
# Harmonized EAC Medicines Registration Guidelines; Introduction & Structure/Format of Dossier

# Outline

- Introduction
- Developed and Approved Documents
- Marketing Authorization Process
- CTD Triangle
- General Issues
- MODULE 1
- MODULE 2
- Overviews & Summary
- Module 3
- Module 4
- Module 5

# Introduction (1)

## Today

- 6 National Medicines Regulatory Authorities (NMRAs) in EAC
- Lack/inadequate medicines policies and laws
- Highly variable: Regulators' capacity: Financial, HR, Institutional
- Disparity in technical requirements and formats, lack of clear guidelines
- Minimal transparency, No clear timelines
- Reference evaluations[1] underleveraged

## Future

- Harmonized medicines regulatory policies and Laws
- Stronger, institutionalized regulatory capacity & systems strengthening programs
- Single set of requirements, Clear guidelines, Fewer dossiers to prepare
- Transparent regulatory processes with clear timelines
- Resource pooling and information sharing
- Earlier approval of more essentials medicines

1. WHO prequalification, Article 58 positive opinions, stringent regulatory approval, certificate of pharmaceutical product (CPP)

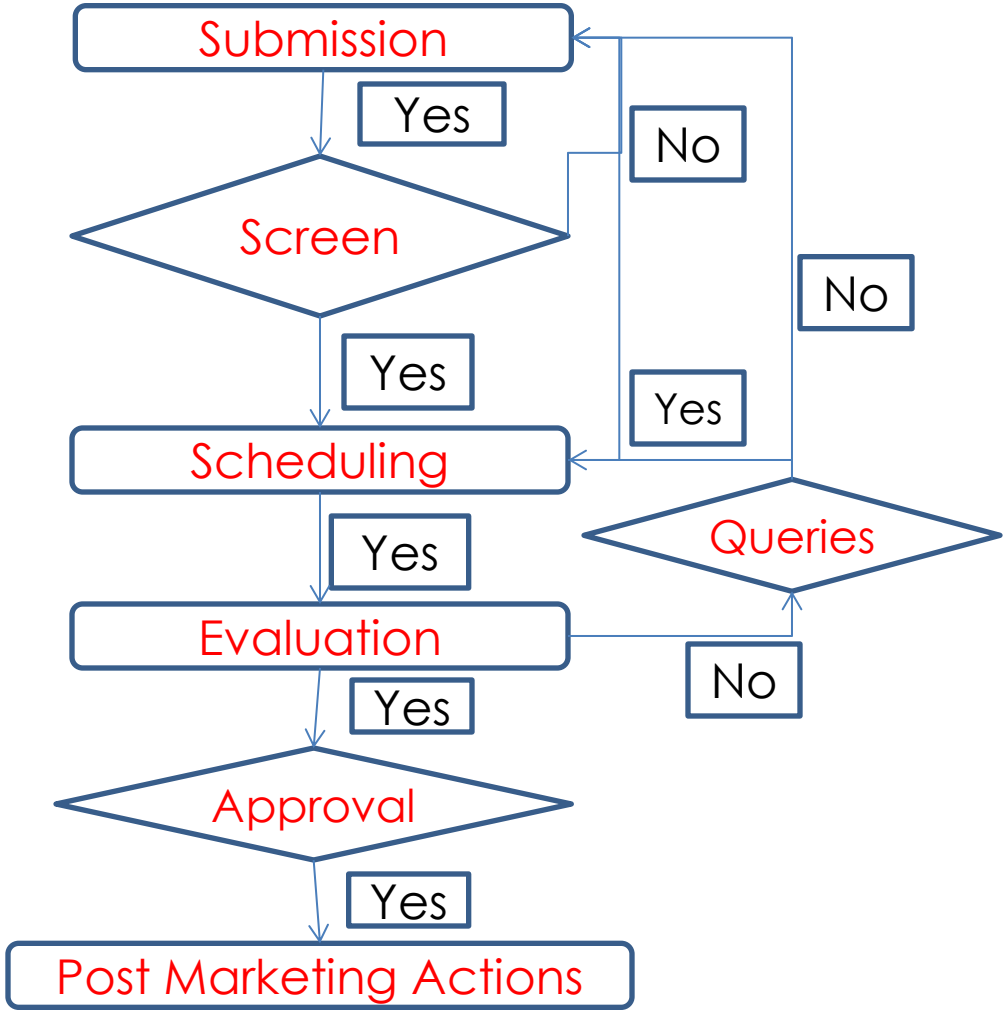
# Introduction (2)

- Based on International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – Common Technical Document, CTD
- For submission of dossiers for Registration of Medicines to the EAC-NMRA.
- **Scope**
  - Medicinal products containing APIs of synthetic or semi-synthetic origin.
  - Not covered by guidelines: Veterinary, Biological, Biotechnological and herbal products.

