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Review Article

COMPILATION OF CHEMISTRY MANUFACTURING CONTROLS IN ABBREVIATED NEW DRUG APPLICATION (ANDA)

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ABSTRACT

The generic products importance, generic drug approval by FDA. The format for filing an ANDA, guidelines and requirements for compiling the Chemistry Manufacturing and Controls in an ANDA by the applicant, have been delineated in this work. The approval of an ANDA by the concerned regulatory agency makes a generic drug available to the respective public, at a lower price and of same quality compared to an innovator drug. The regulatory requirements necessary for the compilation of the CMC section in an ANDA application have been clearly reported through this work.

KEYWORDS: *Abbreviated new drug application (ANDA), compilation, chemistry manufacturing controls (CMC), regulatory requirements.*

INTRODUCTION

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD), provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public [1].

Generic Drug:

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) [2].

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

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Listed Drug:

Any drug for which an NDA has previously been approved is deemed to be a listed drug and is listed by FDA in the orange book. Drugs previously approved under ANDA's and Anatibiotics are also regard as listed drugs. An ANDA must include all information required in an NDA except full reports of investigations demonstrating that the drug is safe and effective in use [3].

ANDA additionally must show:

a) Labeling of the drug for which ANDA is sought is same as the approved labeling for the listed drug.
b) Its route of administration, dosage form and strength are the same as the listed drug or supply such information respecting any differences as FDA may require bioequivalence reports.
c) Status of orange book listed patents on the approved drug.

ANDS (Abbreviated New Drug Submission):

A manufacturer uses an Abbreviated New Drug Submission to apply for market authorization for generic drug. The submission needs to demonstrate that the drug is as safe and efficacious as the brand-name drug. Health Canada often authorizes manufacturers to market these drugs by requiring them to submit an Abbreviated New Drug Submission (ANDS) pursuant to section C.08.002.1 of the Food and Drug Regulations. These products will receive a declaration of bioequivalence to a Canadian Reference Product (pursuant to Section C.08.004 (4)], which will be stated on the NOC. (Notice of compliance) [4, 5].

2. CTD (Common Technical Document): [6-10]

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of

Medicines and designed to be used across Europe, Japan and the United States. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. The agreement to assemble all the Quality, Safety and Efficacy information in a common format (called CTD – Common Technical Document) has revolutionized the regulatory review processes, led to harmonized electronic submission that, in turn, enabled implementation of good review practices. For industries, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

Through the ICH process, considerable harmonization has been achieved among the three regions (Japan, Europe, and the United States) in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of a submission.

The common Technical Document is divided into five modules:

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5
3. Quality (Pharmaceutical Documentation)
4. Preclinical (Pharmacology/Toxicology)
5. Clinical - efficacy (Clinical Trials)
6. The CTD should be organized according to the following general outline.

Module 1: Administrative Information and Prescribing Information:

1.1. Table of Contents of the Submission Including Module 1

1.2. Documents Specific to Each Region (for example, application forms, prescribing information)

Module 2: Common Technical Document Summaries:

2.1. CTD Table of Contents
2.2. CTD Introduction
2.3. Quality overall Summary
2.4. Nonclinical Overview
2.5. Clinical Overview
2.6. Nonclinical Written and Tabulated Summary
Pharmacology
Pharmacokinetics
Toxicology
2.7. Clinical Summary
Biopharmaceutics and Associated Analytical Methods
Clinical Pharmacology Studies
Clinical Efficacy
Clinical Safety
Synopses of Individual Studies

Module 3: Quality:

3.1. Module 3 Table of Contents
3.2. Body of Data
3.3. Literature References

Module 4: Nonclinical Study Reports:

4.1. Module 4 Table of Contents
4.2. Study Reports
4.3. Literature References

Module 5: Clincial Study Reports:

5.1. Module 5 Table of Contents
5.2. Tabular Listing of All Clinical Studies
5.3. Clinical Study Reports
5.4. Literature References

3. CMC (Chemistry Manufacturing and Controls): [11, 12]

Chemistry Manufacturing and Controls (CMC) constitutes that part of pharmaceutical development that deals with the nature of the drug substance and drug product, the manner in which both are made and the manner by which the manufacturing process is shown to be in control. The CMC section is synonymous with the Quality section in the format Common Technical Document (CTD) i.e., the Module 3 in CTD. The Quality section of the Common Technical Document (CTD) (M4Q) provides a harmonized structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier. The table of contents includes sections on Drug Substance and Drug Product. There are also sections for regional specific information as well as some appendices [6].

