose, consistently generate accurate and reliable results, and are aligned with the quality specifications of the drug substance.

For non-compendial (in-house) methods, and compendial methods with modifications, the following ICH Q2(R1) validation parameters must be addressed, as appropriate for the method type:

- **Specificity**
- **Linearity**
- **Range**
- **Accuracy**
- **Precision** (repeatability and intermediate precision)
- **Limit of Detection (LOD)** and **Limit of Quantitation (LOQ)**
- **Robustness**
- **System suitability testing** (SST)

Each validation report must include:

⇒ A summary of the method principle and equipment used

⇒ Description of sample and standard preparation

⇒ Detailed tables and graphs presenting validation data

⇒ Acceptance criteria and conclusions

If method validation is performed across multiple laboratories (e.g., for technology transfer or regional testing), a summary of inter-laboratory validation or comparability results should be included.

For biological API, method validation must be adapted to account for complex molecular structures, heterogeneity, and biological variability. The following specific considerations apply:

- ⇒ Potency assays (e.g., cell-based assays, ELISA) must be validated for:
  - Accuracy relative to a reference standard
  - Reproducibility across operators and systems
  - Detection of active vs. inactive forms
  - Assay robustness and signal-to-noise range
- ⇒ Identity methods such as peptide mapping or mass spectrometry must demonstrate discrimination between variants and isoforms.
- ⇒ Glycan profiling, charge variant analysis, and aggregate detection methods should include validation of resolution, quantification limits, and method linearity across expected levels.
- ⇒ For host cell protein (HCP) and residual DNA assays, validation must include:
  - Spike recovery studies
  - Specificity against product matrix
  - Limits of quantification near regulatory thresholds

Where platform methods are used (i.e., validated across multiple products within a company), the method must be qualified for the specific product through a bridging study.

Compendial Methods

If a compendial method is used without modification, full validation is generally not required. However, the applicant must:

Confirm that the method is applicable to the specific product

- ⇒ Provide system suitability data
- ⇒ Justify the method's performance on the intended sample matrix

If any modification to a compendial method is made, the applicant must validate the method as an in-house method.

All validation data should confirm that each method can reliably support batch release, stability testing, and impurity control throughout the product's lifecycle.

3.2.S.4.4 Batch Analyses

This section must include detailed batch analysis data for the drug substance, confirming that the manufacturing process produces material that consistently meets the proposed specifications. The data submitted should provide evidence of process consistency, analytical method performance, and compliance with release criteria across multiple batches.

- ⇒ Submit complete Certificates of Analysis (CoAs) for at least two production-scale batches of the drug substance. If production-scale batches are not yet available (e.g., for early submissions), pilot-scale batch data may be accepted with appropriate justification.
- ⇒ For each batch, include:
  - Batch number
  - Batch size
  - Date of manufacture
  - Manufacturing site
  - Results for each test listed in the proposed specification (Section 3.2.S.4.1)
- ⇒ Batch results must be presented in tabular format, clearly showing:
  - Measured values
  - Acceptance criteria
  - Indication of whether results are within limits (e.g., "Pass/Fail")
- ⇒ If multiple manufacturing sites or API sources are proposed, data must be provided per site, and comparabilitymust be demonstrated between sources.

For biological API, batch analysis must cover:

- ⇒ Process validation/commercial batches, including consistency lots used in clinical trials or comparability studies
- ⇒ Summary of in-process data for critical stages (e.g., yield, purity at key steps)
- ⇒ Data for product- and process-related impurities, including:
  - Aggregates
  - Isoforms
  - Host cell proteins (HCP)
  - Residual DNA
  - Viral safety indicators (where applicable)
- ⇒ Potency/bioactivity assay results for each batch, expressed relative to the reference standard
- ⇒ Glycan profile, charge variants, or other structural characteristics, depending on product complexity

If comparability studies were performed following process changes (e.g., scale-up or site transfer), relevant pre- and post-change batch data must be provided to support product equivalence, consistent with ICH Q5E.

Presentation and Traceability

Data should be presented in a manner that allows easy traceability to the manufacturing process, analytical procedures, and validation data.

Batch analysis results must correlate with:

- ⇒ Analytical methods (3.2.S.4.2)
- ⇒ Method validation (3.2.S.4.3)
- ⇒ Specifications (3.2.S.4.1)

Any out-of-specification (OOS) or out-of-trend (OOT) results must be addressed with an investigation summary and impact assessment.

If multiple batches were tested across different time points or laboratories (e.g., regional testing), all variations should be clearly labeled and justified.

3.2.S.4.5 Justification of Specification

This section must provide a scientific and regulatory justification for each test included in the proposed drug substance specification, as detailed in Section 3.2.S.4.1. The justification must demonstrate that the selected tests, acceptance criteria, and frequency are appropriate to ensure the consistent quality, safety, and performance of the active substance throughout its shelf life.

For each parameter included in the specification, justify:

- ⇒ Why the test is necessary (e.g., critical quality attribute, safety concern, manufacturing consistency)
- ⇒ How the limits were established, referencing:
  - Data from batch analyses (3.2.S.4.4)
  - Results from stability studies (3.2.S.7)
  - Process capability data
  - Toxicological thresholds or qualification limits (e.g., per ICH Q3A/B or M7)
- ⇒ Method suitability, including reference to analytical procedures (3.2.S.4.2) and their validation (3.2.S.4.3)
- ⇒ Any regulatory or compendial basis for the acceptance criteria (e.g., USP/Ph. Eur. monograph, ICH limits)

If certain parameters are excluded (e.g., heavy metals, microbial limits), provide a clear rationale for their omission, supported by risk assessment or scientific evidence.

Where tighter internal limits are applied in GMP release testing compared to the registered specification, explain the purpose of the working range and confirm that the registered specification remains suitable for product control.

For biological substances, justification of specifications must reflect:

- ⇒ Product complexity and manufacturing variability
- ⇒ The criticality of each parameter for clinical performance, safety, or immunogenicity

- ⇒ Historical data from process development, clinical lots, and commercial batches
- ⇒ Acceptance criteria for:
  - Potency/bioactivity: Justified with reference to biological relevance and statistical consistency.
  - Product-related impurities: (e.g., aggregates, fragments, isoforms) set based on clinical experience, analytical capability, and comparability assessments.
  - Process-related impurities: (e.g., HCP, residual DNA, leachables) justified based on toxicological thresholds and validated clearance data.
  - Glycosylation pattern / charge variants: Limits should reflect clinical comparability and analytical detection limits.

The specification must also reflect any biosimilarity, comparability, or post-change equivalence studies where applicable.

All justification must support the conclusion that the proposed specification adequately controls all attributes critical to the identity, strength, purity, and quality of the drug substance, and that it ensures consistency across batches and throughout the product lifecycle.

3.2.S.5 Reference Standards or Materials

This section must describe the reference standards or materials used in the analytical procedures for testing the drug substance. The reference material must be appropriately characterized, qualified, and suitable for its intended use, whether for identity, assay, impurity quantification, or potency measurements.

For each reference standard used in routine testing:

- ⇒ Provide the name and source (e.g., in-house, compendial, WHO, EDQM, or certified external vendor).
- ⇒ State the **intended use** (e.g., for identity testing, assay, impurity analysis, or residual solvent quantification).
- ⇒ Describe the **lot number**, **purity**, and **qualification method**, including:

- NMR, HPLC, MS, elemental analysis, titration, or other characterization data
- Assigned potency or purity value (with units and calculation method)

⇒ Include a **Certificate of Analysis (CoA)** for each reference standard, or a summary of results if CoA is not appended in this section.

If an official compendial standard (e.g., USP, Ph. Eur.) is used without modification, state this explicitly and confirm its suitability for the method.

In-House Reference Standards

If a non-compendial (in-house) primary or secondary reference standard is used:

⇒ Provide a description of how the standard was established, including:
- Source of material
- Purification and processing steps
- Method of purity assignment

⇒ Outline the qualification strategy, including comparison with an official standard if available.

⇒ Describe storage conditions, retention period, and requalification frequency.

Biological reference materials are often more complex due to the nature of the molecule and the reliance on relative potency assays. For biological APIs:

⇒ The primary reference standard must be well-characterized and traceable to an international or regional standard (e.g., WHO international standard for biologics), if available.

⇒ Include details of:
- Source (e.g., in-house purified bulk, comparator product)
- Lot number and assigned potency (with units, e.g., IU/mg)
- Methods used for characterization (e.g., SDS-PAGE, SEC, bioassay)

⇒ Reference standards for bioassays (e.g., ELISA, cell-based assays) must be qualified for:
- Linearity

- Parallelism
- Relative response

⇒ For biosimilars, comparison with the reference biological product (RBP) must be described in Module 3.2.R and referenced here if the RBP is used as a system calibrator or assay comparator.

If secondary or working standards are used, describe the relationship to the primary standard, including bridging or qualification studies to ensure consistent performance in analytical assays.

