Central Administration for Pharmaceutical Products
General Administration of Human Pharmaceuticals Registration
Administration of Technical Affairs for Human Pharmaceuticals

Notice to Applicant

Guidance on Quality Module File

Most Common Deficiencies

Year 2022

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- **Scope:**

  This guidance applies for any human pharmaceutical product submitted for evaluation of CTD Quality Module according to different Ministerial decrees and Technical committee decisions.

- **Objective:**

  This guidance aims to provide applicants with the most common deficiencies and requirements on documents and information required for preparation and submission of the CTD Quality Module for human pharmaceutical products submitted according to different ministerial decrees and technical committee decisions.

  Reviewing this document could help the applicant to minimize the number of rejected applications within the acceptance review process and also minimize the number of comments and enquiries after technical assessment of the quality module, which results in enhancing and fastening the process of review for the submitted quality module.

MODULE 3	Item	Common Deficiencies
3.1	**Table of contents of module 3**	
3.2	**BODY OF DATA**	
3.2.S Drug substance - Active Pharmaceutical Ingredient (API) (S part)		
3.2.S.1	**General information**	
3.2.S.1.1	**Nomenclature**	▪ Chemical name and IUPAC name are not submitted ▪ Incorrect CAS number
3.2.S.1.2	**Structure**	▪ Drawing structure doesn't show chiral center ▪ Relative molecular mass for hydrated form is missing
3.2.S.1.3	**General Properties**	▪ Aqueous Solubility in Different pHs is not Discussed ▪ Solubility in Different Organic Solvents is not Discussed ▪ Particle size distribution for low soluble API is not discussed ▪ Hygroscopicity is not discussed ▪ Polymorphism for low soluble API is not discussed
3.2.S.2	**Manufacture**	
3.2.S.2.1	**Manufacturer(s)**	▪ Absence of discussion for the responsibility of each manufacturer involved in the manufacturing process of the API.

3.2.S.2.2	**Description of Manufacturing Process and Process Controls**	▪ Flow diagram of the synthetic process(es) is not describing all the manufacturing steps and critical process parameters.
3.2.S.2.3	**Control of Materials**	▪ Absence of control of all raw materials. ▪ Details concerning API starting materials preparation is insufficient or missed. ▪ Specification of starting material is missing important test "e.g. Purity, Related Substance …"
3.2.S.2.4	**Controls of Critical Steps and Intermediates**	
3.2.S.2.5	**Process Validation and/or Evaluation**	▪ Process Validation of API aseptic processing and sterilization is not submitted.
3.2.S.2.6	**Manufacturing Process Development**	▪ Manufacturing process development is not submitted.
3.2.S.3	**Characterization**	
3.2.S.3.1	**Elucidation of Structure and other Characteristics**	▪ Not all Essential Techniques are performed. ▪ Chromatograms, spectrum or thermograms are not Clear. ▪ Absence of Interpretation table. ▪ Enumerated Structure for NMR is not submitted. ▪ Zooming Spectrum for NMR is not submitted.
3.2.S.3.2	**Impurities**	▪ Potential impurities are not discussed, especially for non pharmacopieal API. ▪ Excluding identified impurities specified in an official compendial monograph and are not controlled by the proposed routine in-house analytical procedure <u>without Justification.</u> ▪ Setting Acceptance criteria for impurities exceeding ICH Q3A guideline Acceptance criteria <u>without justification.</u> ▪ Carry over impurities from starting material are not discussed. ▪ Elemental impurities and Genotoxic impurities Risk assessment are missing. ▪ Residual solvent risk assessment for solvents used early in manufacturing process and aren't controlled in the specifications. ▪ Risk assessment for benzene as impurity in solvents is missing.
3.2.S.4	**Control of Drug Substance**	