The Technical section of CMC includes:

- How is the product made?
- How is raw material quality monitored?
- What procedures assure product consistency and quality?
- Are quality attributes adequately identified and characterized?
- Are there appropriate tests to monitor product quality?
- How long does the product maintain its quality after it is made (expiry)?

CMC comprises of the detailed information regarding Drug Substance and Drug Product.

4. Drug Substance Compilation in ANDA: [12-14]

MODULE 3: 3.2.S. Drug Substance:

3.2. S.1 General Information:

3.2. S.1.1 Nomenclature: In this section information on the nomenclature of the drug substance is to be provided. For example:

a) Recommended International Non-proprietary Name (INN)

b) Chemical name in line with IUPAC or IUB C) Company or Laboratory code

d) Chemical Abstracts Service (CAS) registry number e) Compendia) status 0 Therapeutic category

The listed chemical names should be consistent with those appearing in scientific literature (e.g. pharmacopoeia) and those appearing on the product labelling (e.g. Product Monograph, container label). Where several names exist, the preferred name should be indicated. When an in-situ conversion of the drug substance occurs during the manufacture of the drug product (e.g. formation of a salt or complex), the compound in the final dosage form should also be described.

3.2. S.1.2 Structure: The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. For drug substances existing as salts and/or hydrates/solvates, the molecular formula and molecular mass of the free base or free acid or unsolvated moiety should also be provided.

The information to be provided is:

a) Molecular formula
b) Structural formula
c) Molecular weight
d) Stereochemistry

3.2.S.1.3 General Properties: A list should be provided of physicochemical and other relevant properties of the drug substance. This information can be used in developing the specifications, in formulating dosage forms, and in the testing for release and stability purposes. Provide information on the physical and chemical properties of the drug substance such as the physical description, solubility's in common solvents

3.2. S.2 Manufacture Drug Substance (Active Pharmaceutical Ingredient):

3.2. S.2.1 Manufacturer: The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

1) The name and full address of the facility (ies)
2) Contact information for an agent at the facility (phone, fax numbers and email address)
3) Function or responsibility
(4) U.S Agent's name (if applicable)
(5) The Type II DMF number for the API
(6) CFN, FEI or DUNS numbers (if available)
(7) Additional sources of API and information (1 through 6) as applicable.

The company profile is to be provided. The function and responsibility of company is to carry out all manufacturing, processing, packaging, labeling, control operations and holding of drug in plant in confirmation with cGMP.

3.2. S.2.2 Description of manufacturing process and process control: The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls.

Reference ICH guidance's Q5A, Q5B, and Q6B.

3.2. S.2.3 Controls of materials: Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided.

3.2. S.2.4 Control of critical steps and intermediates: Critical Steps : Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the Process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

3.2. S.2.5 Process Validation and/or evaluation: Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

3.2. S.2.6 Manufacturing Process Development: A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance.

3.2. S.3 Characterization:

Contains characterization information for the API. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance. All potential impurities should be listed in tabular format as follows:

3.2. S.4 Control of Drug Substance (Active Pharmaceutical Ingredient):

Contains all information about the controls of the drug substance. 3.2.5.4.1 Specification Contains the drug substance specifications. These specifications include the tests, acceptance criteria, and references to methods in tabular form. If the application contains a sterile substance for use in a sterile drug product, this section will also contain the microbiological specification for the drug substance.

