Development of Regulatory Affair Dossier for Export Registration of Esomeprazole Magnesium in French West Africa

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Abstract - *This Technical dossier presents the comprehensive registration documentation of Esomeprazole Magnesium Tablets USP 40 mg for pharmaceutical export within the WAEMU (UEMOA) region of French West Africa. The document outlines the evolving regulatory landscape shaped by harmonization efforts under WAEMU, enabling centralized drug registration across eight member countries. It highlights the economic significance of pharmaceutical exports and the critical need for standardized registration processes to ensure regulatory efficiency, compliance, and patient access. The dossier follows the Common Technical Document (CTD) format and includes detailed administrative, quality, non-clinical, and clinical summaries. Module 1 provides administrative and marketing information, while Module 2 summarizes the product's technical profile including its quality, active substance, and finished product data. Module 3 offers in-depth analysis of the drug substance—Esomeprazole Magnesium—including its chemical synthesis, physicochemical properties, analytical methods, impurities, stability studies, and reference standards. The finished dosage form is characterized, validated, and evaluated for critical quality attributes and long-term stability. Non-clinical studies (Module 4) are not applicable as this is a generic product, while clinical data (Module 5) are based on literature referencing established efficacy and safety. The dossier supports the product's compliance with USP standards, confirming its quality, safety, and efficacy for use and distribution across WAEMU member states. This study aims to critically examine and apply the regulatory requirements for pharmaceutical product registration in French West Africa by designing a complete Common Technical Document (CTD) dossier for Esomeprazole Magnesium tablets. Through this work, we seek to bridge the gap between regulatory expectations and practical dossier development, providing a strategic model for facilitating efficient drug registration and export compliance within the harmonized WAEMU/UEMOA framework.*

Key words – Technical Dossier, Harmonization, Esomeprazole Magnesium.

1. Introduction

Regulatory Affairs is a vital function in the Pharmaceutical, Biotechnology, and Medical Device Industries, responsible for ensuring that companies comply with all applicable regulations and guidelines for the development, approval, manufacturing, and marketing of healthcare products. This discipline serves as a bridge between the company and national or international regulatory authorities such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) [1].

A regulatory dossier is a structured set of documents submitted by pharmaceutical or biotechnology companies to regulatory authorities to seek approval for conducting clinical trials or marketing a medical product. It serves as a comprehensive record that demonstrates the safety, efficacy, and quality of the product and compliance with regulatory requirements [2].

The Common Technical Document (CTD) is the globally harmonized format developed by the International Council for Harmonization (ICH) to streamline regulatory submissions across multiple regions, including the U.S., EU, and Japan [3]. The CTD format is divided into five modules:

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Module 1: Regional Administrative Information
Module 2: Common Summaries
Module 3: Quality Information
Module 4: Non-clinical Study Reports
Module 5: Clinical Study Reports [3]

In the African context, especially within the West African Economic and Monetary Union (WAEMU/UEMOA), the regulatory dossier is aligned with the CTD structure and regional harmonization efforts led by institutions such as WAHO (West African Health Organization) and AMA (African Medicines Agency) to facilitate faster and more uniform access to medicines [4].

A well-prepared regulatory dossier ensures efficient review and approval processes and reduces the likelihood of delays due to deficiencies in data presentation or compliance [5].

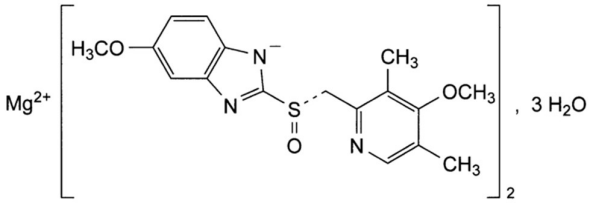
Introduction to Esomeprazole Magnesium [6][7]

Drug Profile : Esomeprazole magnesium

Description: Molecular formula: $C_{34}H_{36}MgN_6O_6S_2$

Molecular weight: 767.17 g/mol

Structure:



Esomeprazole magnesium is the magnesium salt form of esomeprazole, the S-isomer of omeprazole, a proton pump inhibitor (PPI). It is widely used in the management of acid-related gastrointestinal disorders. By irreversibly inhibiting the H^+/K^+-ATPase enzyme system located at the secretory surface of the gastric parietal cell, esomeprazole effectively reduces gastric acid secretion.

