C. **Initial Application**

**Part I: Administrative Data and Product Information**

**Sec. A** Introduction

**Sec. B** Table of Contents

1. Integrated Application Form
2. Letter of Authorization (where applicable)
3. Certifications
4. Labeling
5. Product Information

**Sec. C** Guidance on the Administrative Data and Product Information

1. Application Form
2. Letter of Authorization (where applicable)
3. Certifications

   For contract manufacturing:
   a. License of pharmaceutical industries and contract manufacturer
   b. Contract manufacturing agreement
   c. GMP certificate of contract manufacturer

   For manufacturing “under-license”
   a. License of pharmaceutical industries
   b. GMP certificate of the manufacturer
   c. Copy of “under-license” agreement

   For locally manufactured
   a. License of pharmaceutical industries
   b. GMP certificate (country specific)

   For imported products
   a. License of pharmaceutical industries/importer/wholesaler (country specific)
   b. Certificate of Pharmaceutical Product issued by the competent authority in the country of origin according to the current WHO format

4. Labeling

5. Product Information
   5.1. Package Insert
   5.2. Summary of Product Characteristics (Product Data Sheet)

**Part II: Quality**

**Sec. A** Table of Contents

**Sec. B** Quality Overall Summary

**Sec. C** Body of Data

   **Drug Substance (S)**

   **S 1** General Information
S 1.1. Nomenclature
S 1.2. Structural Formula
S 1.3. General Properties
S 2 Manufacture
S 2.1. Manufacturer(s)
S 2.2. Description of Manufacturing Process and Process Controls
S 2.3. Control of Materials
S 2.4. Control of Critical Steps and Intermediates
S 2.5. Process Validation and/or Evaluation
S 2.6. Manufacturing Process Development
S 3 Characterization
S 3.1. Elucidation of Structure and Characteristics
S 3.2. Impurities
S 4 Control of Drug Substance
S 4.1. Specifications
S 4.2. Analytical Procedures
S 4.3. Validation of Analytical Procedures
S 4.4. Batch Analyses
S 4.5. Justification of Specifications
S 5 Reference Standards or Materials
S 6 Container Closure System
S 7 Stability

Drug Product (P)
P 1 Description and Composition
P 2 Pharmaceutical Development
P 2.1. Information on Development Studies
P 2.2. Components of the Drug Product
  P 2.2.1. Active Ingredients
  P 2.2.2. Excipients
P 2.3. Finished Product
  P 2.3.1. Formulation Development
  P 2.3.2. Overages
  P 2.3.3. Physicochemical and Biological Properties
P 2.4. Manufacturing Process Development
P 2.5. Container Closure System
P 2.6. Microbiological Attributes
P 2.7. Compatibility
P 3 Manufacture
P 3.1. Batch Formula
P 3.2. Manufacturing Process and Process Control
P 3.3. Controls of Critical Steps and Intermediates
P 3.4. Process Validation and/or Evaluation
P 4 Control of Excipients
P 4.1. Specifications
P 4.2. Analytical Procedures
P 4.3. Excipients of Human and Animal Origin
P 4.4. Novel Excipients
P 5 Control of Finished Product
P 5.1. Specifications
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2. Content and Structural Format

Sec. C Nonclinical Written and Tabulated Summaries
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   1.2. General Presentation Issues
2. Content of Nonclinical Written and Tabulated Summaries
   2.1. Pharmacology
       2.1.1. Written Summary
           2.1.1.1. Primary Pharmacodynamics
           2.1.1.2. Secondary Pharmacodynamics
           2.1.1.3. Safety Pharmacology
           2.1.1.4. Pharmacodynamic Drug Interactions
       2.1.2. Tabulated Summary
   2.2. Pharmacokinetics
       2.2.1. Written Summary
           2.2.1.1. Absorption
           2.2.1.2. Distribution
           2.2.1.3. Metabolism
           2.2.1.4. Excretion
           2.2.1.5. Pharmacokinetic Drug Interaction (Nonclinical)
       2.2.2. Tabulated Summary
   2.3. Toxicology
       2.3.1. Written Summary
           2.3.1.1. Single-Dose Toxicity
           2.3.1.2. Repeat-Dose Toxicity
           2.3.1.3. Genotoxicity
           2.3.1.4. Carcinogenicity
           2.3.1.5. Reproductive and Developmental Toxicity
               2.3.1.5.1. Fertility and Early Embryonic Development
               2.3.1.5.2. Embryo-Foetal Development
               2.3.1.5.3. Prenatal and Postnatal Development
           2.3.1.6. Local Tolerance
           2.3.1.7. Other Toxicity Studies (if available)
       2.3.2. Tabulated Summary
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   2.1.  Written Study Reports
      2.1.1.  Primary Pharmacodynamics
      2.1.2.  Secondary Pharmacodynamics
      2.1.3.  Safety Pharmacology
      2.1.4.  Pharmacodynamic Drug Interactions
3.  Pharmacokinetics
   3.1.  Written Study Reports
      3.1.1.  Analytical Methods and Validation Reports
      3.1.2.  Absorption
      3.1.3.  Distribution
      3.1.4.  Metabolism
      3.1.5.  Excretion
      3.1.6.  Pharmacokinetic Drug Interaction (Nonclinical)
      3.1.7.  Other Pharmacokinetic Studies
4.  Toxicology
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      4.1.2.  Repeat-Dose Toxicity
      4.1.3.  Genotoxicity
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         4.1.4.2.  Short or Medium Term Studies
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         4.1.5.1.  Fertility and Early Embryonic Development
         4.1.5.2.  Embryo-Foetal Development
         4.1.5.3.  Prenatal and Postnatal Development
         4.1.5.4.  Studies in which the Offspring are Dosed and/or further Evaluated
      4.1.6.  Local Tolerance
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         4.1.7.2.  Immunotoxicity
         4.1.7.3.  Dependence
         4.1.7.4.  Metabolites
         4.1.7.5.  Impurities
         4.1.7.6.  Other