# Developed and Approved Documents

| Name of Document | Reference |
|---|---|
| EAC Guideline on Submission of Application for Human Medicinal Products (Main Guideline) | EAC-TF-MED-REG-PD-N1R0 |
| EAC Common Glossary of Terms | EAC-TF-MED-MER-FD-GDL-N12R0 |
| EAC List of Standard Terms used in Pharmaceutical Dosage Forms | EAC-TF-MED-MER-FD-GDL-N6R0 |
| EAC Guidelines on Procedural Aspects for Applications for Registration of Pharmaceutical Product | EAC-TF-MED-MER-FD-GDL-N7R0 |
| EAC Guideline on Stability Testing Requirements for APIs and FPPs (Talk on Stability later) | EAC-TF-MED-MER-FD-GDL-N8R0 |
| EAC Guidelines on Therapeutic Equivalence Requirements (Talk on BE later) | EAC-TF-MED-MER-FD-GDL-N5R0 |
| EAC Guideline on SmPC (Talk on Product Information later) | EAC-TF-MED-MER-FD-GDL-N9R0 |
| EAC Guidelines on PIL Requirements (Talk on Product Information later) | EAC-TF-MED-MER-FD-GDL-N10R0 |
| EAC Guideline on Labeling Requirements (Talk on Product Information later) | EAC-TF-MED-MER-FD-GDL-N11R0 |
| EAC Evaluation Guidelines for Authorization of Medicinal Product Dossier (Talk on Evaluation later) | EAC-TF-MED-MER-FD-GDL-N13R0 |

# Marketing Authorization Process




- Screening: 30 working days
- Scheduling of Dossiers on First In-First Out (FIFO) basis.
- Timeline for review and approval: within 12 mths (Normal) or 6 mths (Priority).
- EAC NMRA processing fee @ submission
- Abridged or full evaluation
- Response to Queries within 180 days for re-evaluation.
- Valid
- GMP/GCP compliance.
- Post-Marketing Activities
  - Retention, Post Market variations & Pharmacovigilance

