PREPARATION AND REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROL (CMC) SECTIONS OF CTD DOSSIER FOR MARKETING AUTHORIZATION

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REVIEW ARTICLE

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ABSTRACT

The present article summarizes & simplify the marketing application requirements i.e. the critical aspects of marketing application in different CTD using countries, Process to prepare and review the requirements for CMC section (Chemistry manufacturing & Control) for filing an application in regulated market. Study shows the compilation of dossier as per CTD format with minimum errors during filing. The focus is on the application filing & Query part that may come after submission & during approval process. So one has to focus on the requirements of dossiers with minimal queries & study the probable queries that may arise after filing an application to regulated countries. Once approved, the applicant can market the safe, effective, stable & quality generic drug product with low cost to the public. The complete marketing application is based as per CTD format gives understanding of critical aspects of Marketing Application and better understanding of dossier filing.

Keywords: CTD, CMC, Module, ICH, Dossier, Active Pharmaceutical Ingredients (API), Certificate of Analysis (COA).

INTRODUCTION (1)

CTD Triangle: CTD triangle is set of documents contain the information about product's manufacturer detail, known as administrative information, product's quality details in brief, Non-clinical and clinical study reports and summary of all this data which are submitted to regulatory agency by applicant for manufacturing, marketing or sell in the respective country.

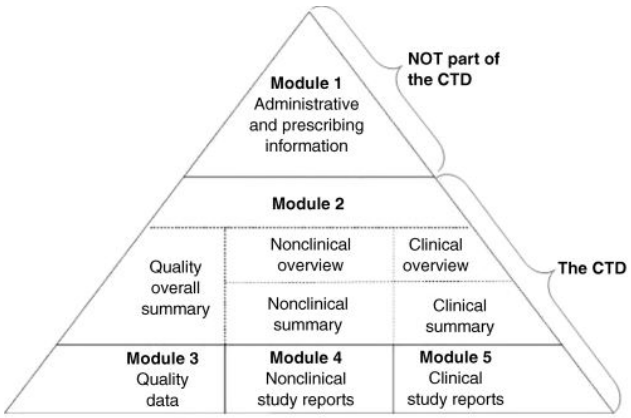

Figure 1: CTD Triangle

The full form of CTD is Common Technical Document (CTD). It is organized into five modules:

Module 1: Administrative section (not a part of CTD)

Module 2: Quality Overall Summaries

Module 3: Quality

Module 4: Non-Clinical Study reports

Module 5: Clinical Study reports

This CTD format mainly used for the registration of pharmaceutical quality product in various ICH harmonized country like **USA, Europe and Japan**. This CTD documents are submitted to the regulatory agency of this country as per their countries guideline. In this CTD format main focus is to harmonizing the quality information mainly includes **Chemistry Manufacturing and Control (CMC)** which is submitted in an application format.

Chemistry Manufacturing and Control (CMC) (2, 3)

CMC information in dossier is detailed and an important section which support clinical trial as well as marketing applications. This section must update during the drug development and study.

C: Chemistry means Composition of drug product

M: Manufacturing means how we make the product/ formulation

C: Controls means ensures whether products meet their predetermined specification/quality attribute.

ICH guidelines gives general idea about CMC but there lack of exact content of guidance documents.

Content depends upon the type of product like if it pharmaceutical, biological, Biosimilars, generics or vaccines.

Details of the sections depend upon the type of the product and countries specific requirements. If it is Pharma product than it contains least content and it is well described/ characterized.

In ICH all guidance documents are described in detail about CMC. The required format, data and content are also given in ICH.