Esomeprazole magnesium is indicated for the treatment of gastro esophageal reflux disease (GERD), erosive esophagitis, Zollinger-Ellison syndrome, and for the prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs). It is also used in combination with antibiotics for the eradication of Helicobacter pylori.

Compared to its racemic counterpart, omeprazole, esomeprazole demonstrates improved pharmacokinetic properties including higher bioavailability and more consistent acid suppression. It is formulated as delayed-release tablets or capsules, and intravenous forms are available for clinical use when oral administration is not feasible.

Pharmaceutical regulatory landscape in French West Africa: The pharmaceutical regulatory landscape in French West Africa has seen major reforms, driven by the West African Economic and Monetary Union (WAEMU/UEMOA). Covering eight member states—Benin, Burkina Faso, Côte d'Ivoire, Guinea-Bissau, Mali, Niger, Senegal, and Togo—the region aims to harmonize regulatory standards to ensure medicine quality. Since the launch of the WAEMU pharmaceutical harmonization initiative in 2010, a centralized registration system has enabled companies to submit a single dossier valid across all member states.[8],[9]

The regulatory structure operates on three levels:

- Regional: WAEMU sets overarching guidelines and standards.
- National: Each country's regulatory authority adapts these to its local context while staying aligned with WAEMU.
- Local: Focuses on enforcement and market surveillance.[10]

Adopting the Common Technical Document (CTD) format has standardized dossier submissions, streamlining reviews and reducing duplication. Support from WHO and other partners through training and technical assistance has further strengthened regulatory capacity and quality systems.[11]

In this research paper, we are developing a regulatory affairs dossier for the export registration of Esomeprazole Magnesium tablets in French West Africa, with a focus on compliance with the harmonized regulatory framework established by WAEMU/UEMOA. The study involves the preparation of all five modules of the Common Technical Document (CTD), including administrative

information, quality data, non-clinical and clinical summaries, and product-specific technical documentation. This research aims to demonstrate a structured and region-specific approach to regulatory submission. All manuscripts must be in English. These guidelines include complete descriptions of the fonts, spacing, and related information for producing your proceedings manuscripts. Please follow them.

This template provides authors with most of the formatting specifications needed for preparing electronic versions of their papers. Margins, column widths, line spacing, and type styles are built-in; examples of the type styles are provided throughout this document and are identified in italic type, within parentheses, following the example. PLEASE DO NOT RE-ADJUST THESE MARGINS. Some components, such as multi-leveled equations, graphics, and tables are not prescribed, although the various table text styles are provided. The formatter will need to create these components, incorporating the applicable criteria that follow.

2. Materials and Methods

This study was conducted through the systematic development of a regulatory affairs dossier for Esomeprazole Magnesium tablets (40 mg) intended for export registration in French West Africa, under the WAEMU/UEMOA regulatory framework. The methodology followed the structure of the Common Technical Document (CTD) format, comprising five key modules:

Module 1: Includes administrative and regional information such as marketing authorization applications, GMP certificates, and company details.

Module 2: Provided overviews and summaries of quality, non-clinical, and clinical data.

Module 3: Detailed the quality aspects of the drug substance and finished product, including manufacturing process, analytical methods, specifications, stability studies, and validation protocols.

Modules 4 and 5: Compiled available preclinical and clinical data supporting the safety and efficacy of the product.

Pharmaceutical data were gathered from validated internal documentation, including certificate of analysis, batch manufacturing records, and stability reports, all in compliance with USP and ICH standards. Analytical techniques such as NMR, IR, and Mass Spectrometry were used to characterize the active pharmaceutical ingredient (API). The regional regulatory requirements were reviewed based on WAEMU/UEMOA guidelines and WHO recommendations. The final dossier was constructed to reflect harmonized procedures aimed at centralized product registration across UEMOA member states.

3. Case Study

Module 1: Regional Administrative Information

The administrative section of the dossier includes essential documents required for registration in WAEMU/UEMOA countries. This includes the marketing permission letter, application form, manufacturer's license, GMP certificate, and site details. It also provides information on the product's regulatory status, list of approved UEMOA countries, and marketing history. The Summary of Product Characteristics (SmPC), packaging details, and package insert are included to ensure compliance with regional labelling and language requirements.