All reference standards must be handled and maintained under appropriate storage and requalification programs, and documentation must be made available upon request. The suitability of each standard must be ensured throughout the product lifecycle.

3.2.S.6 Container/Closure Systems

This section must describe the container closure system (CCS) used for the storage and transportation of the drug substance. The information provided must demonstrate that the container system is appropriate, protective, and compatible with the API throughout its proposed shelf life.

For each drug substance packaging configuration:

⇒ Identify the container and closure materials, including:
- Immediate container (e.g., bottle, drum, bag)
- Closure (e.g., screw cap, stopper, seal)
- Liner or gasket (if used)

⇒ Specify:
- Material type (e.g., high-density polyethylene (HDPE), stainless steel, glass, fluoropolymer bags)
- Dimensions or volume (e.g., 5 L amber glass bottle)
- Manufacturer (if available)

⇒ Indicate whether the system is single-use, reusable, or multi-dose (for biologicals)

State whether the CCS is:

⇒ Non-sterile (typical for APIs)
⇒ Sterile (if the drug substance is sterile or for parenteral use)

Provide confirmation that the packaging:

⇒ minimizes contamination and degradation
⇒ Maintains integrity under storage conditions (temperature, humidity, light exposure)
⇒ Does not interact with or leach into the drug substance

Extractables and Leachables

For plastic or elastomeric container materials, especially for long-term storage, applicants should provide:

⇒ A statement of compliance with relevant pharmacopoeial standards (e.g., USP <661.1>, Ph. Eur. 3.2.2)
⇒ If applicable, results of extractables and/or leachables studies
⇒ A risk-based justification if no testing is performed, supported by prior use or literature data

Biological drug substances are often sensitive to temperature, moisture, light, and oxygen, and may require specialized storage. Therefore:

⇒ The container must be shown to preserve the physical and biological integrity of the API (e.g., prevent aggregation, oxidation, adsorption).
⇒ For APIs stored in cryogenic or frozen conditions, describe:
  - Packaging durability at low temperatures
  - Suitability for freeze–thaw cycles (if applicable)

⇒ For APIs in liquid form, container compatibility with proteinaceous materials should be evaluated to avoid binding or denaturation.

If the API is stored in **bags or vials**, provide:

⇒ Data on container closure integrity (CCI), especially for sterile or high-value APIs

⇒ Justification of container volume, headspace, and fill ratio

All container components must be:

⇒ Pharmacopoeial grade where applicable

⇒ Supported by stability data (see Section 3.2.S.7)

⇒ Properly labelled and handled under GMP conditions

Cross-reference to any vendor certification documents, technical specifications, or material data sheets can be included in Module 3.2.R if not submitted within this section.

3.2.S.7 Stability

This section must summarize the stability data supporting the proposed retest period and storage conditions of the drug substance, in line with ICH M4Q, ICH Q1, and the Kuwait Guidelines for Stability Testing.

3.2.S.7.1 Stability Summary and Conclusions

Include a summary of study duration, tested parameters (e.g., assay, degradation products, appearance, water content), and the storage container system. The proposed retest period and labelled storage precautions must be based on this data.

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

If full long-term data is unavailable at the time of submission, a post-approval commitment must be provided. It should include:

⇒ Ongoing testing of commercial-scale batches
⇒ Storage under Zone III conditions for up to the full proposed shelf life
⇒ Use of validated, stability-indicating methods
⇒ Testing frequency;
⇒ Description of the conditions of storage; and
⇒ Other applicable parameters specific to the drug substance.

3.2.S.7.3 Stability Data

Include tabulated results for at least three batches (preferably commercial or pilot scale), stored in the intended packaging**.** Parameters tested should include identity, assay, impurity profile, water content (if applicable), and appearance. Results must demonstrate compliance with specifications throughout the proposed shelf life.

Additional Requirements for Biotechnological/Biological APIs:

Due to their sensitivity, additional data is required:

⇒ Refrigerated or frozen storage conditions (e.g., 2–8 °C, –20 °C)
⇒ Freeze–thaw stability, in-use stability (when applicable), and excursion testing
⇒ Stability-indicating parameters: potency, aggregation, charge variants, PTMs
⇒ Compliance with ICH stability guidelines expectations

3.2.P Drug Product

This part of the dossier provides detailed information on the formulation, manufacturing, control, and stability of the finished pharmaceutical product (FPP). It must demonstrate that the product is consistently manufactured to meet quality, safety, and efficacy requirements, using an appropriate control strategy throughout the lifecycle.

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

This section must provide:

- ⇒ The dosage form (e.g., film-coated tablet, sterile injectable solution, lyophilized powder)
- ⇒ Strength(s) of the drug product
- ⇒ Route(s) of administration
- ⇒ Container closure system for the commercial product
- ⇒ Composition Table

Include a clear composition table listing:

- ⇒ All components of the finished product, including:
  - Active ingredient(s) (with amount per unit, including overages if used)
  - Excipients (quantitative amounts for all, including overages if used)
  - Processing aids (if retained in final product)
  - Coating materials or capsule shell contents (if applicable)
- ⇒ The function of each component (e.g., filler, binder, preservative, stabilizer)

Clearly distinguish between core formulation, coating, and solvent systems, if applicable.

Other Considerations

- ⇒ State the theoretical weight of each dosage unit.
- ⇒ If the product is a fixed-dose combination (FDC), show the quantitative composition per active.

For biological products:

- ⇒ Include the quantity per container in terms of total protein content or IU (international units), where applicable.
- ⇒ Describe the formulation buffer, including pH and excipient concentrations.
- ⇒ If overfill is used (e.g., to compensate for losses in delivery devices), state the rationale and volume clearly.
- ⇒ Include reference to container/closure integrity for parenteral dosage forms.

⇒ Any preservatives, adjuvants, or stabilizers must be listed with their function and justification.

3.2.P.2 Pharmaceutical Development

This section must describe the rationale and development history of the drug product, including formulation design, manufacturing process selection, container closure system, and any critical factors impacting product quality, safety, and efficacy. The development should follow a science- and risk-based approach, consistent with ICH Q8(R2) and principles of Quality by Design (QbD) where applied.

3.2.P.2.1 Components of the Drug Product

This section must describe the rationale for selecting all components used in the formulation, including the drug substance and excipients, based on physicochemical, biological, and functional considerations. The information provided should demonstrate that each component is suitable to ensure the safety, stability, performance, and manufacturabilityof the finished product.

3.2.P.2.1.1 Drug Substance

Provide a summary of the relevant physicochemical and biological properties of the drug substance that influenced formulation development, such as:

⇒ Solubility and pKa
⇒ Particle size and polymorphic form
⇒ Hygroscopicity and stability profile
⇒ pH sensitivity or thermal sensitivity

For biological drug substances, include:

⇒ Description of the molecule (e.g., monoclonal antibody, recombinant protein, vaccine antigen)
⇒ Known sensitivities (e.g., shear stress, aggregation, oxidation)

⇒ Stability characteristics under formulation conditions (e.g., pH, ionic strength, light exposure)

The form of the drug substance used in the product (e.g., salt, base, polymorph) must be justified based on bioavailability, stability, or manufacturability.

3.2.P.2.1.2 Excipients

List and justify the choice of each excipient used in the formulation. For each:

- State the name, function, and quantity used
- Indicate whether it complies with a pharmacopoeial monograph (e.g., USP, Ph. Eur.)
- Justify the selection based on:
    - Compatibility with the drug substance
    - Functionality in the dosage form (e.g., filler, binder, disintegrant, preservative, stabilizer)
    - Historical or regulatory precedence for use in similar formulations
    - Safety in the intended patient population (especially for pediatrics or parenteral routes)

For biological products, additional justification must be provided for:

- Buffers (e.g., phosphate, histidine)
- Stabilizers (e.g., sugars, polyols, amino acids)
- Surfactants (e.g., polysorbates) used to prevent aggregation
- Preservatives or antimicrobial agents (where applicable), including preservative efficacy data

If a novel excipient is used or a non-compendial excipient is included, supporting safety and quality data must be provided in Module 3.2.A.3.

3.2.P.2.2 Drug Product

This section must provide a detailed account of the formulation design and evolution of the drug product. It should demonstrate how the formulation was developed to achieve the intended quality, performance, and stability, and how it is suitable for the intended route of administration, patient population, and packaging system.