Importance of CMC Section in CTD Dossier (2, 3)

- For any marketing application or clinical trials CMC (chemistry, manufacturing and controls) section is a very important and detailed section.
- If the manufacturing process cannot be shown to its highest quality standard and do not satisfied the regulators need as well as product have not their quality standard as mentioned in Pharmacopoeia than it might be chance to drug may lost the marketing approval.
- So it is important to show the standard quality process and parameter of drug manufacturing details and other parameter cover in module 3 Quality contain Chemistry, manufacturing and Control.
- The chemistry, manufacturing and controls (CMC) section is a very important part of any clinical trial or marketing application. Drugs can be denied marketing approval if the quality of the product and the manufacturing process cannot be shown to be of a sufficiently high standard to satisfy regulators.
- The ICH guideline Q1A(R2) (Stability Testing of New Drug Substances and Products) defines the stability data package required for new drug substances and products submitted for approval in each of the major regions that accept the ICH guidelines (i.e., US, Japan and EU).

DOSSIER TECHNICAL SECTION COMPILATION

One has to save time during product approval; process during filing an application & to get rid from unnecessary queries that may lengthen the approval process Therefore one has to focus on the probable queries that may arise after submission of marketing application. Once approved, the applicant may manufacture and market the generic drug product to provide safe, effective and stable & quality product with low cost to the public. The queries of CMC section compiled in CTD format as per ICH guideline: "The Common Technical Document for the Registration of Pharmaceuticals for Human Use [M4Q (R1)] which gives good understanding of critical aspects of marketing application in ICH harmonized countries like US, Europe and Japan and their market requirements.

MODULE 3: QUALITY (4, 5)

3.2 Body of Data

3.2. S DRUG SUBSTANCE

3.2. S.1 General Information

3.2. S.1.1: Nomenclature

Section Queries:

1. USAN, BAN, IUPAC, names, CAS not provided

3.2. S.1.2: Structure

Section Queries:

1. Stereochemistry, Isomerism structure and discussion on the drug substance used in formulation is absent.

3.2. S.1.3: General Properties

Section Queries:

1. In the presentation, nature of drug is not discussed. Drug known to be a polymorphic in nature.
2. Polymorphism and chirality is not mentioned adequately.
3. The physical constants such as solubility in organic solvent, water, buffers at different pH values are poorly described.
4. Existence/absence of polymorphism and chirality is not discussed.
5. Particle size distribution, Hygroscopicity, granularity, flowability etc. not described in detail.
6. A description on solubility based on different pH buffers (pH 1.2, 4.6 & 6.8) not provided.
7. pKa value not included in section.

3.2. S.2: Manufacture

3.2. S.2.1: Manufacturer(s)

Section Queries:

1. Though Active Pharmaceutical Ingredients (API) is manufactured from two different manufacturers. Name and complete contact details of each API-Vendor are not given.
2. Good manufacturing practice (cGMP) certificate which given from an authorized regulatory body is necessary to be submitted for API manufacturer.

3.2. S.2.2: Description of Manufacturing Process & Process Controls

Section Quarries:

1. In the API synthesis full details of the reactions steps used is not described. The API purification steps are not provided. The specifications of reagents, starting materials, intermediates, catalysts, and solvents used in the reaction are not fully described.
2. In case of Advanced Intermediate the Chemistry of the same not included.
3. Route of manufacturing, brief process and reaction scheme details are not given.
4. Intermediates formed during the reaction (synthesis), starting materials, solvents and reagents specifications are confusing and incomplete.
5. By two different route of synthesis the final product is manufactured. Though no consideration has been given to each route of the impurity profiling of the drug product.
6. In the synthesis of the Drug substance and product most unsafe chemicals Cyanide is used. On the other hand route of synthesis may be changed but the same requires substitution with another secure chemical/reagent.
7. The synthesis of the API involves many stages. But no one is mentioned about residual impurities come from starting materials and also from intermediates which are formed during the synthesis reaction
8. The starting materials resource not disclosed.
9. The starting materials involve harmful and lethal reagents in route of synthesis.

3.2. S.2.3: Control of Materials

Section Queries:

1. The residual metals from the reaction procedure are poorly addressed.
2. The raw materials, reagents, intermediates and solvents used in the process are not described properly for possible impurities.