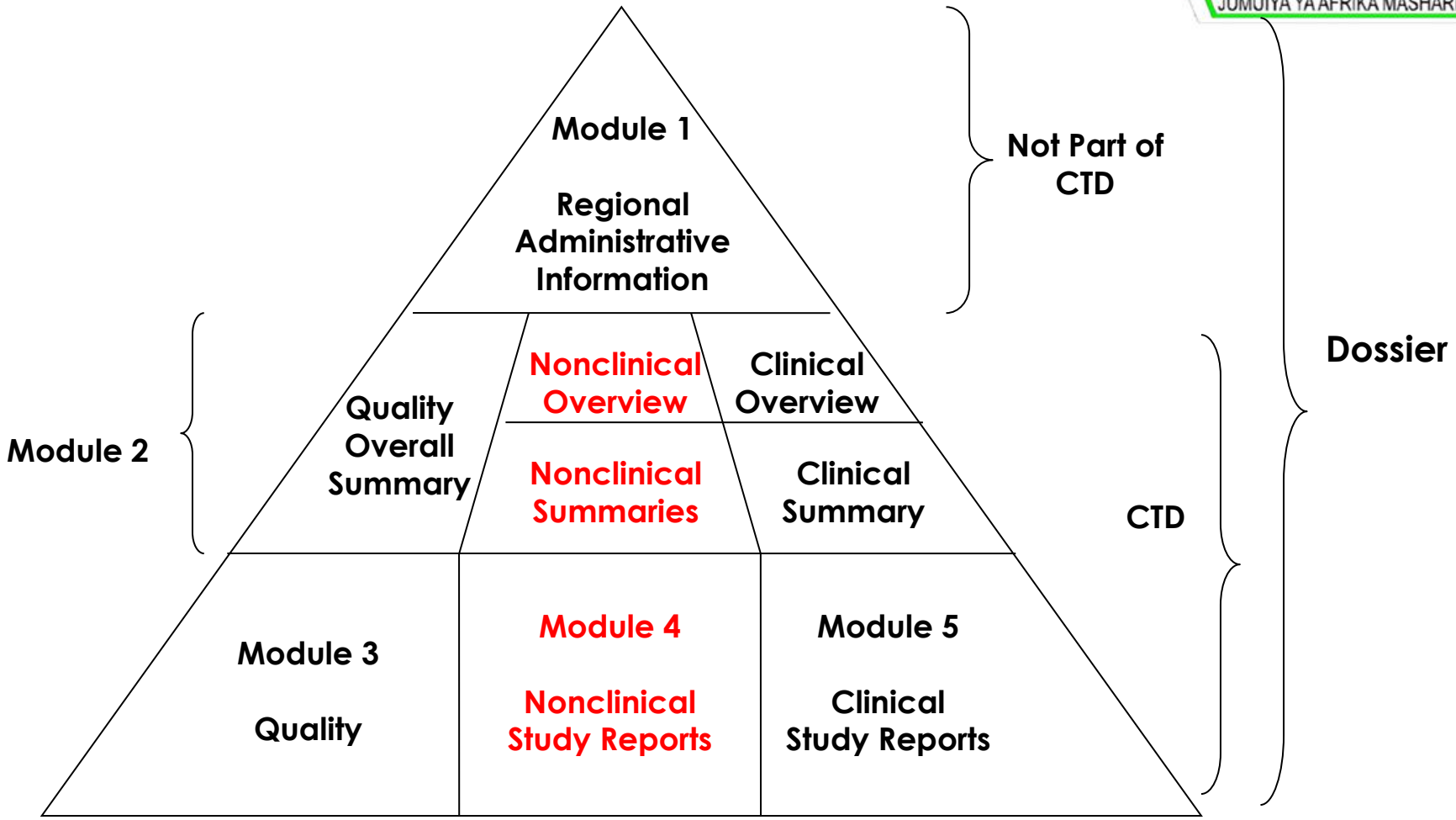
# General Issues (1)

- Official language: English.
- Provided in a single volume except annexures
- Text and tables should be prepared using margins that allow the document to be printed on A4 paper both sides NLT 600gsm (File) & 80g/$m^2$ (paper).
- The left-hand margin should be sufficiently large that information is not obscured by the method of binding.
- Font sizes for text and tables should be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text.
- Every page sequentially numbered
- Sample: For full specifications analysis plus one repeat
- Validity: 5 yrs

# General Issues (2)

- Renewal: NLT three months prior to expiry.
- Documents required:
  - Duly filled in application form for registration.
  - Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months.
  - Details of all changes during validity of the registration.
  - Sample: Full specifications analysis plus one repeat.
  - A site master file for manufacturing facilities.
  - Non refundable evaluation fee plus GMP and GCP inspection fees.

# The CTD Triangle



# General Organization

- Module 1: Administrative Information and Prescribing Information requirements.
- Module 2: Overview and Summaries, Quality, Non-clinical, and Clinical modules.
- Module 3: Quality Module
- Module 4: Non- Clinical Module: Study reports
- Module 5: Clinical Module

**Note:**

- Applicants not allowed to modify the overall organization of the document.
- Any additional data: addenda to relevant part
- Supplements: Additional expert review into relevant summary or overview.

# Module 1 (1)

- Has 12 Sections
- Application forms, certifications, Labelling
- Information for General correspondence and annexes.
- Parts include
  - Comprehensive table of contents for all modules & Module 1 (1.1 & 1.3)
  - Cover letter signed by MAH (1.2)
  - Annex II – Application form: dated, signed and stamped plus Attachments (1.4)
  - Product Information: Package inserts, labels, SmPC, PIL, Container labeling, Mock-ups and specimens - multiple strengths and/or pack sizes require one representative specimen. (1.5)

# Module 1 (2)

- Experts Information (1.6): Omitted when information in Module 2
  - Brief on educational background, training and occupational experience.
  - Expert Declarations of professional involvement with MAH: Annex III – Sample declaration form
    - Confirmation who prepared report.
    - Reports based on independent assessment of dossier
    - Provide references: any additional claims not supported by dossier.
- Copy of Certification of API (1.7):
  - Certificates of Suitability of European pharmacopoeia monographs (CEP); WHO API prequalification; WHO-APIMF; EAC-APIMF;
  - Letter of Access to CEP; WHO API prequalification; WHO-APIIMF; EAC-APIMF or from API manufacturer.