3.2.P.2.2.1 Formulation Development

Describe the scientific rationale and development strategy used to design the final formulation. This should include:

- ⇒ A summary of initial formulation trials and prototype batches
- ⇒ Evolution of the formulation from early-stage to commercial development
- ⇒ Bridging between clinical trial formulations and the final marketed product (if applicable)
- ⇒ Justification for the selection of the dosage form based on drug substance properties, patient use, and regulatory expectations

Key considerations should include:

- Dose uniformity
- Drug release or dissolution characteristics
- Palatability (for oral liquids)
- Leachables
- Reconstitution properties (for lyophilized or powder forms)
- pH, osmolality, and tonicity (for parenterals)

For **biological products**, formulation development should address:

- ⇒ Selection of excipients for protein stabilization
- ⇒ Control of physical degradation mechanisms (e.g., aggregation, adsorption)
- ⇒ Maintenance of biological activity and structural integrity
- ⇒ Avoidance of leachables or extractables from containers

If multiple strengths or dosage forms are proposed, justify proportionality or composition differences, and include performance comparison where needed or applicable (e.g., dissolution, reconstitution time, bioequivalence data).

3.2.P.2.2.2 Overages

If any component (typically the active ingredient or an excipient like preservative or antioxidant) is added in excess of the labelled amount to compensate for loss during manufacture or storage, provide:

- ⇒ A clear statement of the quantity and purpose of the overage
- ⇒ Scientific justification based on ,manufacturing variability, or handling losses
- ⇒ Assurance that the overage does not impact safety, efficacy, or product performance

For biological products, overages must be carefully controlled and justified due to the potential sensitivity of protein structures to formulation variability.

Regulatory agencies typically discourage overages unless unavoidable. Any overage must be justified based on data-driven need and not as a substitute for robust manufacturing control.

3.2.P.2.2.3 Physicochemical and Biological Properties

Summarize the critical physicochemical and (where relevant) biological properties of the final drug product that influenced and supported the formulation design.

For all products, include:

- Physical state (e.g., solid, solution, suspension, emulsion)
- Appearance and pH (where applicable)
- Osmolality or tonicity (for parenterals and ophthalmics)
- Viscosity (for injectable solutions or suspensions)
- Dissolution or disintegration behavior (for oral solids)
- Reconstitution time and behavior (for powders or lyophilized products)

For **biological products**, include discussion of:

- ⇒ Protein content and concentration range
- ⇒ Stability of the biological molecule under formulation and storage conditions
- ⇒ Key indicators of biological activity, such as potency assays or structural integrity markers
- ⇒ Degradation pathways, including aggregation, oxidation, and deamidation
- ⇒ Impact of excipients (e.g., surfactants, sugars, buffers) on maintaining conformation and activity

These properties must be consistent with the target product profile, clinical use, and storage conditions, and must be monitored through validated analytical procedures during stability and batch release.

3.2.P.2.3 Manufacturing Process Development

This section must describe the development and rationale of the manufacturing process for the finished product, including how the process was designed, scaled, and optimized to ensure consistent product quality, batch reproducibility, and compliance with critical quality attributes (CQAs).

Process Design and Optimization

- ⇒ Provide a summary of the **development strategy** from laboratory scale through pilot to commercial scale.
- ⇒ Identify **critical process parameters (CPPs)** and their relationship to **CQAs**.
- ⇒ Describe any **modifications** to the process over time, such as:
    - Equipment changes
    - Process condition optimizations (e.g., blending time, granulation parameters, lyophilization cycle)
    - Site transfer or scale-up

The rationale for the selected process should demonstrate:

- Process robustness and control strategy
- Suitability for routine manufacturing and in-process testing
- Justification for manufacturing steps such as granulation, compression, drying, or aseptic processing

For **immediate-release products**, key factors may include:

⇒ Blend uniformity
⇒ Flow properties
⇒ Content uniformity
⇒ Dissolution performance

For **modified-release products**, development should focus on:

⇒ Coating or matrix control mechanisms
⇒ In vitro release testing and correlation with in vivo behavior (IVIVC, if applicable)

Process Scalability and Reproducibility

⇒ Discuss the approach used to scale the process (e.g., linear scale-up, use of geometric similarity, process modeling).
⇒ Include data from process development batches or engineering lots, and validation/consistency batches that support scalability and reproducibility.

Biotechnological and Biological Products

For biologicals, process development must cover both formulation and filling/ finishing operations:

- Description of bulk drug product handling, including any pooling, storage, or transfer steps
- Aseptic processing development and validation (if applicable)

- Control of conditions such as temperature, shear, and light exposure during formulation and filling
- Rationale for choice of formulation vessel, filters, and container closure system

Where applicable, describe how the sterile fill-finish process was developed and validated, including:

- Selection of sterilization method (e.g., aseptic vs terminal sterilization)
- Fill volume accuracy
- Control of bioburden, endotoxins, and particulates

If the product is a biosimilar or follows a platform process, reference development comparability studies or prior knowledge to support the process design.

3.2.P.2.4 Container Closure System

This section must describe the development and justification of the selected container closure system (CCS) used for the drug product, demonstrating its ability to protect product quality, ensure compatibility, and support safe administration under the proposed conditions of storage, transport, and use.

General Justification

Identify each component of the container closure system, including:

- Immediate container (e.g., bottle, vial, blister, syringe barrel, sachet)
- Closure (e.g., cap, stopper, crimp seal)
- Any liners, desiccants, or secondary packaging (if critical)

Specify the material composition, such as Type I borosilicate glass, HDPE, PVC, rubber elastomers, aluminum, polypropylene, or stainless steel.

Justify the selection based on:

- Protection from environmental factors (e.g., moisture, light, oxygen)
- Chemical compatibility with the formulation
- Mechanical integrity under storage and shipping conditions
- Suitability for the route of administration and intended patient use

If the product is packaged in multiple configurations (e.g., different pack sizes, vial vs pre-filled syringe), provide justification for each format.

Material Safety and Regulatory Compliance

State whether the materials of construction comply with recognized pharmacopoeial standards (e.g., USP <661.1>, <381>, Ph. Eur. 3.2.1–3.2.9).

If non-compendial materials are used, provide supporting information such as ~~on~~:

⇒ Toxicological safety
⇒ Leachables and extractables
⇒ Biocompatibility, where relevant

If a desiccant or light-protective secondary packaging is critical, include a rationale for its inclusion and impact on product stability.

Container Closure Integrity (CCI)

If the drug product is sterile or intended for parenteral or ophthalmic use, include:

⇒ A description of the container closure integrity (CCI) strategy
⇒ Results from leak testing, dye ingress, or helium leak detection (as applicable)
⇒ Justification that the system prevents microbial or gas ingress over shelf life

Biological and Biotechnological Products

- Include studies demonstrating compatibility and stability of the biological product with the container over shelf life
- Justify the choice of surfactants, fill volume, and headspace
- Evaluate any potential for leachables, particularly from rubber stoppers or plastic syringes

If using a pre-filled syringe, auto-injector, or other combination product, cross-reference device development documentation (if applicable) and ensure that delivery accuracy and dose integrity are maintained.

The CCS must be suitable for the entire intended shelf life, compatible with the delivery system, and support stability, sterility (if applicable), and patient usability.

3.2.P.2.5 Microbiological Attributes

This section must describe the microbiological specifications and control strategies for the drug product, including justification for the selected sterility assurance approach, bioburden control, and/or antimicrobial preservative content. The purpose is to ensure the safety and integrity of the product throughout its shelf life, especially for parenteral, ophthalmic, and other high-risk routes.

Sterile Drug Products

For sterile products (e.g., injectables, ophthalmics, surgical irrigations), this section must include:

⇒ The sterility assurance approach, identifying whether the product is:
  - Terminally sterilized (preferred by EMA and WHO)
  - Aseptically processed (if terminal sterilization is not feasible)

⇒ Description and justification of:
  - Sterilization method (e.g., moist heat, dry heat, filtration)
  - Process validation, cross-referenced to Module 3.2.P.3.5

- Container closure integrity (see 3.2.P.2.4)

⇒ Bioburden control strategy prior to sterilization or aseptic processing

⇒ Acceptance criteria and methods for:

- Sterility testing
- Endotoxins testing (for parenterals, in accordance with referance pharmacopias
- Particulate matter (as applicable to the dosage form)

Biologicals :

Provide additional justification for:

⇒ Choice of filtration method and filter compatibility

⇒ Control of bioburden, environmental monitoring, and operator qualification

⇒ Minimization of microbial contamination during filling

Non-Sterile Drug Products

For non-sterile dosage forms (e.g., oral tablets, solutions, capsules, suspensions, topical creams, gels), the following must be addressed:

- Justification for microbial limits testing (e.g., Total Aerobic Microbial Count, Total Yeast and Mold Count, and objectionable organisms such as E. coli or Pseudomonas spp.)
- Compliance with relevant compendial requirements (e.g., Ph. Eur. 5.1.4 or USP <61>, <62>)
- Description of preservative content, if included, and:
  - Justification of concentration
  - Preservative efficacy testing (PET), in accordance with Ph. Eur. 5.1.3 or USP <51>
- If the product is intended for pediatric, ophthalmic, nasal, or dermal use, special consideration should be given to:
  - Safety of preservatives (e.g., benzalkonium chloride, phenol, parabens)
  - Potential for irritation or toxicity

- Justification for preservative-free systems (if applicable), including design features of the CCS

Additional Considerations

- State whether antimicrobial preservatives, antioxidants, or chelators are used, and assess their effect on microbial stability and/or enhance product stability.
- For multi-dose containers, show how microbial integrity is maintained over the in-use period.