3.2. S.2.4: Control of Critical Steps & Intermediates

1. The Control of Materials not complemented by the supplier & the In-house Certificate of analysis.
2. Critical Steps not checked with the Process Development report & are not co-related. Further a proper justification should be in place for classifying them as Critical (this information must be present in the Development report)

3.2. S.2.5: Process Validation and/or Evaluation

Section Queries:

1. During process validation three consecutive batches must be provided.

2. Three different batches are performed for stability study not performed on Process Validation.
3. Process Validation Protocol (PVP) & Report has to be co-related with the Batch manufacturing Records & must be verified for all in-process & critical parameters. Critical parameters should be captured in the PVP & must be connected to the Development Report.
4. In process validation three different batch sizes are used as batch analysis.

3.2. S.2.6: Manufacturing Process Development

Section Queries:

1. Particle size distributions, Hygroscopicity, granularity, flowability, etc. are not described in brief.
2. PDR (Pharmaceutical development reports) are not complete.

3.2. S.3: Characterization

3.2. S.3.1: Elucidation of Structure and other Characteristics

Section Queries:

1. Proper scientific information should be provided for the Polymorphism & Identification of Stereochemistry of the Active Ingredient amongst other spectral studies. (For e.g. IR, UV, NMR, Mass, DSC, XRD etc.)
2. The spectral data such as NMR, X-ray Diffraction, Elemental Analysis and IR as a means for evidence of chemical structure is missing.
3. In the presentation nature of API is not discussed while drug known to be polymorphic in nature.
4. Polymorphism and chirality are not properly addressed.
5. For Drug substance spectral graphs for UV Spectra, NMR & IR studies performed are unacceptable and interpretation of the studies is inadequate.
6. The API exhibits polymorphism which can potentially affect the quality and efficacy of the finished product. Based on the provided information, the API has three polymorphic form of A, B &C type. Polymorph C is the acceptable one due to sufficient solubility to ensure optimal bioavailability. However, the specification does not consider inclusion of polymorphic forms, as it has critical quality attributes to the finished product. It is assumed that the FPP manufacturer should have a protocol and mechanism of verification to ensure the consistent supply of the desired polymorphic form. However, nothing is said on this important issue either on the pharmaceutical development data or on the process validation. Provide the precautions and testing procedures undertaken to confirm consistent the supply of the right polymorph. In addition, provide the conditions that lead the interconversion of the polymorphs. Furthermore, the precautions that is taken during the manufacture of the finished product to prevent interconversion among the polymorphs at the FPP manufacturing conditions. (Wet granulation, drying, blending and compression).

3.2. S.3.2: Impurities

Section Queries:

1. Apart from the normal Process impurities, Residual Solvents & Degradation impurities, impurities due to the Starting material should be included in the write up.
2. The impurities must be also appropriately captured in the Specification of the Final Product.
3. However toluene is used as solvent in the synthesis but not tested the same for presence of residual benzene.
4. The product from each source impurity profiling is not given.
5. In the synthesis process residual solvent levels are exceeding the Pharmacopoeias limit.
6. The lot number, source and purity of the impurity standards are not described.
7. Potential impurities are not described in the impurity profile.
8. For the impurities measurement methods are used are not qualified.
9. The Finished product manufacturer needs to have a mechanism for controlling impurities, and residual solvents and should include in its own API specification. However, such information is not considered and provided

in the API part of the submitted dossier. This may imply that you are directly accepting the API manufacturer's specification and certificate of analysis (COA) without verification. Please clarify and justify this issue against the guideline.

10. In the synthesis raw materials and intermediates are used. Their specifications of are not described. Although hazardous reagents and inorganic toxic substances are used in the reaction but the same residual limits are not given.
11. Benzene is class I solvent used in the synthesis of the drug substance and products. The residual limits for class I solvent are not described tested at any point.
12. The source of raw materials is not disclosed.
13. The unknown impurities present in the API are more than ICH limits.
14. For certain basic substance where no specific HPLC method for analysis of API basic in nature is available on specific methods such as Non aqueous titration by Perchloric acid is permitted by FDA. However, in such cases the impurities must by analysed by HPLC/GC.
15. All known impurities, Single unknown & total impurities needs to control.