Module 2: Summary of Technical File – Quality Summary

This section includes the table of contents, introduction, data on the active substance and finished product, clinical and non-clinical summaries, and annexes. The Introduction provides product identification details:

Generic Name: Esomeprazole Tablets,

Form: Oral Tablet

Indications: duodenal ulcer, gastric ulcer, reflux oesophagitis, and Zollinger-Ellison syndrome.

It is noted that the product may be used in combination with antibiotics for H. pylori-related ulcers. The Active Substance Summary covers an overview of the substance, its manufacturing process, characterization, control methods, reference standard, container details, and stability data. The Finished Product Summary includes the product description and composition, pharmaceutical development, manufacturing process, control of excipients and final product, reference standard used, packaging details, and results of stability testing

Module 3:

Module 3 is divided into two main parts:

- 3.1.S – Drug Substance
- 3.2.P – Drug Product

In Drug substance we study about General Information like Nomenclature, Structure, Physicochemical Properties, Description of the production processes, Characterization, Control of the drug substance, Reference Standard, Container/ Closure System, Stability, etc.

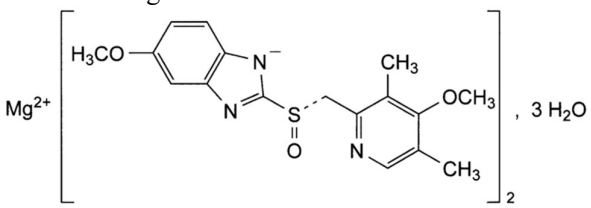
For the finished product it contains Description and composition of the Pharmaceutical Product, Pharmaceutical Development, Manufacturer of the FPP, Control of Excipients, Control of Finished Products, Reference Standards or substances, Container and closure system, Stability testing, etc.

3.1.S – Drug Substance

3.1.1 General Information:

The chemical name of the Esomeprazole Magnesium is 1*H*-Benzimidazole,5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2pyridinyl)methyl]sulfinyl]-,magnesium salt(2:1)trihydrate;5-Methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]benzimidazole, magnesium salt (2:1)trihydrate.

Molecular formula of Esomeprazole Magnesium is $C_{34}H_{36}MgN_6O_6S_2$ and its molecular weight is 767.17 g/mol and structural formula is following



Physicochemical Properties: Esomeprazole Magnesium is White or slightly coloured powder. Slightly soluble in water, soluble in methanol, practically insoluble in heptane, its water content is 6.0 % - 8.0 % and content of magnesium is 3.30 % – 3.55 % on anhydrous basis.

3.1.2 Chemical Route of Synthesis of Esomeprazole Magnesium:

Two-stage process starting with 2-Chloromethyl-3,5-Dimethyl-4-Methoxy Pyridine Hydrochloride and 2-Mercapto-5-Methoxy Benzimidazole, followed by purification and drying to 6-8% moisture.

3.1.3 Process Validation and Evaluation:

Prospective process validation of Esomeprazole Magnesium USP was conducted on three consecutive batches to ensure consistent performance as per predefined specifications. Validation followed confirmation of equipment and raw material suitability.

Batch records were reviewed for critical process and quality parameters, with acceptance limits as per the Master Formula. Results showed all parameters remained within limits, confirming process consistency across batches, times, and material sources.

3.1.4 Manufacturing Process Development:

At the manufacturing site, chemical synthesis and operating parameters were first developed at the laboratory scale. After successful lab-scale production, critical process parameters were identified, and the process was validated.

During scale-up, these parameters were revised as needed, and the first three commercial batches were validated. Stability studies, including accelerated and long-term storage conditions, were also conducted to confirm product stability.