This section must clearly demonstrate that the product meets appropriate microbiological quality standards, that the risk of microbial contamination is controlled, and that the patient is protected during product use.

3.2.P.2.6 Compatibility

This section must provide data and justification demonstrating that the drug product is compatible with any intended diluents**,** reconstitution fluids**,** delivery devices, or administration materials under the conditions of clinical or marketed use. Compatibility must be established to ensure that identity, strength, purity, potency, and performance of the product are not adversely affected during preparation and administration.

Reconstitution and Dilution (if applicable)

For products that require reconstitution (e.g., lyophilized powders) or dilution prior to administration, the following must be addressed:

⇒ Identity and composition of the recommended diluent(s) (e.g., Water for Injection, 0.9% NaCl, 5% glucose)
⇒ Reconstitution instructions (e.g., volume, method of mixing, time to dissolve)
⇒ In-use stability of the reconstituted/diluted product under:
  - Intended storage conditions (e.g., 2–8 °C, room temperature)
  - Time periods (e.g., 24 hours, 48 hours)

- Container type (e.g., glass vial, infusion bag)

Data must include:

⇒ Physical observations (e.g., precipitation, color change, turbidity)
⇒ pH, potency, and impurity profile post-reconstitution
⇒ Microbial stability or justification for microbial control during in-use period (especially for multi-dose or reconstituted biologics)

Compatibility with Administration Devices

If the product is administered via a specific delivery system or common medical devices like microdosers, compatibility must be demonstrated with:

⇒ Syringes, needles, infusion sets, or IV bags
⇒ Auto-injectors, pen injectors, nebulizers, or infusion pumps (if applicable)
⇒ Filters used during administration

Provide data on:

⇒ Drug adsorption or degradation when in contact with device materials (e.g., plastics, rubber)
⇒ Loss of potency, particulates, or change in osmolality
⇒ Evidence that device components do not leach substances into the product

Biological and Biotechnological Products

For biological products, compatibility must account for the fragility of the active substance. Key considerations include:

- Risk of protein aggregation, denaturation, or precipitation due to pH changes, dilution, or surface interaction
- Impact of surfactants or stabilizers on maintaining structural integrity
- Sensitivity to mechanical stress (e.g., shaking, excessive flow rates)
- Container adsorption (e.g., loss of protein to glass or plastic)

Stability of reconstituted biological products must be confirmed under clinically relevant conditions including:

- ⇒ Storage at 2–8 °C and/or room temperature
- ⇒ Use within defined timeframes
- ⇒ Compatibility with standard infusion fluids and bags

In all cases, compatibility claims must be supported by stability-indicating analytical data and align with instructions included in the product labeling (SmPC or PI).

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

This section must list all manufacturing, packaging, and quality control sites involved in the production of the drug product. The objective is to demonstrate that all facilities are appropriately authorized, qualified, and compliant with Good Manufacturing Practices (GMP). For the finished product, no more than two sites shall be accepted for each activity—manufacturing, packaging, and batch release—unless otherwise scientifically and regulatorily justified.

Information to Include: For each manufacturer, clearly state:

- Company name
- Full physical address
- Responsibility (e.g., bulk formulation, filling, primary/secondary packaging, release testing, labeling, warehousing)
- Manufacturing authorisation number or GMP license (if available)

If the product is manufactured at multiple sites (e.g., primary site and alternative site), both must be listed and supported with equivalent documentation to allow for post market survailance of the diffffernet batch numbers from the differen sites. For contract manufacturing arrangements, the contract giver and contract acceptor must be clearly defined with clear validity & duration.

If a testing laboratory, packager, or labeler is located at a different site from the production facility, that must also be listed.

GMP Compliance

Each site involved in manufacturing or testing must comply with GMP requirements, in accordance with:

- ICH Q7 for APIs
- EU GMP, WHO TRS 986, US cGMP, or GCC DR 111 (for drug products)

Applicants must ensure that:

- Valid GMP certificates are available for inspection upon request
- On-site inspections may be performed by the national regulatory authority (in this case, Kuwait Ministry of Health or GCC-affiliated bodies)

For biological drug products, facilities used for aseptic processing, formulation, or fill-finish must be specifically noted and must have capacity to meet environmental and sterility standards applicable to biological products.

3.2.P.3.2 Batch Formula

This section must provide the quantitative composition of a representative batch of the drug product, corresponding to the proposed commercial batch size. The batch formula should reflect the final formulation, including all materials used in the manufacture of a single batch, as actually weighed or measured.

A clearly structured table must be provided, listing:

- Name of each component
    - Drug substance(s)
    - All excipients (including coating agents, solvents, pH adjusters, preservatives, etc.)
    - Processing aids (e.g., lubricants, glidants) if retained in the final product

- Quantity per unit (e.g., per tablet, vial, mL)
- Quantity per batch
- Function of each component (e.g., active ingredient, binder, disintegrant, stabilizer)

For coated tablets or multi-part systems, separate subtables may be used for:

- Core formulation
- Film-coating or sugar-coating composition
- Capsule shell (if applicable)
- Diluent or reconstitution medium (if supplied as part of the kit)

Biological and Biotechnological Products

- Specify the amount of drug substance per vial or syringe, expressed as:
    - mg/mL (protein content)
    - IU (international units)
    - µg or other relevant activity-based units
- Clearly indicate overfill volumes, stabilizers, buffers, bulking agents, surfactants (e.g., polysorbate 80), and cryoprotectants (e.g., sucrose, trehalose) used in the formulation
- Include the final volume or mass per container, especially for lyophilized products or pre-filled syringes
- If the product includes a diluent or reconstitution solution, this must also be described in terms of composition, volume, and container type.

A batch formula for all proposed individual batch sizes must 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 must 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 Ministry of Health approval

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

This section must describe the full commercial-scale manufacturing process of the drug product. It should clearly outline each manufacturing step in the order it is performed, including in-process controls and parameters critical to ensuring product quality and consistency.

A narrative description or flow diagram should cover:

- Dispensing of raw materials and identity verification
- Granulation or blending (wet, dry, or direct compression methods) – For solid dosage forms
- Compression, filling, or encapsulation – For solid dosage forms
- Film-coating, tablet polishing, or capsule banding (if applicable) – For solid dosage forms
- Solution preparation for liquids or injectables
- Homogenization or emulsification for semisolids or suspensions
- Lyophilization, if used
- Aseptic processing or sterilization steps (for sterile products)
- Final packaging and labelling
- Equipment types (e.g., high-shear granulator, tablet press, lyophilizer), without brand names
- Operational parameters that impact product quality (e.g., mixing time, drying temperature, vacuum pressure)
- Expected yield ranges and in-process hold times (with time limits and storage conditions)
- Identification of any process intermediates (e.g., wet granules, bulk solution)

- In-process controls performed at each critical step (e.g., blend uniformity, moisture content, fill weight, visual inspection)

Process Controls:

- Describe how critical process parameters (CPPs) are monitored and controlled
- Indicate where sampling occurs and which acceptance criteria apply
- Justify control strategy used to ensure consistent production of drug product meeting specifications

For Biological and Biotechnological Products:

- Describe formulation steps including buffer preparation, excipient addition, and mixing
- Detail sterile filtration and fill-finish operations (e.g., filling of vials, syringes, or cartridges)
- Provide freeze-drying cycle parameters if lyophilization is used
- Indicate use of overfill (if any), container volume, and headspace management
- Highlight sensitivity to shear, agitation, or temperature, and how these risks are mitigated
- Include information on:
    - Container closure integrity testing
    - Cleanroom environment (e.g., ISO Class)
    - Aseptic process control (e.g., filtration hold times, bioburden limits)
    - Viral inactivation/removal steps (if applicable)

3.2.P.3.4 Controls of Critical Steps and Intermediates

This section must describe the in-process controls and monitoring strategies applied to critical manufacturing stepsand any intermediates used or produced during the drug product manufacturing process. These controls ensure the product consistently meets its predefined quality attributes.

- Identify each critical step in the manufacturing process (e.g., blending, granulation, filling, coating, filtration, lyophilization).
- Define the process parameters monitored at each critical step (e.g., mixing time, granulation endpoint, drying temperature, compression force).
- List in-process control tests (IPCs) performed during manufacturing, such as:
  - Blend uniformity
  - Granule particle size and moisture content
  - Tablet weight ,hardness and friability
  - Fill volume or weight of capsules or vials
  - Coating thickness or dissolution
  - Visual inspection for defects (e.g., chips, discoloration)
- Specify the acceptance criteria for each IPC and the sampling plan (e.g., frequency, number of units).
- Indicate how failures are handled and whether reprocessing or batch rejection criteria are defined.
- Provide justification for each critical control point based on development studies or risk assessment.