3.2. S.4: Control of Drug Substance

3.2. S.4.1: Specification

Section Queries:

1. API specifications lack attributes additional to compendia monograph, e.g. residual solvents, particle size distribution, chirality, polymorphism, crystal structure.
2. The quality of the APIs meet only the requirements of specific monographs but does not meet to specifications described in the general monographs of a pharmacopoeia.
3. The specific test for the control chirality of the drug substance is not provided.
4. The quality of the APIs meets only the requirements of specific monographs but does not meet to specifications described in the general monographs of a pharmacopoeia.
5. An XRD test is a must should the molecule exhibit a polymorph.
6. Catalyst if any used in the synthesis of the API may be controlled (not necessary if absence in 3 batches shown)
7. Residual Solvents needs to be included. Benzene is class I solvent used in synthesis of the drug products. These solvents limits are not described.

3.2. S.4.2: Analytical Procedures

Section Queries:

1. Assay & Related substances will have to have a Stability indicating method (although the compendia method may be titration/TLC etc.)
2. The method reference (compendia/ in house) should be included in the specification page of the DMF.
3. In the product chiral impurities are present. The part assay process is insufficient to control chiral impurities.
4. The Limit of Quantification (LOQ) and the limit of detection (LOD) are not provided for GC and HPLC methods used to control residual solvents and impurities in the Drug substance.
5. The HPLC method employed for assay of the impurities and API is similar. From method validation data it has been observed that the method is inadequate for the assay of the impurities but appropriate for the assay of drug substance.
6. The method used for the study of Drug substance is not specific. For the Analysis of impurities specific method is used which are not provided.
7. In-house method has been provided by Common Technical Documents holder by his own for the study of impurities and API without any validation information.
8. For definite isomeric/chiral impurities the starting source/materials are not studied which can be accepted ahead.
9. The In-house analytical method validation reports not described in brief. For final purification solvent and water used, the quality of the same is not described.

3.2. S.4.3: Validation of Analytical Procedures

Section Queries:

1. Definite validated GLC/HPLC methods for qualify the impurities are unavailable. Using qualitative TLC test impurity profiling is performed

2. The In-house analytical method used for the drug product needs through validation. In MOH laboratory the tests performed for validation is indicated vague.
3. For determination of residual solvents by GC you were compulsory to modify the validation, which should have included intermediate precision, robustness and inter laboratory validation.
4. The method validated should be the same as that of the final method adopted to test the Drug substance.
5. For determination of residual solvents by GC you were compulsory to modify the validation, which should have included intermediate precision, robustness and inter laboratory validation.
6. Typical chromatograms may be provided for a particular batch of the API.

3.2. S.4.4: Batch Analyses

Section Queries:

1. For 3 initial batches of API production the test result provided are in abbreviated form.
2. Significant differences between the API manufacturers and FPP manufacturer's batch study/analysis were noted for acetone, isopropyl alcohol and methanol
3. The COA's (certificate of analysis) should have the batch size mentioned among other typical details.

3.2. S.4.5: Justification of Specification

Section Queries:

1. Justification for use of highly hydrates form of API used in the product is not provided.

3.2. S.5: Reference Standards or Materials

Section Queries:

1. Certificate of Analysis (COA) for working/ secondary standards are not provided by manufacturer.
2. Reference standards/materials must be well characterized.
3. The C of A's of all working standards are provided without typical chromatograms. In case of Reference standards used then the proper Lot number needs to be given.

3.2. S.6: Container Closure System

Section Queries:

1. IR spectra of the Polybags needs to be submitted. (Identification for the material of construction)
2. For immediate container of the API product polymer is used need to be tested, identified and characterized as per specifications given in Pharmacopeia's General Monographs.