# Module 1 (3)

- Good Manufacturing Practice (GMP) Status (1.8): For all medicines, irrespective of the country of origin manufacturing facilities must comply with EAC GMP guidelines.
  - WHO-type certificate of GMP: *EAC Guidelines on Good Manufacturing Practice*.
  - GMP certificates for EAC- NMRA and/or SDRA
  - Evidence for application for GMP inspection.
- Good Clinical Practice (GCP) or Good Laboratory Practice (GLP) accreditation certificate for sites participating in the clinical studies (1.9)
- Regulatory status of product (1.10)
  - Registration status from countries with SDRAs – 1.10.1
  - Registration status in EAC Partner States – 1.10.2: Evidence of submission.
  - List of countries submitted – 1.10.3 plus dates of submission and the status of these applications - Approvals (with indications).
  - Statement on rejection, withdrawal or repeatedly deferred in the EAC Partner States – 1.10.4

# Module 1 (4)

- Manufacturing and Marketing authorization (1.12)
  - Certificate of Pharmaceutical Product in format with a valid Manufacturing Authorization for pharmaceutical production.
  - If available, evidence for prequalification of medicinal product by WHO should be submitted.
- Evidence of API and/or FPP prequalified by WHO (1.11)
- Product samples (1.15)
  - Sufficient number of samples full specification analysis plus one repeat.
  - Batch number, Manufacturing Date and Expiry Date dynamically printed on packages.
  - Restricted space: Printing on secondary packages with the primary pack having at least batch number and expiry date.

# MODULE 2

- Overall CTD Table of contents (2.1)
- CTD Introduction (2.2)
- **Quality Overall Summary (2.3):** summary of scope and outline of Module 3 – body of data.
  - Typically 40 pages, excluding tables, figures
  - Emphasize and discuss critical key quality parameters of product for integration of module 3 and other modules
  - Data or justification not included in Module 3 or in other parts of CTD not accepted.

**Recommended format:**

- 2.3: Introduction
- 2.3.S: Drug Substance
- 2.3.P: Drug Product
- 2.3.A: Appendices
- 2.3.R: Regional Information

# Overviews (1)

- Discussion:
  - Critical issues (unresolved issues, deviations or limitations in clinical and non-clinical studies).
  - Associations with quality characteristics
- Explanation why product should be marketed in EAC.
- Generic product exempted; however, in some cases such as changes in safety impurity profile, the safety assessment studies.
- Typically 30 pages

- **Non-clinical overview (2.4):** An integrated and critical overall assessment of pharmacologic, pharmacokinetic, and toxicologic evaluation
- **Recommended format:**
  - Nonclinical testing strategy (2.4.1)
  - Pharmacology (2.4.2)
  - Pharmacokinetics (2.4.3)
  - Toxicology (2.4.4)
  - Integrated overview and conclusions (2.4.5)
  - List of literature references (2.4.6)

# Overviews (2)

- **Clinical overview (2.5.):**
  - Critical summary and analysis of clinical data for efficacy and safety, and pertinent animal data or quality issues.
  - Typically 30 pages

- Recommended format:
  - Product Development Rationale (2.5.1)
  - Overview of Biopharmaceutics (2.5.2)
  - Overview of Clinical Pharmacology (2.5.3)
  - Overview of Efficacy (2.5.4)
  - Overview of Safety (2.5.5)
  - Benefits and Risks Conclusions (2.5.6)
  - Literature References (2.5.7)

# Summary (1)

- Summary: factual comparisons and analysis of results across studies
  - should not exceed about 30 pages
- **Nonclinical Written and Tabulated (2.6)**
- Generic exempted; however, in some cases such as changes in safety impurity profile, the safety assessment studies.