3.2.S.4.1	**Specification**	▪ Absence of one of the universal tests (e.g. description, identification, assay and impurities). ▪ Absence of reference column with the number of general chapters in case of pharmacopeial methods. ▪ Absence of FPP manufacturer's specifications (used in routine testing of API). ▪ Usage of one single chromatographic retention time procedure for identification test.
3.2.S.4.2	**Analytical Procedures**	▪ Absence of analytical procedures for one test or more.
3.2.S.4.3	**Validation of Analytical Procedures**	▪ Absence of verification report for compendial methods. ▪ Absence of validation report for one test or more. ▪ Absence of chromatograms (Specificity, Forced degradation & system suitability).
3.2.S.4.4	**Batch Analyses**	▪ Recent batch analyses of at least two batches are not submitted. ▪ Discrepancy between specifications in section S.4.1 & S.4.4. ▪ Absence of batch number, size, date, type and production site.
3.2.S.4.5	**Justification of Specification**	▪ Absence of justification for some test (e.g. limit of impurity & limit of residual solvents). ▪ Absence of justification for non-routine testing.
3.2.S.5	**Reference Standards or Materials**	▪ Absence of COA of working standard of API. ▪ Absence of legible copies of the IR of the primary and secondary reference standards run concomitantly. ▪ Absence of structural elucidation for the batch of the API which has been fully characterized to be used as primary standard. ▪ Absence of discussion of impurities reference standards.
3.2.S.6	**Container Closure System**	▪ Incomplete description of Packaging materials. ▪ Incomplete specifications of container closure system. ▪ Absence of Identification spectrum (IR) of reference and test packaging materials. ▪ Data or explanation about the suitability of selection of the immediate packaging materials. ▪ Absence of COA of packaging materials.
3.2.S.7	**Stability**	
3.2.S.7.1	**Stability Summary and Conclusions**	▪ Absence of detailed description of Stability conclusion (storage conditions). ▪ In complete data for stability protocol (type of batch, batch size, containers, date of stability starting time, period cover with stability data…etc). ▪ Absence of Summary of stability results.

3.2.S.7.2	**Post-approval Stability Protocol and Stability Commitment**	▪ Absence of Commitment letters.
3.2.S.7.3	**Stability Data**	▪ Absence of Up-to-date stability results and update the summary of stability. ▪ Absence of the ongoing stability study for the recent batches. ▪ Absence of forced degradation study and chromatograms.

In case of Option 2: Certificate of suitability of the European Pharmacopoeia (CEP);

- CEP is withdrawn or suspended.
- CEP does not contain all the annexes (Manufacturer – Analytical procedures of any additional tests not specified in the European Monograph…)
- Box of authorization in the CEP is not filled or signed by the CEP holder.
- Absence of the acknowledgement commitment letter by the applicant to EDA in case of CEP withdrawal or updates.
- Absence of required sections of the S-Part (not covered by CEP),

Example:

- Absence of 3.2.S.6 (Container Closure System) (when CEP is not including the description of Container Closure System)
- Absence of stability data (when CEP is not including retest period).

- Specifying a different reference quality standard for the API other than the European Pharmacopeia (ex: USP, In-House).
- Absence of the API Specifications.
- Absence of Batch Analysis for 2 API batches. (at least).

3.2.P Drug product (P part)		
3.2. P.1	**Description and Composition of the Drug Product**	▪ Reference quality standard of API not comply with S-Part. ▪ Grades of excipients not declared. ▪ The equivalence of API is not stated or incorrect. ▪ Note for potency of API not specified. ▪ Overage of API is not specified. ▪ Note for ingredients removed during manufacturing process is not mentioned. ▪ Absence of Composition of capsule shell or coating materials used. ▪ Difference between composition in Q.F and any approval containing composition or CPP.
3.2. P.2	**Pharmaceutical Development**	▪ The Innovator or reference product is not mentioned. ▪ Quality Target Product Profile , Critical Quality Attributes and Critical Process Parameters are not identified.
3.2.P.2.1	**Components of the Drug Product**	

3.2.P.2.1.1	**Drug Substance**	▪ In case of using excipient(s) not mentioned in the composition of Innovator or reference product, a compatibility study between API and excipients is missing.
3.2.P.2.1.2	**Excipients**	
3.2.P.2.2	**Finished pharmaceutical product**	
3.2.P.2.2.1	**Formulation Development**	▪ Absence of comparison with the reference product or not enough data and studies concerning the details of formulation development.
3.2.P.2.2.2	**Overages**	▪ Absence of justification for addition of overage specifying all the steps "where the loss occurs" during manufacturing.
3.2.P.2.2.3	**Physicochemical and Biological Properties**	
3.2.P.2.3	**Manufacturing Process Development**	▪ Absence of justification for selection of sterilization process.
3.2.P.2.4	**Container Closure System**	
3.2.P.2.5	**Microbiological Attributes (name, dosage form)**	
3.2.P.2.6	**Compatibility**	▪ Absence of compatibility with diluent, medical devices (not API – excipient) if it not mentioned in the stability.
3.2.P.3	**Manufacture**	
3.2.P.3.1	**Manufacturer(s)**	▪ Absence of discussion for the responsibility of each manufacturer involved in the manufacturing process of the FPP. ▪ For Imported products: Manufactures in this section are different than that in the CPP.
3.2.P.3.2	**Batch Formula**	▪ A batch formula is not covering all commercial batch sizes or not including overage and overfills if applicable. ▪ Batch formula not including potency calculation.
3.2.P.3.3	**Description of Manufacturing Process and Process Controls**	▪ Flow diagram of manufacturing process is not included or is not describing all the manufacturing steps and critical process parameters. ▪ Holding time is not specified and supportive stability data is not submitted. ▪ Absence of precautions and storage requirements during manufacture or transfer between different manufacturing sites.