Characterization:

Description of the characterization method: The elucidation of structure of Esomeprazole Magnesium USP is based on appropriate physical and chemical test results

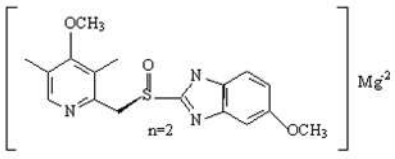
1. NMR Spectrum
2. IR Spectrum
3. Mass Spectrum

NMR Spectra of Esomeprazole Magnesium USP:

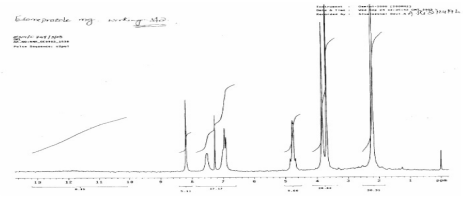
^{1}H NMR Spectrum:

Instrumentation: The NMR Spectrum of Esomeprazole Magnesium was conducted on Model Brucker AC80.

Interpretation: The proton positions are as follows:



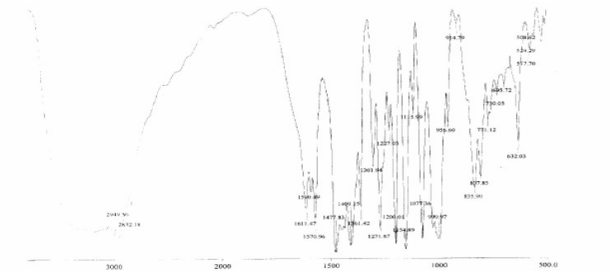
The NMR data shows the proton environment with chemical shifts and corresponding assignments: signals between 7 to 8 ppm represent 4 aromatic protons, a peak at 4.8 ppm corresponds to 6 protons of methoxy groups (-OCH3), a signal at 3.9 ppm indicates 2 protons of methylene groups (CH2), and a peak at 2.1 ppm corresponds to 6 methyl protons (CH3).



Infra Red Spectrum of the Drug Susbtance*:*

Instrumentation: The IR spectrum of Esomeprazole Magnesium was recorded using a Shimadzu IR 408 spectrophotometer.

Interpretation: Key absorption bands observed include 2949 cm^{-1} (CH3 stretching), 1477 & 1409 cm^{-1} (CH2 & CH3 deformations), 1361 cm^{-1} (OCH3 stretching), 999–1270 cm^{-1} (C–N stretching), and 1077 cm^{-1} (S=O group).

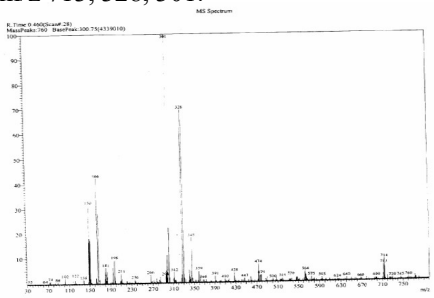


The IR spectrum obtained for Esomeprazole Magnesium manufactured by us is concordant with IR spectrum of the working standard.

Mass Spectrum of the Drug Substance:

Instrumentation: A mass spectrum of Esomeprazole Magnesium was obtained using LC/MS on a Seiex API III quadrupole mass spectrophotometer.

Interpretation: Principal ions at m/z 713, 328, 301.



3.1.5 Impurities Magnesium content (By Complexometry - Between 3.0 % & 4.0 % on anhydrous basis)

Impurities in Esomeprazole Magnesium USP: Controlled by chromatographic purity (HPLC) tests per USP, potential impurities include Omeprazole N-oxide, Omeprazole Sulfone, Omeprazole, and the R-enantiomer.

Acceptance Criteria Basis: Impurities are controlled via chromatographic tests; residual solvents like toluene are monitored per ICH guidelines.
Active Substance Control: Appearance as white/slightly coloured powder, slight water solubility, IR identification, water content 6.0%–8.0%, related substances ≤0.5%, assay 98.0%–102.0%, and magnesium content 3.30%–3.55%, all measured by validated methods

3.1.6 Analytical Methods for Esomeprazole Magnesium USP

Physical Properties: White or slightly coloured powder, slightly hygroscopic. Soluble in methanol, slightly soluble in water, insoluble in heptane.
Esomeprazole Magnesium USP contains 98.0%–102.0% active (anhydrous basis) and is identified by IR and general tests. Assay is performed via HPLC with strict system suitability. Impurities (heavy metals, residual solvents, and organics) are controlled per USP limits: R-Omeprazole and individual impurities ≤0.10%, total impurities ≤2.0%. Water content is ≤0.5% (anhydrous) or 6.0%–8.0% (trihydrate); magnesium 3.30%–3.55%. Enantiomeric purity is ensured by chiral LC. All methods meet USP validation standards.