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Part  Clinical Document
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1.  Product Development Rationale
2.  Overview of Biopharmaceutics
3. Overview of Clinical Pharmacology
4. Overview of Efficacy
5. Overview of Safety
6. Benefits and Risks Conclusions

Sec. C Clinical Summary
1. Summary of Biopharmaceutic Studies and Associated Analytical Method
   1.1. Background and Overview
   1.2. Summary of Results of Individual Studies
   1.3. Comparison and Analyses of Results across Studies
   Appendix 1
2. Summary of Clinical Pharmacology Studies
   2.1. Background and Overview
   2.2. Summary of Results of Individual Studies
   2.3. Comparison and Analyses of Results across Studies
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   3.3. Comparison and Analyses of Results across Studies
      3.3.1. Study Populations
      3.3.2. Comparison of Efficacy Results of all Studies
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   3.4. Analysis of Clinical Information Relevant to Dosing Recommendations
   3.5. Persistence of Efficacy and/or Tolerance Effects
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      4.1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies
      4.1.2. Overall extent of Exposure
      4.1.3. Demographic and Other Characteristics of Study Population
   4.2. Adverse Events
      4.2.1. Analysis of Adverse Events
         4.2.1.1. Common Adverse Events
         4.2.1.2. Deaths
         4.2.1.3. Other Serious Adverse Events
         4.2.1.4. Other Significant Adverse Events
         4.2.1.5. Analysis of Adverse Events by Organ System or Syndrome
      4.2.2. Narratives
   4.3. Clinical Laboratory Evaluations
   4.4. Vital Signs, Physical Findings, and Other Observations Related to Safety
   4.5. Safety in Special Groups and Situations
      4.5.1. Patient Groups
      4.5.2. Drug Interactions
      4.5.3. Use in Pregnancy and Lactation
4.5.4. Overdose
4.5.5. Drug Abuse
4.5.6. Withdrawal and Rebound
4.5.7. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

4.6. Post-Marketing Data

Appendix 4

5. Synopses of Individual Studies

Sec. D Tabular Listing of All Clinical Studies

Sec. E Clinical Study Reports (if applicable)

1. Reports of Biopharmaceutic Studies
   1.1. Bioavailability (BA) Study Reports
   1.2. Comparative BA or Bioequivalence (BE) Study Reports
   1.3. In vitro-In vivo Correlation Study Reports
   1.4. Reports of Bioanalytical and Analytical Methods for Human Studies

2. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials
   2.1. Plasma Protein Binding Study Reports
   2.2. Reports of Hepatic Metabolism and Drug Interaction Studies
   2.3. Reports of Studies Using Other Human Biomaterials

3. Reports of Human Pharmacokinetic (PK) Studies
   3.1. Healthy Subject PK and Initial Tolerability Study Reports
   3.2. Patient PK and Initial Tolerability Study Reports
   3.3. Population PK Study Reports

4. Reports of Human Pharmacodynamic (PD) Studies
   4.1. Healthy Subject PD and PK/PD Study Reports
   4.2. Patient PD and PK/PD Study Reports

5. Reports of Efficacy and Safety Studies
   5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
   5.2. Study Reports of Uncontrolled Clinical Studies
   5.3. Reports of Analyses of Data from more than One Study, Including any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses
   5.4. Other Clinical Study Reports

6. Reports of Post-Marketing Experience

7. Case Report Forms and Individual Patient Listing

Sec. F List of Key Literature References

Additional Requirements:
1) Representative Sample with corresponding Certificate of Analysis
2) Risk Management Plan
3) For imported products: 
   (a) Foreign GMP Clearance
4) For Vaccines: 
   (a) List of Countries where the product is already licensed and the date of approval
(b) Names of the medical director of the importer/distributor and local manufacturer who will monitor event/s reactions and prepare appropriate report to be submitted to FDA
(c) Person/s responsible for production and control of the product (Name/s Position, Department, and sample of signature)
(d) Information on the number system of the lots or batches
(e) System for the re-processing of the product in event of rejection of the lot or batch by the manufacturer’s QA/QC
(f) Summary Lot Protocol
(g) Lot to Lot Consistency from three (3) consecutive batches
(h) Description of the cold-chain procedures employed from the origin to the port of entry and in the Philippines (how and where)

B. Renewal Application

1) Integrated Application Form
2) Periodic Safety Update Report (PSUR) and Risk Management Plan (RMP)
3) Certification that there were no changes during the 5-year period. If there were any, the summary changes made by the manufacturer for the 5-year period shall be incorporated
4) Labeling Materials (actual/commercial labels)
5) Actual commercial sample

Additional Requirements:

1) Post-marketing commitments (if any)
2) For vaccines:
   (a) Summary Lot Protocol
   (b) List of Countries where the vaccine is already licensed and date of approval
   (c) Adverse event following immunization report (Summary of Annual Reports)
3) MR/E to Initial:
   (a) Risk Management Plan (RMP)
   (b) Periodic Safety Update Report (PSUR)

Notes:

- All documentary requirements must be in PDF format to be submitted to PAIR
- Image files should be at least 150 dots per inch (dpi)
- A hard copy of the integrated application form is required
- Samples may be submitted at a later date, e.g. when the application has already been decked as indicated in the Document Tracking System
- ICH Common Technical Document format is acceptable provided that the products are approved in ICH member countries/regions