3.2.P.3.4	**Controls of Critical Steps and Intermediates**	▪ Discussion of critical process parameters are not included.
3.2.P.3.5	**Process Validation and/or Evaluation**	▪ Absence of Process Validation on 3 primary batches. (If applicable) ▪ Process validation of all batch sizes is missing.
3.2.P.4	**Control of Excipients**	
3.2.P.4.1	**Specifications**	▪ Absence of specifications of the in-house excipients.
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**	▪ Absence of TSE &BSE certificates for 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	**Specification(s)**	▪ Absence of reference column with the number of general chapters in case of pharmacopeial methods. ▪ Absence of one of the universal tests (e.g. description, identification, assay and impurities). ▪ Usage of one single chromatographic retention time procedure for identification test. ▪ Amount of dissolved active “Q” is missing in the acceptance criteria of dissolution test.
3.2.P.5.2	**Analytical Procedures**	▪ Absence of in-house analytical method.
3.2.P.5.3	**Validation of Analytical Procedures**	▪ Absence of validation for the in-house analytical methods. ▪ Absence of the validation chromatograms.

3.2.P.5.4	**Batch Analyses**	▪ Absence of batch description (size, strength, number, date, site and type). ▪ Submission of only one batch while it should be at least 2 batches. ▪ In quantitative tests, results are written as "Conform" instead of numerical value. ▪ Discrepancy between specifications in section P.5.1 & P.5.4. ▪ The submitted batch analysis are not recent.
3.2.P.5.5	**Characterization of Impurities**	▪ Absence of elemental impurity risk assessment. ▪ Absence of Information on impurities arising as degradation product or synthetic impurities (source, structure and how to control (limit)
3.2.P.5.6	**Justification of Specification(s)**	▪ Absence of justification for some test (e.g. limit of impurity, non-routine tests).
3.2.P.6	**Reference Standards or Materials**	▪ Absence of Lot number In case of using primary RS ▪ Absence of COA of working RS, Lot number of the primary RS that was standardized against it and IR of the primary RS and secondary RS run concomitantly in case of using working RS .
3.2.P.7	**Container Closure System**	▪ Incomplete description of Packaging materials. ▪ Incomplete specifications of container closure system. ▪ Absence of Identification spectrum (IR) of reference and test packaging materials. ▪ Absence of Data or explanation about the suitability of selection of the immediate packaging materials. ▪ Absence of COA of packaging materials.
3.2.P.8	**Stability**	
3.2.P.8.1	**Stability Summary and Conclusion**	▪ Absence of Summary of stability results. ▪ Absence of detailed description of Stability conclusion (storage conditions). ▪ In complete data for stability protocol (type of batch, batch size, containers, date of stability starting time, period cover with stability data…etc). ▪ Absence of Summary of stability results. ▪ Absence of photo stability study.
3.2.P.8.2	**Post-approval Stability Protocol and Stability Commitment**	▪ Absence of Commitment letters.
3.2.P.8.3	**Stability Data**	▪ Absence of Up to date stability results ▪ Absence of the ongoing stability study for the recent batches. ▪ Absence of in use stability study.
3.2.A Appendices		

3.2.A.1	**Facilities and Equipment**(Not Applicable)	
3.2.A.2	**Adventitious Agents Safety Evaluation**	
3.2.A.3	**Novel Excipients**	
3.2.R Regional Information		
3.2.R.1	**Production documents**	
3.2.R.1.1	**Executed production documents**	▪ Absence of the production batch record of the manufactured three batches
3.2.R.1.2	**Master production documents**	
3.2.R.2	**Analytical Procedures and Validation information**	
3.3 Literature References		
3.3	**Literature References**	