Control of Intermediates (if applicable):

- Describe any isolated intermediates (e.g., bulk tablets, granules, solutions) stored before final processing.

- Specify testing performed on intermediates (e.g., identity, assay, microbial limits).
- Define holding time limits and storage conditions (e.g., temperature, container type).
- Justify how intermediate controls ensure final product quality is not compromised.

For Biological and Biotechnological Products:

- Identify and justify control parameters for:
    - Solution preparation (e.g., buffer composition, pH, conductivity)
    - Sterile filtration (e.g., pre-filtration bioburden, filter integrity testing)
    - Fill volume, headspace, and container uniformity
    - Freeze-drying stages (e.g., endpoint detection for primary/secondary drying)
- Define acceptance criteria for bulk intermediate drug product if it is stored (e.g., protein content, biological activity, sterility).
- If pooling of batches or containers occurs, describe pooling controls and validation of homogeneity.
- Address specific attributes such as:
    - Protein aggregation
    - pH drift
    - Residual solvents (e.g., ethanol in formulation buffers)
    - Endotoxin and bioburden levels before final fill

3.2.P.3.5 Process Validation and/or Evaluation

This section must summarize the process validation strategy used to demonstrate that the manufacturing process is robust, reproducible, and consistently produces the drug product within its predefined quality attributes.

- State whether process validation has been completed, is ongoing, or will be conducted post-approval (with a commitment).
- Describe the type of validation:
    - Prospective validation (preferred for commercial products)
    - Concurrent validation (with justification)

- Provide details of the validation batches, including:
    - Batch size and manufacturing scale (must reflect intended commercial scale)
    - Manufacturing site
    - Equipment used (must match routine production)
    - Number of validation batches (minimum of three recommended)
- Include a summary of validation results, showing:
    - Critical process parameters (CPPs) monitored
    - In-process control results (e.g., blend uniformity, weight variation, fill volume)
    - Yield and rejection rates
    - Final product test results (e.g., assay, impurities, dissolution, sterility)
- Confirm that results met predefined acceptance criteria and that the process is under control.
- For aseptically filled products, environmental monitoring and media fill simulation results must be provided or cross-referenced.

For Lifecycle or Post-Approval Commitments:

- If validation is planned post-approval, include a protocol summary, outlining:
    - Number of batches
    - Validation criteria
    - Timeline for submission of results (aligned with GCC or Kuwaiti authority expectations)

For Biological and Biotechnological Products:

- Validation must address:
    - Aseptic processing or sterile filtration steps
    - Container closure integrity
    - Fill volume accuracy and uniformity
    - Lyophilization cycle reproducibility
    - Biological activity or potency testing

- Include process performance qualification (PPQ) summaries if applicable, as per US FDA process validation guidance.
- Viral clearance validation (if applicable) must be described under Module 3.2.A.2 but referenced here if part of the drug product stage.

3.2.P.4 Control of Critical Materials

This section must describe the controls applied to critical raw materials used during the manufacturing of the drug product. Critical materials include those that directly impact the quality, safety, or performance of the final product and may not be fully removed during processing.

- Identify critical materials, including:
  - Solvents
  - pH adjusters or buffering agents
  - Stabilizers or preservatives
  - Coating materials
  - Processing aids (if retained in the final product)
  - Water (e.g., Purified Water, Water for Injection)
- Specify grade, source, and compendial compliance for each material (e.g., USP, Ph. Eur., JP).
- Provide acceptance criteria and supplier specifications, if different from pharmacopoeial standards.
- Describe testing performed by the manufacturer or qualified supplier before use.
- Justify the criticality of the material and explain why it requires specific control.

TSE/BSE Risk Compliance (for materials of animal origin):

- For any raw materials or excipients derived from animal origin, such as gelatin, lactose, magnesium stearate, or enzymes, a TSE/BSE risk assessment must be provided.

- TSE refers to Transmissible Spongiform Encephalopathies, a group of rare but fatal neurodegenerative disorders, including Bovine Spongiform Encephalopathy (BSE), also known as “mad cow disease.”
- Materials must comply with European Pharmacopoeia monograph 5.2.8 on minimising the risk of TSE transmission.
- Submit a TSE Certificate of Suitability (TSE-CEP) issued by the European Directorate for the Quality of Medicines (EDQM) where available.
- If a TSE-CEP is not available, provide a declaration on the manufacturer’s official letterhead that:
    - Specifies the species and tissue origin of the material
    - Confirms that the material is sourced from countries and suppliers compliant with TSE/BSE safety regulations
    - Demonstrates that no ruminant-derived materials from BSE-endemic regions are used
    - Justifies any material exposure to inactivation procedures, where applicable

This requirement is mandatory under Medicine and Medical Products Registration and Regulatory Administration guidelines to ensure that no component of the drug product poses a risk of prion transmission to patients.

For Biological and Biotechnological Products:

- Identify critical raw materials such as:
    - Buffers (e.g., phosphate, citrate)
    - Surfactants (e.g., polysorbate 80 or 20)
    - Cryo-/lyoprotectants (e.g., sucrose, trehalose, mannitol)
    - Media components or additives (if present in downstream drug product formulation)
- Provide risk assessments for:
    - Source of materials (e.g., animal origin, synthetic, recombinant)
    - Endotoxin levels
    - Microbial bioburden

- For surfactants and stabilizers, include information on oxidative stability and any relevant degradation products.

3.2.P.5 Control of Drug Product

This section must describe the specifications, analytical methods, validation, batch test results, and justification of specifications for the final finished product to ensure it meets defined quality standards throughout shelf life.

3.2.P.5.1 Specification(s)

- Provide the drug product specification in tabular format.
- Include the test parameters, acceptance criteria, and analytical method reference for each test.
- Typical tests may include:
  - Appearance
  - Identification
  - Assay (content of active ingredient)
  - Impurities/degradants
  - Dissolution or disintegration
  - Uniformity of dosage units
  - Microbial limits
  - Water content (if applicable)
  - pH and osmolality (for injectables, ophthalmics)
  - Container closure integrity (for sterile products)
- Ensure the specification covers release and, where applicable, shelf-life criteria (with justification if different).

3.2.P.5.2 Analytical Procedures

- List and describe the analytical methods used for each specification parameter.
- Include:
  - Method type (e.g., HPLC, UV, IR, GC, titration)
  - Sample preparation procedure
  - Key chromatographic conditions (column, mobile phase, flow rate, detection)
  - Reference standards used

- Reference compendial procedures where applicable (e.g., USP, Ph. Eur.), and detail any modifications.

3.2.P.5.3 Validation of Analytical Procedures

- Provide a summary of validation data for all non-compendial or modified compendial methods.
- Include validation parameters per ICH Q2(R1):
  - Specificity
  - Linearity
  - Accuracy
  - Precision (repeatability and intermediate)
  - Range
  - Detection and quantitation limits (LOD/LOQ)
  - Robustness
- Cross-reference detailed validation reports (can be included in appendices).

3.2.P.5.4 Batch Analyses

- Include batch release data for at least two or three commercial-scale batches, or pilot-scale batches if justified.
- Provide:
  - Batch numbers
  - Batch sizes
  - Manufacturing site
  - Testing results for all parameters listed in the product specification
- Use tabular format for clarity, showing actual values vs. acceptance criteria.

3.2.P.5.5 Characterisation of Impurities

- List and identify all product-related impurities and degradation products.
- Describe the:
  - Source of impurity (e.g., manufacturing by-products, excipient interaction, degradation)
  - Structural elucidation (if known)
  - Qualification status (per ICH Q3B)
  - Toxicological justification (if levels exceed qualification thresholds)

3.2.P.5.6 Justification of Specification(s)

- Provide rationale for each test and acceptance criterion in the specification.
- Justify limits using:
  - Batch release data and trends
  - Stability data
  - Clinical and safety data
  - Pharmacopoeial requirements
  - ICH Q6A/Q6B, Q3B, and Q1 guidelines
- For impurities, justify limits per ICH Q3B or M7 (if genotoxic risks apply).
- If shelf-life limits are wider than release limits, provide supporting justification.

Additional Notes for Biological and Biotechnological Products

- Specifications must address:
  - Potency or biological activity (with validated bioassay)
  - Product-related variants (e.g., aggregates, isoforms)
  - Process-related impurities (e.g., host cell proteins, DNA, residual ligands)
  - Glycosylation profile (if applicable)
  - Endotoxin and sterility (for parenterals)
- Analytical methods must be sensitive and validated for biological complexity.
- Characterisation of impurities must include:
  - Structural variants
  - Degradation products
  - Post-translational modifications (e.g., oxidation, deamidation)
- Justification of specifications should include clinical relevance and comparability to reference biological product (for biosimilars).