3.2. S.7: Stability

3.2. S.7.1: Stability Summary and Conclusions

3.2. S.7.2: Post-approval Stability Protocol and Stability Commitment

3.2. S.7.3: Stability Data

Section Queries:

1. The actual studies for stability are not provided. Data is provided from literature of forced degradation study.
2. For stability studies the stability indicating method has not been used.
3. In Stability summary does not concluded about primary packaging material, proposed storage conditions.
4. For ongoing stability study: Post Approval stability commitment not provided.
5. Check the Stability specification against the test protocol (Stability protocol), the Stability condition & Stability time points. Check parameters like Polymorphism etc.
6. Microbial Attributes test not provided and/or not provided at Initial and final stage in stability data.

3.2. P DRUG PRODUCT

3.2. P.1 Description and Composition of the Drug Product

1. API Overages qty. not mentioned in formula.
2. Formula of API assay potency calculation details not provided.
3. Functions of material details not provided.
4. Information on the quantity dispensed with respect to API taking into the Assay (on as is basis or anhydrous basis). Weight adjustment with respect to the quantity of

diluent needs to be provided as per the calculations of the BMR.
5. Solvents not present in the product should be clearly mentioned.
6. The Qualitative & Quantitative certificate of a colorant needs to be appropriately provided.

3.2. P.2: Pharmaceutical Development

3.2. P.2.1 Components of the Drug Product

3.2. P.2.1.1 Drug Substance

Section Queries:

1. No discussion on formulation with respect to reference product. No mention of BA study/clinical studies or study batch details.
2. Active and process detail discussed. Each Excipient discussed. But for compatibility conclusion provided but method and no actual data has been provided. Documents (PDR) needs to be developed accordingly.
3. Polymorphism, Stereochemistry, Isomerism studies and discussion on the drug substance used in formulation is absent.

3.2. P.2.1.2 Excipients

Section Queries:

1. Please clarify the need of the preservatives in this tablet dosage form and explain the conditions of manufacture and overall relevant composition that let you use such preservatives. Your justification should be supported with relevant comparator product composition or specification and pharmaceutical guidelines/Excipient books. In addition, the amount used has to be justified if the additions of them are scientifically justifiable and acceptable.
2. Although you have used preservatives, microbial limit tests and such information are not provided in the pharmaceutical development data or later in the commercial scale batch manufacturing specifications. Clarify this.
3. PDR (Pharmaceutical development reports) are not complete.
4. A quantitative estimation of excipients may be necessary to prove equivalence b/w the Test & the innovator.

3.2. P.2.2: Drug Product

3.2. P.2.2.1 Formulation Development

Section Queries:

1. The final product is manufactured using critical raw materials from two different suppliers. However, no special attention has been given to differences in quality of the end product.
2. The development report should be prepared by taking into consideration QbD concept.
3. The process control details such as moisture (range), blend uniformity, bulk and tapped densities and particle size distribution are not provided.
4. Discriminatory dissolution methods will have to be developed, the influence of particle size will have to be studied.

3.2. P.2.2.2 Overages

1. Formula of API assay potency calculation details not provided.

3.2. P.2.2.3 Physicochemical & Biological Properties

Section Queries:

1. Physicochemical parameters & Microbiological attributes not addressed properly.

3.2. P.2.3: Manufacturing Process Development

Section Queries:

1. The process control information such as, weight variation, average weight hardness, friability, thickness and disintegration time are not provided for tablet dosage form.
2. The manufacturing development should be a reproducible during the actual batch manufactured. The In-process checks & the intermediates defined in the development report needs to be captured aptly during the actual manufacturing (3.2.P.3)

3.2. P.2.4: Container Closure System

Section Queries:

1. Primary packaging material Certificate of Analysis (COA) & Standard Test Procedure (STP) are not given.
2. Pack style and pack size discussion is not provided.