- Recommended format:
  - Introduction (2.6.1)
  - Written Summary of Pharmacology (2.6.2)
  - Tabulated Summary of Pharmacology (2.6.3)
  - Written Summary of Pharmacokinetics (2.6.4)
  - Tabulated Summary of Pharmacokinetics (2.6.5)
  - Written Summary of Toxicology (2.6.6)
  - Tabulated Summary of Toxicology (2.6.7)

# Summary (2)

- **Clinical Summary (2.7):**
  - Factual summary and support for conclusions and critical issues identified in clinical study
  - any meta-analyses or other cross-study analyses of full reports included in Module 5;
  - post-marketing data for marketed products in other regions.
  - Analysis of all relevant information for dosing recommendations
  - Typically 30 pages (excluding tables)

- Recommended format:
  - Biopharmaceutical Studies and Associated Analytical Methods: Generic applications (2.7.1)
  - Clinical Pharmacology Studies (2.7.2)
  - Summary of Clinical Efficacy (2.7.3)
  - Summary of Clinical Safety (2.7.4)
  - Literature References (2.7.5)
  - Synopses of Individual Studies (2.7.6)

# Module 3

| | |
|---|---|
| 3.1 | MODULE 3 TABLE OF CONTENTS |
| 3.2 | BODY OF DATA |
| 3.2.S | DRUG SUBSTANCE |
| 3.2.S.1 | General Information |
| 3.2.S.2 | Manufacture |
| 3.2.S.3 | Characterisation |
| 3.2.S.4 | Control of Drug Substance |
| 3.2.S.5 | Reference Standards or Materials |
| 3.2.S.6 | Container Closure System |
| 3.2.S.7 | Stability |

| | |
|---|---|
| 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.3 | Manufacture |
| 3.2.P.4 | Control of Excipients |
| 3.2.P.5 | Control of Drug Product |
| 3.2.P.6 | Reference Standards or Materials |
| 3.2.P.7 | Container Closure System |
| 3.2.P.8 | Stability |

# 3.2.S: Information on API

- **Option 1:** Full details in the Product Dossier (PD)
- **Option 2:** Certificate of suitability of European Pharmacopeia Monographs(CEP)
  - A complete copy of the CEP (including any annexes)
- **Option 3:** API pre-qualified by WHO
- **Option 4:** EAC Active Pharmaceutical Ingredient Master File (EAC-APIMF)
- Note:
  - Letter of Access to CEP; WHO API prequalification; WHO-APIMF; EAC-APIMF or from API manufacturer (Module 1.7 – Annex V).
  - Written commitment to inform EAC in case of CEP; WHO API prequalification; WHO-APIMF withdrawal.

# Options 2 &3: API's with CEP or prequalified by WHO

- Data summarized in QOS
  - *3.2.S.1.3 General properties* –additional applicable physicochemical properties not controlled e.g. solubilities and polymorphs.
  - *3.2.S.3.1 Elucidation of structure and other characteristics* – Identification of polymorphic form and particle size distribution not specified.
  - *3.2.S.4.1 Specification* – FPP manufacturer specifications: all tests, limits & acceptance criteria and any additional tests not controlled.
  - *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – for any tests in additional CEP; WHO API prequalification..

- *3.2.S.4.4 Batch analysis* – results from two batches of at least pilot scale by FPP manufacturer compliance to API specifications.
- *3.2.S.5 Reference standards or materials* of FPP manufacturer.
- *3.2.S.6 Container-closure system* – specifications including descriptions and identification of primary packaging components.
- *3.2.S.7 Stability* – except when the CEP or WHO specifies a re-test period and applicant maintains the same.
- Sterile APIs: API Sterilization process data, including validation data.

# Option 1 & 4: EAC-APIMF

- Require Full details of API information submitted by API manufacturer - all information listed under Module 3.2S – **Sections 3.2.S.1 through to 3.2.S.7 (see next slides)**
- Open and restricted Parts
- Responsibility FPP Manufacturer ensure submission of restricted part to directly EAC by API manufacturer.
- Copy of the letter of access in the product dossier in Module 1.

# 3.2.S.1.1 General Information

- **3.2.S.1.1 Nomenclature:** consistent with scientific literature & product labelling information
- **3.2.S.1.2 Structure, including relative and absolute stereochemistry, molecular formula and relative molecular mass**
  - APIs existing as salts: molecular mass of free base or acid
- **3.2.S.1.3 General Properties of the API(s):** Physicochemical and other relevant properties of the API.
  - Physical description, solubilities in common solvents, quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, particle size distribution, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc.