3.2.P.6 Reference Standards or Materials

This section must describe all reference standards or materials used for testing the drug product, including assay, identification, impurity quantification, and potency measurements. The suitability, traceability, and characterization of each reference standard must be clearly justified.

- Identify each reference standard by:
  - Name of the substance
  - Source or supplier (e.g., USP, Ph. Eur., WHO, in-house)
  - Type of standard (primary or secondary)
  - Intended use (e.g., assay, related substances, identity, bioassay)
- For compendial standards:
  - State the pharmacopoeial designation and monograph reference
  - Confirm that no modifications have been made (or justify if they have)
- For in-house standards:
- Provide details on:

- Source or origin of the material
- Manufacturing or purification procedure (if applicable)
- Assigned potency or purity
- Characterization data (e.g., HPLC, NMR, MS, elemental analysis)
- Method of value assignment (e.g., titration, comparison with certified standard)
- Include or reference a Certificate of Analysis (CoA)

- Describe storage conditions and requalification strategy (e.g., retesting interval, expiry date)

For Secondary Standards:

- If a secondary or working standard is used routinely:
  - Describe the qualification process against the primary standard
  - Provide traceability and demonstrate equivalence
  - Justify any variability or batch-to-batch reassignment procedures

For Biological and Biotechnological Products:

- Reference standards may include:
  - In-house reference proteins or monoclonal antibodies
  - International reference standards (e.g., WHO International Standard for Erythropoietin)
  - Activity-based units (e.g., IU/mg, ng/mL)

Application to Include:

  - Potency assignment strategy using validated bioassays or ELISA
  - Characterization data confirming identity, purity, and structural integrity
  - Bridging data if the reference standard is changed or requalified
  - Description of handling and storage conditions to preserve stability (e.g., −80 °C, protected from light)
- For biosimilars, if the reference biological product (RBP) is used during development or assay calibration, clearly define its role and relationship to internal standards.

3.2.P.7 Container Closure System

This section must describe the container closure system (CCS) used for the commercial drug product, including all components that are in direct contact with the dosage form, and those that contribute to its stability, sterility, or delivery.

- For each packaging component, include:
  - Type of container (e.g., bottle, blister pack, vial, pre-filled syringe)
  - Type of closure (e.g., screw cap, rubber stopper, flip-off seal)
  - Material of construction (e.g., Type I glass, HDPE, PVC, aluminum, elastomer)
  - Whether it is single-dose or multi-dose
  - Volume or size per container
- State the manufacturer, grade, and compliance with relevant standards:
  - Pharmacopoeial references (e.g., USP <661>, Ph. Eur. 3.2.1–3.2.9)
  - Food-grade or medical-grade certifications (if applicable)
- Confirm that the packaging system:
  - Protects the drug product from light, moisture, and oxygen
  - Maintains physical, chemical, and microbiological stability through shelf life
  - Is compatible with the drug product formulation (especially important for biological products and sensitive formulations)
- For sterile products:
  - Confirm the system supports container closure integrity (CCI)
  - Indicate whether components are sterilized (and by what method)
  - Cross-reference microbiological testing and aseptic validation (3.2.P.2.5 and 3.2.P.3.5)

For Biological and Biotechnological Products:

- Evaluate and justify:
  - Protein adsorption or loss due to surface interactions
  - Leachables or extractables from container materials (especially rubber and plastic)
  - Potential for shear-induced aggregation during use (e.g., in syringes or cartridges)
- If the container is part of a device combination (e.g., auto-injector, pump), cross-reference the device description or submission in Module 1 or 3.2.R.

3.2.P.8 Stability

This section must demonstrate that the drug product maintains its intended quality, safety, and efficacy throughout its proposed shelf life under storage conditions relevant to the intended market. All studies should follow ICH and Kuwait Stability Guidelines. For Kuwait, long-term studies must be conducted under Climatic Zone III/IV conditions.

3.2.P.8.1 Stability Summary and Conclusions

The Kuwait 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). This section must summarize the stability studies conducted on the finished product and present conclusions regarding the shelf-life, storage conditions, and container closure system, based on the results generated under the prescribed conditions and in accordance with Kuwait stability guidelines.

The types of studies conducted, protocols used, and the results of the studies must be summarized.
The summary must 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 must 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.P.5.2, descriptions and validation of the methodology used in stability studies must be provided.

For products requiring reconstitution, dilution, or mixing prior to administration, a validated in-use stability study must also be summarized here, including time, storage conditions, and container specifications.

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

The stability of the drug product must 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 program must 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 must 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 must be scientifically justified.

3.2.P.8.3 Stability Data

This section must include the actual stability study data for the drug product used to justify the proposed shelf life and storage conditions, as described in 3.2.P.8.1. Stability studies must follow the stability protocol described in 3.2.P.8.2, using validated, stability-indicating methods.

Results of the stability studies must be presented in a tabular format. The results of all testing parameters related to each batch for the entire testing period must 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 must be provided in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it must be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms".
Dissolution results must 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 must be included. Information on characterization of impurities is located in 3.2.P.5.5.

3.2.A Appendices

Module 3.2.A contains supplementary scientific information that supports the overall quality assessment of the drug substance and drug product. The following appendices must be included where applicable:

3.2.A.1 Facilities and Equipment (Only for Biotechnological /Biological Products)

- For biological or biotechnological drug products only, provide a description of the manufacturing facilitiesinvolved in the production of the drug substance and/or drug product.
- Include information on:
  - Name and address of each site
  - Facility layout and classification (e.g., ISO classes, cleanroom zones)
  - Flow of materials and personnel (schematic diagrams)
  - Segregation of activities (e.g., viral vector areas, fermentation vs. purification)
- A description of major equipment used in critical manufacturing steps (e.g., bioreactors, lyophilizers, sterile fill lines) should also be provided or referenced.
- This section is not applicable to synthetic small molecule products.

3.2.A.2 Adventitious Agents Safety Evaluation

- Required for any product that involves materials of animal origin, biological processing, or recombinant technologies.
- Include a summary of controls for:
  - TSE/BSE risk in compliance with Ph. Eur. 5.2.8 and GCC guidelines (cross-reference TSE-CEP in Module 1 or 3.2.S)
  - Use of animal-derived materials (e.g., gelatin, enzymes, serum, media supplements)
  - Viral safety studies, including:
    - Testing of raw materials and cell banks for adventitious viruses

        - Viral clearance validation (if performed)
    - Confirm that no ruminant-derived materials from BSE-risk regions are used, or justify and document mitigation strategies.

3.2.A.3 Excipients of Novel, Human or Animal Origin

- Provide documentation for any excipient used in the drug product that is derived from human or animal tissue, including:
    - Name and function of the excipient
    - Source and species of origin
    - Country of origin
    - Certificate of Suitability (CEP), if available
    - TSE/BSE declaration
- Where no CEP is available, include:
    - A risk assessment for potential transmission of infectious agents
    - Manufacturer's declaration of safety
    - Details of any viral inactivation/removal processes (if relevant)
- Applicable examples include lactose, gelatin, magnesium stearate, heparin, and albumin

3.3 Literature References

This section should include copies of scientific literature that are explicitly cited in Module 3 (Drug Substance, Drug Product, Appendices, or Regional Information)

Examples of acceptable literature references:

- Peer-reviewed journal articles
- Pharmacopoeial monograph citations (when not fully quoted in Module 3)
- WHO or ICH scientific guidelines (if referenced directly in justification)
- Official technical reports from national or international regulatory bodies

Do not include: Unreferenced or irrelevant publications or Promotional material or internal company presentations

Module 4 – Nonclinical Study Reports

This module contains full study reports from nonclinical pharmacology, pharmacokinetics (PK), and toxicology evaluations. These studies support the safety of the drug substance and/or drug product prior to human use and are typically conducted under Good Laboratory Practice (GLP) where applicable. Study selection and design should comply with ICH S-series guidelines and consider any GCC specific requirements. Special considerations are required for biological products, particularly in species selection and immunogenicity evaluation.

4.1 Table of Contents of Module 4

A comprehensive, section-based list of all nonclinical study reports included in this module. This must follow CTD structure and reference each report by study type and study number/title.

4.2 Study Reports

This section includes the full study reports grouped by discipline.

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

Presents studies demonstrating the intended pharmacological action of the drug substance, including receptor binding, functional effects, and disease model studies. For biologics, species relevance based on receptor affinity or expression must be justified.

4.2.1.2 Secondary Pharmacodynamics

Reports on pharmacological effects unrelated to the therapeutic target. These

studies are important for understanding off-target activity that may inform clinical safety monitoring.

4.2.1.3 Safety Pharmacology

Includes core studies assessing effects on vital organ systems (CNS, cardiovascular, respiratory), typically in line with ICH S7A and S7B**.** Extended safety pharmacology may be required for drugs acting on ion channels or neurotransmitters.