3.2. P.2.5: Microbiological Attributes

Section Queries:

1. Microbial Contamination results are missing.
2. Pathogen Count and Total Count not provided.

3.2. P.2.6: Compatibility

Section Queries:

1. All Excipients are not used during the compatibility study with API.

3.2. P.3: Manufacture

3.2. P.3.1: Manufacturer(s)

Section Queries:

1. Manufacturer complete address for manufacturing plant & Head office with contact of Quality person not mentioned.

3.2. P.3.2: Batch formula

Section Queries:

1. In batch formula some of the Excipients used in the drug formulations is not included.
2. The standard and quantity for some Excipients not indicated in the unit and batch formula.
3. The batch formula not mentioned for the exhibit as well as the proposed commercial batch. The manufacturing process & the in-process controls are to match with the Product development report.
4. The composition and test methods for the commercial colorant mixtures are used for tablet coating are not described in details.
5. In drug formulation titanium dioxide is used as Opacifier but mentioned in batch formula. Also the complete composition of the coating materials is not provided.
6. For film coating of product organic solvent are used. It is not mentioned anywhere.
7. The information on some hazardous materials like reagent and solvent is hidden.
8. All excipient and raw materials not mentioned in batch formula.
9. Provide justification/declaration stating that the submitted qualitative-quantitative formula corresponds to the subject drug product. Note that the reflected product name in the submitted documents in product.

3.2. P.3.3: Description of Manufacturing Process & Process Controls

Section Queries:

1. The manufacturing process write up should be generic in nature & should not stress on the manufacturing operational parameters as it may vary during actual manufacturing process & this may lead to an unnecessary variation post approval.

3.2. P.3.4. Control of Critical Steps and Intermediates

1. The process control details such as average weight, weight variation, hardness, thickness, friability and disintegration are not provided for your tablet dosage form.
2. Critical parameters defined/captured in Process validation should always be concordant with the Product development

3.2. P.3.5: Process Validation / Evaluation

Section Queries:

1. Process validation report on first 3 commercial batches is not provided.
2. The Prospective Process Validation on 3 initial batches has not been provided. The retro prospective Process Validation data submitted is inadequate to conclude that your manufacturing process is valid.
3. A co-relation with the PVP & the PVR with the executed BMR needs to be properly done.

3.2. P.4: Control of Excipient

3.2. P.4.1: Specification

Section Queries:

1. Excipients are provided in In-house specification despite of that the same are present in Pharmacopoeia.

3.2. P.4.2: Analytical Procedures

1. Excipients limits are not complying as per the Pharmacopoeia monograph.

3.2. P.4.3: Validation of Analytical Procedures

1. Chromatography condition not as per Specification.
2. Excipients specification provided as In-house but Analytical method validation not provided.

3.2. P.4.4: Justification of Specifications

1. For In-house parameters justification of specification not provided.

3.2. P.4.5: Excipients of Human or Animal origin

1. For the sensitive Excipients e.g. Mg-stearate TSE/BSE declaration is not provided.
2. TSE/BSE aspects of raw materials are totally ignored.
3. TSE/BSE Certificates are not provided as per AR No. used in the batches that are required to be submitted in the marketing application.

3.2. P.4.6 Novel Excipients

Section Queries:

1. The Excipients used for manufacturing your Tablet dosage form is Novel. The manufacturers have not provided enough data on its source, synthesis, characterization and safety.

3.2. P.5: Control of Drug Product

3.2. P.5.1: Specification

Section Queries:

1. Make sure that the specification is scientifically designed & the levels of impurities need to be justified as per ICH depending on the daily dose of the drug.
2. In FP (Finished Product) specification microbial limit is not included.
3. General Specifications provided for the drug substances are totally ignored. While the product is analyzed as per specifications provided in British Pharmacopeia.
4. The submitted finished product specification corresponds to the subject's drug product. Provide declaration and justification of the statement.
5. Micro test is not mentioned anywhere.
6. The assay limits at release should have been revised to 95-105% wider limits for shelf life could be applied.
7. No test for water as per ICH Q6A for oral dosage form.
8. Besides again if the additions are acceptable, the FPP specification need to include their assay limits and acceptance criteria and should also appear in the stability specifications as one critical stability indicating parameter.