# 3.2.S.2 Manufacture of API(s)

- **3.2.S.2.1 Name and address of API(s) Manufacturer plus responsibility**
- **3.2.S.2.2: Description of Manufacturing Process and Process Controls of the API** (s) – flow diagram and sequential procedural narrative of manufacturing process. Identification & Justification of Reprocessing steps
  - **3.2.S.2.2.1:** Specifications of starting materials, reagents, solvents, catalysts, and intermediates (if isolated during the process) in the synthesis.
  - API starting material: fully characterized – Identity and purity.
- **3.2.S.2.3: Control of materials –** Listed & identified where used.
- **3.2.S.2.4:** Summary of controls performed at **critical steps of the manufacturing process and on intermediates**.
- **3.2.S.2.5: Description of process validation or Evaluation** (e.g., for aseptic processing and sterilization):
- **3.2.S.2.6:** Description & discussion of **API Manufacturing Process Development**

# 3.2.S.3: Characterization of API(s)

- **3.2.S.3.1: Elucidation of Structure and other Characteristics of the API(s)**
  - Methods: Elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), mass spectra (MS) studies, X-ray powder diffraction and differential scanning calorimetry (DSC).
  - *Isomerism/Stereochemistry*: Possible isomers resulting from manufacturing process & steps for introduction of chirality.
  - *Polymorphism*:
  - *Particle size distribution*: influence on FPP processing, stability, content uniformity, dissolution and bioavailability, specifications.

- **3.2.S.3.2 Impurities:** Identification of potential and actual impurities from the synthesis, manufacture and/or degradation
  - Reporting/Identification/Qualification Thresholds
  - Concentration Limits (ppm) for process-related impurities (e.g., residual solvents)

# 3.2.S.4: Control of Drug Substance

- **3.2.S.4.1:** API Specification: Pharmacopeial or non Pharmacopeial – API + FPP manufacturer.
- **3.2.S.4.2:** Analytical procedures for testing API.
- **3.2.S.4.3:** Analytical method Validation: Esp. for residual solvents, assay and impurity depending on route of synthesis.
  - Compendial verification & equivalency for in-house
- **3.2.S.4.4:** Batch analyses – Batch number, batch size, date and production
- **3.2.S.4.5:** Justification of specification:
  - inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc.

# 3.2.S.5 & 3.2.P.6: Reference Standards or Materials

- Reference standards or materials Information used for testing of the API/FPP in routine analysis (identification, purity, assay tests).
  - Source(s): preference – officially recognized pharmacopoeia
  - Classification: $1^0$ or $2^0$ RS
  - Full characterization (e.g. by IR, UV, NMR, MS analyses) esp. for assay less for Identification
  - $2^0$ or in-house RS established against suitable $1^0$ RS, e.g. by comparative IR
  - COA
- For FPP: Same as API plus
  - Information on reference materials of FPP degradation products, not included in API section 3.2.S.5.

# 3.2.S.6 & 3.2.P.7: Container Closure System API and FPP

- Description of CCS, including
  - Identity of construction materials for each $1^0$ packaging
  - Specifications of $1^0$:
    - Description, identification (e.g. IR) and critical dimensions with drawings.
    - For FPP: Limits for thickness or area weight for film and foil materials.
  - Non compendial methods: Validation
  - For non-functional $2^0$ packaging versus functional $2^0$ packaging components: less description in $2^0$.
  - Label copies on $2^0$ packaging: Storage conditions, name/address API /FPP manufacturer, regardless of re-labelling at any stage of distribution.
  - Suitability of CCS e.g. choice of materials, protection from moisture and light, compatibility of construction materials with API/FPP, including sorption to container and leaching, and/or safety of materials of construction.

# 3.2.S.7 & 3.2.P.8 Stability of API(s) & FPP

- Provides evidence: Quality of API/FPP varies with time under the influence of environmental factors (temperature, humidity and light) and product-related factors (interaction of API with excipients & container-closure systems).
- **3.2.S.7.1 & 3.2.P.8.1: Stability Summary and Conclusions –** Summary of study types, protocols used, study results and conclusions: storage conditions and shelf-life, and, in-use stability.
- **3.2.S.7.2 & 3.2.P.8.2: Post-approval Stability Protocol and Stability Commitment:**
- **3.2.S.7.3 & 3.2.P.8.3: Stability Data –** Results of the stability studies (e.g., forced degradation studies and stress conditions) presented in tabular, graphical, or narrative with inclusion of analytical procedures used for generation of data and validation.

# 3.2.P: FPP

- **3.2. P.1 Description and Composition of the dosage form**
- **Description**: physical description, available strengths, release mechanism (e.g. immediate, modified (delayed or extended)).