4.2.1.4 Pharmacodynamic Drug Interactions

Summarizes in vivo studies evaluating the pharmacodynamic interaction of the investigational product with other drugs. Required only if a known or expected interaction exists.

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation

Describes bioanalytical techniques used to measure drug concentrations in plasma or tissue. Method validation should meet **ICH M10** or regional bioanalytical standards.

4.2.2.2 Absorption

Includes data from absorption studies (e.g., Caco-2, in vivo oral bioavailability). For biologics, absorption may be limited or irrelevant due to parenteral administration.

4.2.2.3 Distribution

Covers studies investigating tissue distribution, protein binding, and potential for crossing the blood–brain barrier. For biologics, focus is often on target-specific tissue uptake.

4.2.2.4 Metabolism

Includes identification of metabolites in animals and in vitro systems (e.g., liver

microsomes). May be omitted or limited for biologics, which are often catabolized to peptides and amino acids.

4.2.2.5 Excretion

Provides studies on elimination routes (urine, feces, bile), and excretion kinetics. Less relevant for biologics unless excreted unchanged.

4.2.2.6 Pharmacokinetic Drug Interactions

Includes studies evaluating whether the test article affects or is affected by cytochrome P450 enzymes or drug transporters. May be waived for biologics unless indicated.

4.2.2.7 Other Pharmacokinetic Studies

Any additional PK-related studies such as tissue-specific accumulation, formulation bridging, or PK in disease models.

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity

Acute toxicity studies conducted in two species (rodent and non-rodent), usually by the clinical route of administration. Observations include mortality, clinical signs, and necropsy findings.

4.2.3.2 Repeat-Dose Toxicity

14- to 90-day studies designed to identify dose-dependent toxicity and establish No Observed Adverse Effect Levels (NOAEL). GLP compliance is required for pivotal studies.

4.2.3.3 Genotoxicity

Includes a standard battery of mutagenicity tests (Ames test, chromosomal aberration, micronucleus test) in accordance with ICH S2(R1). Typically waived for biological products unless there is a concern about novel linkers or fusion proteins.

4.2.3.4 Carcinogenicity

Long-term studies required for chronically used compounds or when there is a signal for carcinogenic potential. Per ICH S1, may be omitted for biologics or non-genotoxic short-term agents.

4.2.3.5 Reproductive and Developmental Toxicity

Covers fertility, embryofetal development, and pre-/postnatal studies. Design must follow ICH S5(R3). For biologics, risk is assessed on a case-by-case basis depending on mechanism and placental transfer potential.

4.2.3.6 Local Tolerance

Studies designed to assess irritation or adverse effects at the site of administration (e.g., injection site). Required for parenteral, transdermal, or topical products.

4.2.3.7 Other Toxicity Studies

Includes specialized studies such as:

- **Immunotoxicity**
- **Phototoxicity**
- **Dependency**
- **Antigenicity or anti-drug antibody formation** (essential for biologics)
- **Juvenile animal studies** (if the product is intended for pediatric use)

4.3 Literature References

This section must include full-text copies of all scientific literature that are cited within Module 4, particularly in support of the pharmacology, pharmacokinetics, or toxicology sections. It complements the study reports by documenting peer-reviewed or regulatory-recognized sources used to justify or interpret nonclinical findings.

Module 5 – Clinical Study Reports

Module 5 contains the full clinical study reports and related documentation that support the safety, efficacy, and benefit–risk profile of the drug product. All reports must be conducted in accordance with Good Clinical Practice (GCP) and organized following the ICH E3 or E6 guidance, with additional requirements as defined by EMA, and FDA guidelines.

5.1 Table of Contents of Module 5

A structured list of all clinical documents and reports included in this module. It must follow CTD section numbering and be hyperlinked/bookmarked in eCTD format.

5.2 Tabular Listings of All Clinical Studies

A cumulative tabular summary listing:

- All clinical studies submitted (completed and ongoing)
- Study ID and title
- Design (e.g., randomized, open-label, single-arm)
- Phase (e.g., I, II, III, IV)
- Indication(s) studied
- Country or region
- Subject population (age, gender, number enrolled)
- Status (completed, ongoing, terminated)
- Cross-reference to full report location in 5.3

5.3 Clinical Study Reports

This section includes the full clinical study reports that support the efficacy, safety, pharmacokinetics, and pharmacodynamics of the drug product. Reports should be organized by study type and follow the structure and formatting recommendations of ICH E3. Each report must include all protocol-defined sections

(title page, synopsis, introduction, objectives, methodology, results, discussion, and appendices). Where applicable, good clinical practice (GCP) compliance and ethics committee approval must be documented.

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 must 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 must include:

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

5.3.1.2 Comparative Bioavailability and Bioequivalence (BE) Study Reports

This section must include full study reports of all comparative bioavailability (BA) or bioequivalence (BE) studies conducted to establish similarity between the proposed product and the reference product. These studies are critical to demonstrate that the test product delivers the active ingredient into the systemic circulation in a manner comparable to the reference product. Required for generic submissions or when major changes during the product lifecycle or formulation changes occur during development.

Studies should be in accordance with the ICH M13A guideline titled “Bioequivalence for Immediate-Release Solid Oral Dosage Forms”, bioequivalence (BE) studies must be conducted to demonstrate therapeutic equivalence between a test (generic) and reference medicinal product where a waiver (biowaiver) is not scientifically justified.

ICH M13A applies exclusively to:

- Immediate-release (IR) solid oral dosage forms (e.g., tablets, capsules),
- Containing drugs that are intended to release the active substance(s) promptly after administration,
- Products that are systemically absorbed for their therapeutic action.

Where an in vivo bioequivalence study is not submitted, a detailed scientific justification must be provided here to support a biowaiver request, in line with relevant regulatory guidance.

Modified Release & Other Dosage Forms:

For dosage forms such as modified-release, locally acting, or inhalation products or others, applicants may reference appropriate EMA, FDA guidance or other relavent SRA guidances along with submission of a scientific justification.

Biowaivers:

1. BCS-Based Biowaiver

Biowaiver requests should be submitted to Medicine and Medical Products Registration and Regulatory Administration according to ICH M9 and . supported by EMA/FDA product specific guidance or WHO monographs

2. according to ICH M13B Biowaivers in case of registration of multiple dose strengths.

3. Self evident BE or BA

5.3.1.2 In Vitro–In Vivo Correlation (IVIVC)

- Reports establishing correlation between dissolution and in vivo absorption.
- Includes Level A, B, or C IVIVC models as per FDA and EMA expectations.

5.3.1.3 In Vitro Dissolution/Release Studies

- Includes dissolution profiles of different strengths and batches, as well as comparisons between test and reference products.

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 with their validation reports should be provided.

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 though 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 pharmacodynarnics) must 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 must be provided here. Protein binding data from PK blood and/or plasma studies must 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 must be provided in this section.

5.3.2.3 Reports of Studies Using other Human Biomaterials

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

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments must 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 must be included in Sections 5.3.3.1 and 5.3.3.2 are generally designed to:

- Measure plasma drug and metabolite concentrations over time,
- Measure drug and metabolite concentrations in urine or faeces
- Measure drug and metabolite binding to protein or red blood cells.

Apart from describing mean PK in normal and patient volunteers, PK studies must 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 must 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 must 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 must be placed in this section.

5.3.3.2 Patient PK and Initial Tolerability

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

5.3.3.3 Intrinsic Factor PK Study Reports

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

5.3.3.4 Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors, must 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, must 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 must be provided in this section.
Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, must be provided in Section 5.3.5.

This section must 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
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 P1QPD 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 PIQPD studies

conducted in healthy subjects must be provided in Section 5.3.4.1, and the reports for those studies conducted in patients must 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 must be included in Section 5.3.5, not in Section 5.3.4.

5.3.4.1 Healthy Subject PD and P1C/PD Study Reports

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

5.3.4.2 Patient PD and PK/PD Study Reports

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

5.3.5 Reports of Efficacy and Safety Studies

This section must 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 must 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 must be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies must 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 must be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports must 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 must be included in the appropriate Section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report must 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 must 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 must 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, must be provided in this section.

Where a pharmacodynamic study contributes to evidence of efficacy, it must 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, must be placed in this section.

Controlled safety studies, including studies in conditions that are not the subject of the application, must 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) must 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 must 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 must be presented in a separate report. Such reports must 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), must 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 is not included in Section 5.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it must 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) must 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, must be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

5.4 Literature References

This section contains full-text copies of all scientific and clinical literature references that are explicitly cited in Module 5 – Clinical Study Reports and Module 2.7 – Clinical Summary. These references support the rationale, interpretation, or justification of clinical data and may relate to pharmacology, clinical trial design, statistical methodology, efficacy comparisons, or safety interpretations.