3.2. P.5.2: Analytical Procedures

Section Queries:

1. The assay procedure is nonspecific. The specifications for in-house product are not clear and complete. The test for identity and impurities are not described at all. It's need to be duly validated GC/HPLC based specific assay method.
2. In Certificate of Analysis (COA) the quantitative values provide are below the limit of Quantitation. (LOQ).
3. Carcinogenic solvents like Methanol Acetone and IPA have been used in synthesis. However, these solvents are not analyzed for chance contamination of Class I solvents from which they are prepared.
4. Details for the micro limit test are not given.
5. Provide Certificate of Analysis (COA) of finished product from the same batch of representative sample.
6. Clarify why does the batch size reflected in the Certificate of Analysis is different to submitted Quantitative-Qualitative formula.
7. A check on the presence of Genotoxic impurities needs to be studied which may arise from within the Drug product.
8. Certificate of Analysis (COA) and other Quality Control (QC) documents are not

signed dated and certified by Quality Assurance (QA) department.

3.2. P.5.3: Validation of Analytical Procedures

Section Queries:

1. The tests performed in MOH laboratory indicate that the method unclear.
2. Validation procedure is required for the in-house analytical procedure provided for the product.
3. For impurities or microbiological test validation test are required.
4. Method validation for Assay, Related substances, Dissolution & Residual solvents methods needs to be presented taking into account all the parameters defined as per ICH.
5. Photostability & Forced Degradation Studies needs to be presented.

3.2. P.5.4: Batch Analyses

1. Three Batches data not provided.
2. COA for drug product for all three batches & Raw data &/Chromatograms are missing.

3.2. P.5.5: Characterization of Impurities

Section Queries:

1. Potential impurities are not discussed. Methods used to assess impurities are not qualified.
2. Although inorganic toxic substances and hazardous reagents are used in the process but residual limits are not provided.
3. In the synthesis specifications of raw materials and intermediates used are not provided.
4. In the reaction process Excipients used which may carry reactive impurities such as Hydrogen peroxide (other oxidized species), formaldehyde and Formic Acid. Justification for the use of this Excipient is not provided.
5. Impurities in residual solvents (ICH Q3C) and USP <467> are not adequately described.
6. Genotoxic impurities needs to be studied which may arise from within the Drug product.
7. In batch analysis data the source, lot number, and purity of the impurity standards are not provided.
8. Provide the test method detail for the impurities. Only limits for impurities are provided.
9. In the synthesis the catalysts such as Palladium and Platinum are used of the products. Specify the residual limits for the same.
10. Please determine the residual impurity of the same.

3.2. P.5.6: Justification of Specification

Section Queries:

3.2. P.6: Reference Standards

Section Queries:

1. Reference materials/standards are poorly characterized.
2. Please provide the IR spectra. Dissolution test should be provided.
3. The qualification details should be clearly stated in case a Working standard is qualified (against a Reference standard).

3.2. P.7: Container Closure System

Section Queries:

1. For the proposed blister pack the moisture permeation data are not provided.
2. For final packaging the extractable and leachable study for the plastic containers and stoppers used for the drug product packaging is not provided.
3. Labelling materials (actual/commercial label)

   It was noted that there's a change in the blister design, as well as, inclusion of ADR Reporting Statement in the Unit Carton Box and Package Insert, but no application for change of product labelling (MiV-PA2). Company has to provide the requirements as per ASEAN Variation Guideline for Pharmaceutical Products and pay the corresponding fee.
4. The primary packaging specifications should have included an identification test for aluminium and an IR test for the PVD coating. Additionally, you were required to provide an IR spectrum for PVC coating.

