PREPARATION & COMPILATION OF ACTD DOSSIER (PART II QUALITY)

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REVIEW ARTICLE

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ABSTRACT

ACTD is a critical document for drug substance and produces registration in ASEAN region. The document is essentially divided into 4 parts. Each part provides information under specific head. Out of all the parts, the part II is most important. This part not only evaluates technical suitability of the product but also determines the suitability of active drug and Excipients**.**

The major stress in this part is on formulation, manufacturing, stability and process validation. The information required under this part is suitably detailed in this article.

Keywords: ASEAN, ACTD, Excipients, Compendial.

INTRODUCTION

ACTD is a dossier for marketing authorization of Pharmaceutical / Biologicals / biotechnical products in ASEAN region. It consists of 4 distinct parts named e.g. as Part1, Part 2, Part 3 and Part 4.
Part I provides admin and brief product information
Part II provides Quality related information on the drug substance and drug product. In this one section is completely devoted to QOS and another section is devoted to detailed data on drug substance and drug product
Part III nonclinical profile of the product and
Part IV provides clinical profile of the product
For generic products the most important part is Part II. The part III is virtually not required.
The part IV is required to the extent applicable to BE studies.(1)

PREPARATION & COMPILATION OF DRUG SUBSTANCE PART IN ACTD

The drug substance part is allotted code S and the subsections are listed as S1, S2 and so on. Each subsection is further divided as required.

Table 1: Preparation & Compilation of Drug Substance part in ACTD (2-3,4)

S 1.1	Provide International non–proprietary name (INN),Compendial name ,CAS No ,Chemical name(s)
S 1.2	Provide Structural formula of drug substance
S 1.3	Provide Physico-chemical description, solubility, refractive index , melting point, polymorphism, particle size, chirality of the drug substance
S 2.1	Provide manufacturer's Name and full addresses including the city and country of the manufacturer of active ingredients. Also provide Name and address of Contract manufacturers/contract analytical laboratories, if any
S 2.2	Describe the manufacturing process and process in sufficient details
S 2.3	Describe specification and test methods for raw materials, starting materials, solvents, reagents, catalysts as used in manufacturing
S 2.4	Narrate the critical steps along with their standard values and experimental findings.

	Provide the specifications and analytical procedures for the intermediates isolated during synthesis
S 2.5	Provide Process validation Plan, experimental data and final conclusion. The analytical methods used for validations may be cross referenced / provided suitably
S 2.6	Provide process development details
S 3.1	Describe Confirmation of structure based on synthetic route and spectral studies. Also include Information on isomerism and polymorphism if applicable.
S 3.2	Provide information on general impurities and related products
S 4.1	Provide detailed specification, tests and acceptance criteria for the drug substance. Compendia specifications are adequate. Indicate clearly whether the drug substance is purchased based on specification with a certificate of analysis, or tested by applicant. Indicate if any additional specification are applied
S 4.2	Provide the analytical procedure used for testing the drug substance should be provided in sufficient detail to enable reproducible testing by another laboratory. As far as possible the substance shall be tested as per Compendial methods. However, if the method used is out of compendia the sufficient information on the same shall be provided from the supplier.
S 4.3	Provide experimental data for the validation of analytical procedure used for testing the drug substance. Cover validation parameters such as specificity, precision, repeatability, reproducibility, accuracy, linearity, range, limit of quantitation, limit of detection, robustness and system suitability.
S 4.4	Provide COA of three batches
S 4.5	Provide justification of specifications if the same are different to those detailed in Pharmacopoeia.
S 5	Provide the source and control No of Primary and secondary Reference standard used for analysis
S 6	Describe the identity of materials of construction of, dimensions, drawings, functional characteristics, test methods for primary packaging materials. Provide only a brief description for non-functional secondary packaging components. Discuss where necessary sorption ,leachability and safety Discuss the suitability functional secondary packaging components so as to cover their choice, physical characteristics, compatibility with primary packaging materials
S 7	Provide summary of stability studies conducted, protocols used and the results and conclusions. Describe the forced degradation studies conducted under stress conditions such as high temperature, humidity and hydrogen ion concentrations. , Provide conclusions with respect to storage conditions and retest date or shelf-life, as appropriate. Detail Post-approval Stability Protocol and Stability Commitment Provide Results of the stability studies in tabular/graphical. Provide Information on the analytical procedures used and their technical validity Provide this information from Manufacturer or from your own studies carried on the material.