3.1.7 Batch Analysis:

Esomeprazole Magnesium USP (50 kg), manufactured in 10/2023, was analysed on 15/10/2023 and found compliant with USP specifications. It met all criteria for appearance, solubility, identification, water content (6.0%–8.0%), impurities (≤0.5%), assay (99.56%), and magnesium content (3.27%).

3.1.8 Justification of Specification:

The Specifications of Esomeprazole Magnesium USP are as per USP specifications.
The method followed by us exactly same as detailed in specifications of USP so this part is not discussed here with.

3.1.9 Reference Standard

Reference Standard: USP Esomeprazole Magnesium.
Secondary Standard**:** An in-house Esomeprazole Magnesium USP working standard, qualified against the USP reference, is used for routine analysis. It meets USP specifications, is stored sealed in a dehumidified environment at 20–24°C, and is used for all analytical testing.

3.1.10 Container/ Closure System:

Esomeprazole Magnesium is packed in sealed, labelled polythene bags (25–50 kg) placed in HDPE bags. Labels and packaging are quality-checked for consistency. Stability studies at 40°C/75% RH confirm the product's stability and moisture resistance.

3.1.11 Accelerated Stability Study Report of Three Consecutive Batches Esomeprazole Magnesium

Esomeprazole Magnesium USP (50 kg) was manufactured in 06/2022, 10/2023, and 02/2024, with expiry dates from 05/2027 to 01/2029. Stored at 40°C/75% RH, six-month stability data met all specifications: water (6.014%–6.031%), impurities (0.04%–0.05%), magnesium (3.37%–3.47%), and assay (99.19%–99.56%).

3.1.12 Real Time Stability Study Report Three Consecutive Batches Esomeprazole Magnesium

Esomeprazole Magnesium USP (50 kg) was manufactured in 06/2022, 10/2023, and 02/2024, with expiry dates from 05/2027 to 01/2029. Stored at 30°C ± 2°C/65% ± 5% RH, 60-month stability data confirmed all parameters within limits: water (6.012%–6.081%), impurities (≤0.05%), magnesium (3.33%–3.37%), and assay (99.40% to 98.50%), indicating good long-term stability.

3.2.P - Finished Product

3.2.1 Physical, Chemical and Biological Properties

Physicochemical Properties: The tablet is tan to brown in colour and positively identified as Esomeprazole Magnesium Trihydrate. The average tablet weight is 324.0 mg ± 5.0%. Each tablet contains Esomeprazole Magnesium USP equivalent to 40 mg of Esomeprazole, with an assay specification of not less than 90.0% and not more than 110.0% of the labelled claim.
Biological Properties Esomeprazole Magnesium Proton Pump Inhibitor**,** inhibits the H^+/K^+-ATPase enzyme in gastric parietal cells, blocking the final step of acid production and reducing gastric acidity.
Pharmacokinetics**:** Esomeprazole is fully absorbed in 3–6 hours, ~95% bound to plasma proteins, has a ~40-minute half-life, is primarily metabolized in the liver, and ~80% is excreted in urine with the rest in faeces.

3.2.2 Control of Critical Stages and Intermediates

Various in-process checks: Before operations, housekeeping is checked. Physical parameters monitored every 30 minutes: tablets should be tan to brown, circular, biconvex, enteric coated; average weight 324 mg ±5%; weight uniformity within ±10%. Disintegration tested every 2 hours—max 2 hours in 0.1 M HCl, 1 hour in pH 6.8 buffer. Temperature and humidity checked every 4 hours, kept below 25ºC and 55% RH.

Validation/Process Evaluation: Process validation reports for any 3 batches to be provided.

3.2.3 Control of Excipients:

- Specifications: Specifications for all excipients to be included.
- Analytical Methods: Methods per relevant monographs to be enclosed.
- Justification: Excipients comply with BP/USP standards.
- Excipients of Human/Animal Origin: Not applicable.
- New Excipients: Not applicable.