- **Composition**: List of all ingredients used in manufacturing process, amount per unit basis, function, & reference quality standards
  - All ingredients: May not added to every batch (e.g. acid and alkali), removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers).
  - Composition: active ingredient clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride").
  - All overages clearly indicated with justification.
  - Function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative). Those with multiple functions - Predominant function stated.

- **Description of accompanying reconstitution diluent(s)**: Diluent(s) information provided separately.

# 3.2.P.2 Pharmaceutical development (1)

Studies for Establishing

- Dosage form, formulation, manufacturing process and the control strategy (QRM)
- Excipients & Container-closure system – Type Selection, grade and delivery amount;
- Quality target product profile (QTPP) definition depending on route of administration, dosage form, bioavailability, strength and stability
- Microbiological attributes and usage instructions
- Identification & description of critical formulation and process attributes [critical quality attributes (CQAs)]that influence batch reproducibility & consistency, product performance and FPP quality
- Supportive data and results from specific studies or published literature.

# 3.2.P.2 Pharmaceutical development (2)

- Container Closure Suitability: For FPP
  - in direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
  - used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions and powders/granules for such);
  - used as a protective barrier to help ensure stability or sterility; and
  - Necessary to ensure FPP quality during storage and shipping.

# 3.2.P.3 Manufacture of FPP (1)

- **3.2.P.3.1:** Name, address and responsibility of each manufacturer; list of facilities involved manufacturing, packaging, labelling and testing including contractors.
  - A valid manufacturing authorization for pharmaceutical production and WHO-type certificate of GMP
- **3.2.P.3.2 Batch formula:** List of all components used in manufacturing process, amounts per batch basis, including overages, and quality standards reference.

# 3.2.P.3 Manufacture of FPP (2)

- **3.2.P.3.3 Description of manufacturing process and process controls:** Flow diagram & narrative description of steps of manufacturing process and where materials enter the process.
  - The critical steps and points for process controls, intermediate tests or final product controls are conducted should be identified.
  - Identification of type of equipment(e.g. tumble blender, in-line homogenizer) and working capacity.
  - Maximum holding time for bulk FPP: if ≥ 30 days @ submission – stability data.
  - Description of Novel processes or technologies and packaging operations affecting product quality.
- **3.2.P.3.4 Controls of critical steps and intermediates**
  - tests and acceptance criteria of critical steps identified in 3.2.P.3.3.
  - Quality and control of intermediates isolated during the process.

# 3.2.P.3 Manufacture of FPP (3)

- **3.2.P.3.5 Process validation and/or evaluation:** For critical steps in manufacturing process (e.g. sterilization process or aseptic processing or filling).
  - Product quality review may be submitted in lieu.
  - Copy of the process validation protocol specific to FPP: ID of critical equipment and process parameters and definition of testing parameters, sampling plans, analytical procedures and acceptance criteria;
  - Written commitment:
    - three consecutive, production-scale batches to subjected to *prospective validation* as per protocol.
    - Report availability for verification.
  - Validation information relating to the adequacy and efficacy of any sterilization process.

# 3.2.P.4 Control of excipients (1)

- **3.2.P.4.1 Specifications of excipients** from the FPP manufacturer, including those not done to every batch (e.g. acid and alkali), do not appear in the final FPP (e.g. solvents) and any used during manufacturing process (e.g. nitrogen, silicon for stoppers).
- ORC excipient standard: state requirements of standard with no reproduction of specifications.
- Non-compendial excipient standard: Copy of specification.
- For excipients of natural origin, require inclusion of microbial limit testing in specifications.
- For oils of plant origin (e.g. soy bean, peanut): demonstration of absence of aflatoxins or biocides.
- Colours permitted: Japanese pharmaceutical excipients, EU List of permitted food colours, & USFDA FDA Inactive ingredient guide.
- Flavours the qualitative composition and declaration regarding compliance with foodstuff regulations (e.g. USA or EU).
- Confidential Information submitted directly to the EAC by the supplier with reference to specific related product.