PREPARATION & COMPILATION OF DRUG PRODUCT PART IN ACTD (3-4,5)

The drug product part is allotted code P and the subsections are listed as P1, P2 and so on. Each subsection is further divided as required**.**

Table 2: Preparation & Compilation of Drug Product part in ACTD

P 1	Provide description of the drug product and its composition. Check that the composition includes list of all components of the dosage form, and their dosage on a per-unit basis (including overages, if any). Further indicate function of each component and its quality standards Specify the composition of any diluents required for reconstitution before use. Also indicate the Type of container and closure used for the dosage form
P 2.1	Provide information and data on the development of the dosage form under following heads: The composition development Process development Analytical method development The container closure system development Assignment of final specification, microbiological attributes and usages Assignment of stability and retest period.
P 2.2.1	Provide specifications for Active ingredients. Discuss special characteristics such Water content, solubility, particle size distribution, polymorphism and chirality if applicable
P 2.2.2	Provide the specifications for Excipients. Discuss special characteristics such Water content, solubility, particle size distribution if applicable
P 2.3.1	Discuss the development of the final product with special reference to Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g., bioequivalence)
P 2.3.2	Discuss if overages are included in the dosage form.
P 2.3.3	Discuss the physiochemical and biological properties of dosage form
P 2.4	Discuss the development of final manufacturing process. Provide details on the pivotal batches and validation of three initial batches.
P 2.5	Discuss the selection of the container closure system used for packaging, storage and shipping. The discussion shall cover choice of materials, protection from moisture and light, compatibility, accuracy of delivery
P 2.6	If appropriate discuss microbiological attributes of the dosage form. If microbial studies are not performed discuss the rationale for the same. Discuss the selection and effectiveness of preservatives systems used. Address the integrity of the container closure system to prevent microbial contamination in case of sterile products
P 2.7	The compatibility of the drug product or reconstitution diluents(s) or dosage devices, e.g. precipitation of drug substance in solution, sorption on injection vessels and stability should be addressed to provide appropriate and supportive information for the labeling.

	Literature data are acceptable
P 3.1	Provide the batch formula with name and quantities of all ingredients (active and otherwise) including substance(s) which are removed in the course of manufacture should be included: State the actual quantities (g, Kg, Liters) etc. of all ingredient. State the reason for including the overage State the State total number of dosage unit per batch. Provide description of all stages involved in the manufacturing of the product
P 3.2	Provide flow diagram giving the steps of the process and showing where materials enter the process. Identify and narrate the critical steps and points at which process controls, intermediate tests or final product controls are conducted. Describe the manufacturing process in sufficient details to cover the essential point of each stage of manufacture. For sterile product describe preparation and sterilization of components in detail.
P 3.3	Provide Tests, acceptance criteria and test results for critical steps. Provide information on the quality and control of intermediates isolated during the process
P 3.4	Provide the protocol and results of validation studies
P 4.1	The specification for the Excipients should be provided.
P 4.2	Provide analytical procedure used for the testing of critical Excipients i.e. substances which affect stability and bioavailability of finished product (e.g. preservative, buffer components, dissolution enhancer, and stabilizer) should be provided.
P 4.3.	Provide list of Excipients from human or animal origin separately, if any. (Provide information of sources ,specifications, description and safety data of Gelatin, enzyme, or any such materials)
P 4.4	Provide full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical or clinical) for Excipients used for the first time in a drug product or by a new route of administration,
P 5	Provide summary of the analytical procedure. Provide validation of methods for impurity profiling and assay
P 5.1	Provide the specifications for the finished product
P 5.2	Provide the analytical procedures used for the testing the finished product should be provided.
P 5.3	Provide protocol and experimental data for the verification of analytical procedures use for the testing the finished product. Provide AMV for non-Compendial methods
P 5.4	Provide Batch analyses results of 3 commercial batches.
P.5.5	Provide results of characterization and assay of Compendial and non Compendial impurities.
P 5.6	Justification for Compendial products is not necessary. However, if there is some addition or deletion in Compendial specifications, the same shall be justified.
P 6	Detail the reference standard/working standard used for product analysis. Provide

	relevant COA
P 7	Describe the container closure systems. Please note that test for identity for polymeric materials is quite essential. The specifications should include description critical dimensions and drawings as appropriate. For non-functional secondary packaging components provide only a brief description. For functional secondary packaging components, provide additional technical information
P 8	Provide summary and conclusions of stability studies Provide The post-approval stability protocol and stability commitment, Provide stability data in tabular form
P 9	Provide remarks on Product interchangeability

Additional Guidelines

The designing of ACTD Quality Part is not as easy as it looks. The ASEAN region requires proper information strictly as per the index based on actual experimentation. Data fraud is strongly discouraged. The incomplete, unwanted, falsified information is not entertained for registration. The last but not least the information need to be presented in easily readable format with proper margins, font size and font type.

CONCLUSION

For the marketing authorization of the drug products ACTD the technical documents subdivided 4 parts is essential. The part 2 is a very critical part of the submission. The information on both the drug substance part and the drug product part shall be included in this part as detailed above.

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CONFLICT OF INTEREST

Author declares that there are no conflict of interest.

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