3.2. P.8: Stability

3.2. P.8.1: Stability Summary and Conclusion

3.2. P.8.2: Post approval Stability protocol and stability

3.2. P.8.3: Stability Data

Section Queries:

1. Do not consider zone-conditions for Real-time stability studies.
2. In stability report the packaging details are missing.
3. The expiry date assigned to the product is not matching with the stability data provided.
4. Provide justification/declaration stating that the submitted long-term and accelerated stability studies correspond to the subject drug product.
5. In the drug product specification like release and shelf life should be included. Preservative content should be quantified up to shelf life.
6. During stability study related substance and impurities are must be tested
7. Company XYZ claim stating "Since the product is well established, accelerated stability study is not required" is absolutely unacceptable and the provided real time data is not acceptable unless the above requested quires are sufficiently justified and all the necessary corrections have made. We advise you to commence an accelerated and real time stability study according to our guideline and provide us the information as soon as possible.
8. Release and stability specifications are must provided.
9. In stability summary does not include conclusions with respect to shelf-life and storage conditions.
10. For ongoing stability study: Post Approval stability commitment not provided.
11. For stability studies the stability indicating method has not been used.
12. For In-House product the Shelf life specifications are not clear and complete.
13. Provide justification/declaration stating that the submitted accelerated and long term stability studies correspond to the subject drug product.

"…in conversation with Speaker from the Raaj GPRAC workshop (Badjatya JK: Conversation with: Ms. Rajashri Ojha; 2012 Oct 26-27)."

Additional all Sections Queries (M1 to M5) (6)

1. In the dossier Module IV and V, supportive clinical and nonclinical full text articles are not provided.
2. Literatures refer in Module IV and V is poorly summarized in Module II. Furthermore, the nonclinical and clinical summaries do not match with the full text articles provided in Module IV and V.
3. In Module IV and Module V full reference particulars of literature and photocopies used are illegible and cannot read correctly.
4. Files are bound properly.
5. Table of contents is not complete.
6. In the dossier version number and date assigned are not assigned.
7. Pagination of the submission is out of order.
8. Some of the documents provided in dossier such as method validation, stability studies report and process validation are not in English.
9. Scoring and Engraving details for your formulation/ preparation (e.g, tablet) is not provided.
10. On the label the preservatives used in your injectable dosage forms are not declared.
11. Bio-waver for products of different strengths is poorly justified.
12. On the API (drug substance) section: API overall information according to module III was expected from both the drug substance and FPP manufacturers. Especially, the open part of the drug master file should come from the API supplier according to our guideline. Although you have submitted API information, it is not satisfactory and complete. Therefore, you are requested to provide each part of the API section according the guideline.
13. Good manufacturing practice (cGMP) certificate for API manufacturer which given from a recognized (authorized) body is required to be submitted.
14. Bioequivalence study with the appropriate comparator product is not provided. As it is known that the API is practically in water and there is also a huge concern on the

polymorphic forms as described above, besides, on the basis of Biopharmaceutics classification system (BCS), it does not meet the requirement of biowaiver. Consequently, your waiver request of in-vivo testing is not acceptable. And so, you are kindly requested to provide the necessary information according to our guideline.

15. Integrated form- Not provided in Re-application.
16. In this dossier Finished product specifications are provided for Batch No. (ZY 601, ZY 602 & ZY 603), validation done on batch No. (ZY 302, ZY 401 & ZY 402) and stability data for batch no. (ZY 302 & ZY 201).
17. It was noted that there is a change in the blister design, as well as, inclusion of ADR reporting statement in the Unit carton labeling. Company to provide the requirements as per ASEAN variation guideline for Pharmaceutical products and pay the corresponding fee.

CONCLUSION

Marketing Application is an application for an approval for generic drug product. Application is submitted to ICH regions for marketing authorization, which provides for the review and ultimate approval of generic drug product. Once approved, the applicant may manufacture and market the generic drug product to provide safe, effective and stable drug product with low cost effectiveness to public.

The present study is carried to find out the probable queries that may arise while submitting our marketing application to the agency. This article aim to focus on the Module 3 (CMC Section) queries. Reference for format is brought from ICH guideline – Notice to applicant.

The careful reviewing & compilation helps the Regulatory Affairs professional to minimise the error/probable queries & gives good understanding of critical aspects of marketing application and better understanding of filing of CMC section of the dossier.

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DISCLAIMER

The views and opinions expressed in this article are those of the author and do not reflect or represent the views of the company the author works for in any manner.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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