Additional Considerations

The evaluation of the benefit–risk balance remains subject to ongoing regulatory assessment. As this is a dynamic and continuously evolving field, the authority

reserves the right to request additional data or clarification at any stage of the review process. This approach ensures that decisions are consistently guided by the most current evidence, with patient safety as the paramount concern.

Post Authorization Variations

Any changes/ additions made to a registered product must be submitted to the Pharmaceutical and Herbal Medicines Registration and Control Administration for review and approval.

Refer to Variation guidance

Renewal of Registration

The registration of pharmaceutical product shall be subject to renewal every five (5) years from the date of issuance of the registration certificate.

The Authorised Representative is required to submit the renewal application at least six (6) months prior to the expiration of the current registration.

Transfer of Agency

If the MAH wishes to Transfer products from one agent to another (Transfer of Agency), the following must be submitted:

1. Legalized Letter of appointment issued by the MAH designating the new authorised representative signed by both parties.
2. Termination letter from the MAH confirming the termination of the previous agent, including the effective date of termination along with commitment that the MAH holds the financial responsibility before the date of agency transfer
3. List of products affected by the transfer, detailing product name, concentration, dosage form, and manufacturing company, MAH with address and company registration number.

Cancellation/Suspension of registration

Medicine and Medical Products Registration and Regulatory Administration reserves the right to suspend or cancel the registration of a pharmaceutical product or manufacturing company under the following circumstances:

- If the product or the manufacturing company is suspended in country of origin.
- If the Administration becomes aware- by any means other than from the authorised representative of a warning or suspension issued by an international health authority (e.g., USFDA, EMA, WHO, GCC-DR, or similar) regarding the product or its manufacturing site.
- If the product is found to be non-compliant with its approved specifications, whether issued by the manufacturer or established in an official pharmacopoeia.
- If there is any risk related to safety of the product or product fails to comply with the provisions of this Ministerial Decree.
- If falsified information is submitted as part of the CTD/eCTD, or if significant discrepancies are identified in the submitted documents.
- If the registered pharmaceutical product has not been imported to the State of Kuwait for a continuous period of two (2) years unless justified.
- If the product registration is not renewed following the expiry of the registration certificate.
- Upon official request by the Marketing Authorization Holder to cancel the product registration.

Appendices

Appendix 1: Detailed tables of CTD/eCTD module structure

Module 1: Administrative Information

Section	Requirements
1.0	Cover letter
1.1	Comprehensive Table of content
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-ups)
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	Patent Information
1.7.10	Letter of access or acknowledgment to DMF
1.8	Pricing
1.8.1	Price certificate
1.8.2	Other documents related
1.9	Responses to questions

Module 2: Common Technical Document Summaries

Section	Requirements
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	Overview of the Nonclinical Testing Strategy
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: Pharmacology, pharmacokinetics Toxicology
2.6.1	Introduction
2.6.2	Pharmacology Written Summary
2.6.2.1	Brief Summary
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	2.7.4.6 Post-Marketing Data
2.7.4.7	2.7.4.7 Appendix
2.7.5	2.7.5 References
2.7.6	2.7.6 Synopses of Individual Studies

Module 3: Quality

Section	Requirements
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 R R
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
3.2.R.1	Alcohol Content Declaration
3.2.R.2	Porcine/Pork – content/origin
3.2.R.3	The diluents and coloring agents in the product formula
3.3	Literature References

Module 4: Non-Clinical Study Reports

Section	Requirements
4.1	Table of Contents of Module
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

Section	Requirements
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

Appendix 2: Forms

COVER LETTER FOR INITIAL SUBMISSION

To: Medicine and Medical Products Registration and Regulatory Administration
Ministry of Health
Kuwait

Trade name	
Generic name	
Strength	
Dosage Form	
Pack size	
Manufacturer	
MAH	
Agent	
This Product has	☐ Priority ☐ Fast Track ☐ GCC ☐ EUA ☐ Expedited
Company Representative	
Email	
Mobile	

Company Manager

Name

Signature

Date

Company stamp

COVER LETTER FOR RESPONSE TO INQUIRIES

To: Medicine and Medical Products Registration and Regulatory Administration
Ministry of Health
Kuwait

Trade name	
Generic name	
Strength	
Dosage Form	
Pack size	
Manufacturer	
MAH	
Agent	
Submission No.	
Response to	□ New Registration □ Renewal □Variation
This Product has	□ Priority □ Fast Track □ GCC □ EUA □ Expedited
Company Representative	
Email	
Mobile	

Company Manager
Name
Signature
Date
Company stamp

Application Form for Marketing Authorization of Pharmaceutical Product

This application form to be filled by the principal company. It is mandatory to fill all the information. A separate product registration, and therefore a separate application, is required for each pharmaceutical dosage form, strength, and presentation of the therapeutic product.

This Application is for the Registration of:

- □ New Drug
  - □ Known active substance
  - □ New Chemical Entity
- □ Generic
- □ Biological
  - □ Biological Patent
  - □ Biosimilar
  - □ Blood products
  - □ Vaccines
  - □ Others

*For biologicals, approval from any Reference Health Authority must be appended

Application Type:

□ Fast Track
□ Priority Track
□ Normal Track

*Request for fast track review should be stated with supportive document appended.

Agent Name/Authorized Person(s)/Details:
Agent Name:
Authorized Person:
Tel:
E-mail:

Product Details:
Proposed Trade name:
Active ingredient:
□ Single active substance □ Multiple active substances
Strength:
Dosage form:
Pack size(s):
Description of Primary packaging material:
Route of administration:
Proposed shelf life:
Proposed shelf life after first opening container (if applicable):
Proposed shelf life after reconstitution or dilution (if applicable):
Proposed storage conditions:
Pharmacotherapeutic group:

ATC code:
(If the WHO ATC code is not available at the time of the application submission, “Pending” should be stated in this field.)
Therapeutic Indication (Target group indication):
Leaflet revision date:

Marketing Authorization Holder Details:
Name of Marketing Authorization Holder:
Address:
Country:
Company registration number:
Date of registration:

Manufacturer Details:
Active Ingredient Manufacturer:
Manufacturer name:
Address:
Country:
Excipients Manufacturer:
Manufacturer name:
Address:
Country:
Reference pharmacopoeia

The Site Responsible for Finished Product Manufacturing
Manufacturer name and address:
Do you have MOH Kuwait registration number?
□Yes □ No
If yes, please indicate:
Registration number:
Issue date of MOH registration (dd/mm/yyyy):
Renewal date of MOH registration (dd/mm/yyyy):

The Site Responsible for Primary Packaging:
Packager name and address:
Do you have MOH Kuwait registration number?
□Yes □ No
If yes, please indicate:
Registration number:
Issue date of MOH registration (dd/mm/yyyy):
Renewal date of MOH registration (dd/mm/yyyy):

The Site Responsible for Secondary Packaging:
Packager name and address:
Do you have MOH Kuwait registration number?

□Yes □ No
If yes, please indicate:
Registration number:
Issue date of MOH registration (dd/mm/yyyy):
Renewal date of MOH registration (dd/mm/yyyy):

The Site Responsible for Batch Release:
Batch releaser name and address:
Do you have MOH Kuwait registration number?
□Yes □ No
If yes, please indicate:
Registration number:
Issue date of MOH registration(dd/mm/yyyy):
Renewal date of MOH registration(dd/mm/yyyy):

All manufacturer(s) names and addresses should be consistent throughout all the documents submitted in the application, such as GMP certificates, CPPs and Module 3 of the CTD.

Declaration on Content of Materials of Animal Source: □Yes □No
Invoicing Company Name and Address (if applicable):
Price Certificate: □Yes □No
CTD Modules:

Module 1	□Yes	□No
Module 2	□Yes	□No
Module 3	□Yes	□No
Module 4	□Yes	□No
Module 5	□Yes	□No

Declaration:

I hereby certify that the submitted information is true and accurate and changes will not be made until they are approved by the MOH Kuwait.

Title:
Name:
Signature:
Date:
Company Stamp:

Appendix 3: References

- **Guidelines**

1. **ICH Q1A (R2): Stability Testing of New Drug Substances and Products.**
2. **ICH Q1B: Photostability Testing of New Drug Substances and Products.**
3. **ICH Q1C: Stability Testing for New Dosage Forms.**
4. **ICHQ1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Su bstances and Products.**
5. **ICH. Q1E: Evaluation for Stability Data.**
6. **ICH Q1F : Stability data package for registration in climatic zones III and IV -**
7. **ICH. Q5C: Stability Testing of Biotechnological/Biological Products.**
8. **ICH M4Q: Structure and content of CTD Module 3**
9. **ICH Q8(R2): Pharmaceutical development and scale-up**
10. **understanding**
11. **ICH Q11: Development & scale-up expectations for drug**
12. **substances**
13. **ICH Q10: Pharmaceutical Quality System (process consistency)**
14. **ICH Q12: Lifecycle management and control strategy**
15. **WHO Guidelines**