# 3.2.P.4 Control of excipients (2)

- **3.2.P.4.2 Analytical procedures:** used for testing excipients.
  - Copies of analytical procedures from ORC monographs not required.
- **3.2.P.4.3 Validation of analytical procedures:** used for testing excipients.
  - Copies of analytical validation information not generally submitted except when in-house methods claimed where appropriate.
- **3.2.P.4.4 Justification of specifications:** for the proposed excipient specifications, where appropriate.
  - Discussion on tests supplementary to those in ORC monograph.
- **3.2.P.4.5 Excipients of human or animal origin:** declaration for plant origin regarding adventitious agents and viral safety data for Gelatin, phosphates, stearic acid, magnesium stearate and other stearates.
- **3.2.P.4.6 Novel excipients:** Full details of manufacture, characterization and controls, with supporting safety data (nonclinical and/or clinical), according to the API and/or FPP format

# 3.2.P.5 Control of FPP (1)

- **3.2.P.5.1 Specification(s) of FPP.**
  - Copy of FPP specification(s) from FPP batch release site, dated and signed.
  - Two separate sets of specifications acceptable: after packaging of the FPP (release) and at the end of the shelf-life. Any differences between clearly indicated and justified.
- Skip testing acceptable when justified by results from five production batches for parameters such as
  - Identification of colouring materials and microbial limits.
  - Footnote on specifications, states: at minimum every tenth batch and at least one batch annually is tested. In addition, for stability- indicating parameters such as microbial limits, testing will be performed at release and shelf- life during stability studies.

# 3.2.P.5 Control of FPP (2)

- **3.2.P.5.2 Analytical procedures** used for testing the FPP.
  - Copies of in-house analytical procedures used during pharmaceutical development and for routine testing.
  - Unless modified, copies of ORC analytical procedures not required.
- **3.2.P.5.3 Validation of analytical procedures:** used for testing the FPP.
  - Copies of reports for the in-house analytical procedures during pharmaceutical development and for routine testing.
  - Compendial verification & equivalency for in-house
- **3.2.P.5.4 Batch analyses:** strength and batch number, batch size, date and site of production and use for establishing specification(s) and evaluation of consistency in manufacturing.
  - Not less than two batches of at least one commercial scale batch and two pilot scale batches.

# 3.2.P.5 Control of FPP (2)

- **3.2.P.5.5 Characterization of impurities:** if not previously provided in API Section 3.2.S.3.2 on Impurities.
  - Discussion of all impurities, potential degradation products resulting from interaction of API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

- **3.2.P.5.6 Justification of FPP specification(s):**
  - Discussion on the omission, modification, replacement or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from ORC standard(s), etc.
  - for certain tests, analytical procedures and acceptance criteria (e.g. degradation products, dissolution method development) discussed in other sections not to repeated here but require cross-reference.

# Appendices

| | |
|---|---|
| 3.2.A.1 | Facilities and Equipment |
| 3.2.A.2 | Adventitious Agents Safety Evaluation |
| 3.2.A.3 | Novel Excipients |
| 3.2.R | REGIONAL INFORMATION |
| 3.3 | LITERATURE REFERENCES |

- **3.2.R REGIONAL INFORMATION:** Production documentation: Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.

# Module 4

| | |
|---|---|
| 4.1 | MODULE 4 TABLE OF CONTENTS |
| 4.2 | STUDY REPORTS |
| 4.2.1 | Pharmacology |
| 4.2.2 | Pharmacokinetics |
| 4.2.3 | Toxicology |
| 4.3 | LITERATURE REFERENCES |

- **NON CLINICAL STUDY REPORTS:** Lists all of nonclinical study reports and gives the location of each study report in CTD
- Generally exempt for generics

# Module 5

| | |
|---|---|
| 5.1 | MODULE 5 TABLE OF CONTENTS |
| 5.2 | TABULAR LISTINGS OF ALL CLINICAL STUDIES |
| 5.3 | CLINICAL STUDY REPORTS |
| 5.3.1 | Reports of Biopharmaceutic Studies |
| 5.3.2 | Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials |
| 5.3.3 | Reports of Human Pharmacokinetic (PK) Studies |
| 5.3.4 | Reports of Human Pharmacodynamic (PD) Studies |
| 5.3.5 | Reports of Efficacy and Safety Studies |
| 5.3.6 | Reports of Post-Marketing Experience |
| 5.3.7 | Case Report Forms and Individual Patient Listings |
| 5.4 | LITERATURE REFERENCES |

- *For Generic Products:* EAC Guidelines on bioequivalence requirements and bio-wavers. **(EAC/TF-MED/MER/PD/GDL/N4R0) and** EAC Guidelines on bioanalytical method validation. **(EAC/TF-MED/MER/PD/GDL/N4R0)**

# References

- ICH Website
- WHO prequalification program presentations:
- EAC - Guidelines on Submission of Documentation For Registration Of Human Pharmaceutical Products