3.2.4 Control of Finished Products

Specifications for the Finished Pharmaceutical Product: Esomeprazole Magnesium Tablets USP are stored below 30°C in a cool, dark, dry place and packed in 3x10 Alu-Alu blisters with an insert. They have a 36-month shelf life and are tan to brown, circular, biconvex, enteric-coated tablets. Identification confirms Esomeprazole Magnesium Trihydrate. Average weight is 324 mg ±5%, with weight uniformity allowing max 2 tablets ±5% and none >10% deviation. Disintegration times are ≤2 hours in 0.1 M HCl and ≤1 hour in pH 6.8 buffer. Assay ranges from 90–110% of label claim. Microbial limits include total aerobic count ≤50 CFU/g and absence of yeast/molds.

Remarks: The product is set as per USP Specifications.

Analytical Methods: Each tablet contains 90–110% of labelled Esomeprazole Magnesium. Identification matches standard responses. Assay follows validated USP methods with precision and accuracy between 98–102%. Calculation uses %Esomeprazole = (rU/rS) × (CS/CU) × (2Mr1/Mr2) × 100 (Mr1=345.42, Mr2=713.12). Acceptance range: 90–110%.

Dissolution Test: Performed using USP Paddle method in 0.1 M HCl (2 hours) followed by phosphate buffer pH 6.8 (1 hour 45 minutes). Acceptance: NLT 70% dissolved. Detection by UV at 302 nm.

Uniformity of Dosage Units: Complies with USP standards.

Impurities: Elemental impurities are limited to ≤20 ppm lead, tested via ashing and colour comparison. Residual solvents are analysed by validated headspace GC. Organic impurities follow USP methods, with individual limits ≤0.2%.

Assay uses LC with PDA at 302 nm, ammonium acetate buffer and methanol: acetonitrile mobile phases, requiring resolution ≥1.5 and RSD ≤1.0%.

Validation per USP standards; no impurities detected in tested batches. Three batch Certificates of Analysis included. Specifications comply with pharmacopeial standards, using Esomeprazole Magnesium USP as primary reference standard.

3.2.5 Container / Closure System(S) and Other Packing:

Description of Container Closure System - The packaging components include a 3x10 Alu-Alu blister packing strip, a primary carton, a pack insert, a shipper, and Bopp tape.

3.2.6 Stability

Stability Protocol:

Stability Summary and Conclusion- The following stability studies were performed on 3 batches of Esomeprazole Magnesium USP tablets.

Types of Studies Conducted-

Study Program	Temperature	Relative Humidity	Frequency of Testing
Accelerated	40°C ± 2°C	75% ± 5% RH	Initial, 1,2,3 & 6 Months
Long Term	30°C ± 2°C	65% ± 5% RH	Initial, 3, 6, 9, 12, 18, 24 and 36 Months

Post-approval stability protocol and stability commitment: Not Applicable

Stability Testing Report : Esomeprazole Tablets 40 mg, manufactured in 10/2021 and expiring 09/2024, were packed in 3x10 Alu-Alu blisters (100,000 tablets batch size) and stored at 40°C ± 2°C/75% ± 5% RH. Testing of 20 cartons over 6 months confirmed tan-brown, circular, biconvex, enteric-coated tablets meeting HPLC ID, weight uniformity (322 mg ±5%), and disintegration limits (≤2 hours in 0.1 M HCl, ≤1 hour in pH 6.8). Assay showed ~98.7% Esomeprazole content. Microbial counts were within specifications, with no yeast or molds detected.

3 Summary & Conclusion

This thesis provides a comprehensive framework for understanding pharmaceutical registration in French West Africa, identifying key success factors, challenges, and strategies for market access. It emphasizes the need to balance compliance with harmonized WAEMU/ECOWAS regulations and adapt to country-specific requirements. The study highlights gaps in harmonization implementation, calling for greater regulatory capacity building and collaboration between companies and authorities.

Future research should monitor harmonization progress, assess new regulatory requirements, and explore digital solutions for streamlined submissions. Recommendations include maintaining robust quality systems, generating stability data for Zone IVb, and ensuring effective communication with regulators.

The regulatory dossier for the tablet export demonstrates compliance with GMP, regional, and international standards, covering formulation, manufacturing, quality control, stability, and safety/efficacy data. Its harmonized preparation supports faster reviews, enabling timely access to essential medicines and strengthening trust with regulatory authorities, contributing to improved healthcare outcomes in the region.

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