The following documents re to be enclosed :

1) Specification of API from the API manufacturer
2) Specification of API from the Drug Product manufacturer.

3.2.S.4.2 Analytical Procedures: The analytical procedures used for testing the drug substance should be provided. If the application contains a sterile substance for use in a sterile drug product, this section will also be provided with the microbiological analytical procedures used to test the drug substance.

The following documents are to be enclosed:

1) Analytical Procedure of API from the API manufacturer

2) Analytical Procedure of API from the Drug Product manufacturer

3.2.S.4.3 Validation of Analytical Procedures: Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

1) Full validation reports for in-house methods and their equivalence to United States Pharmacopeia (USP) procedures if available for the drug substance

2) Verification of USP <1226> or DMF procedures, when referenced

3) Legible spectra and chromatograms for reference standards and test samples and

4) Sample Statement(s) of Availability and identification of the drug substance, along with associated lot numbers.

3.2.S.4.4 Batch Analysis:

Description of batches and results of batch analyses should be provided. Contains the batch analysis including the Certificates of Analysis (COAs) from both the drug substance manufacturer (s) and drug product manufacturer for the batches used to produce the exhibit batch (es) of the drug product.

3.2.S.4.5 Justification of Specification: Justification for the drug substance specification should be provided. Contains the justification of the specifications including, but not limited to, references to compendia (e.g., USP, European Pharmacopeia (EP), and the Japanese Pharmacopeia (JP)), ICH, and/or RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization parities and Justification of Limits in Drug Substance.

3.2.5.5 Reference Standards or Materials:

Information on the reference standards or reference materials used for testing of the drug substance should be provided. Contains information about the reference standards or materials.

3.2. S.6 Container Closure System:

A description of the container closure systems should be provided, including the identity of aterials of construction of each primary packaging component, and their specifications. The ecifications should include description and identification (and critical dimensions with rawings, where appropriate). Non compendial methods (with validation) should be included, where appropriate.

3.2. S.7 Stability:

At least three batches of a drug substance should be tested. The ICH guideline Q1A(R2) states that, "Batches must be manufactured at least to pilot scale by the same synthetic route as production batches and using a method of manufacture and procedure that stimulates the final process to be used for production batches." The stability testing should be conducted on products that have been stored in the same type of container that is intended for market use

(e.g., bottles, blister packages).

3.2. S.7.1 Stability Summary and Conclusion:

3.2. S.7.2 Post Approval Stability Protocol and Stability Commitment:

3.2. S.7.3 Stability Data-enclosed:

Contains stability data including the retest date or expiration date of the API.

3.2. S.7.1 Stability Summary and Conclusion: The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions regarding storage conditions and retest date or shelf life, as appropriate.

3.2. S.7.2 Post Approval Stability Protocol and Stability Commitment: The post approval stability protocol and stability commitment should be provided. The Organization has to establish a documented protocol for carrying out stability studies (Accelerated and Long term) as per self-storage conditions and frequency of testing the samples. The details are to be included under 3.2.S.7.1.

3.2. S.7.3 Stability data: Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphic, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

MODULE 3: 3.2.P Drug Product:

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

The quantitative composition and function of each component in the drug product; include solvents and processing aids that are used during manufacture, as applicable.

3.2. P.2 Pharmaceutical Development:

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application.

3.2. P.2.1 Components of Drug Product:

3.2. P.2.1.1 Drug Substance:

- Physicochemical Properties
- Source – (API source)
- Chemical name
- Description
- Chemical structure
- Molecular formula
- Molecular weight
- Melting point
- CAS number
- pKa
- Solubility
- Therapeutic category
- Anticipated dose
- Indications and usage
- Package and storage

3.2. P.2.1.2 Excipients:

3.2. P.2.1.2.1 Selection of Excipients: The ingredients are selected based on experience, comprehensive, review of authoritative reference books on the pharmaceutical and analytical parameters and attributes of the chosen drug.

An extensive online search relating to the specific drug substance, drug product and the excipients was conducted.

3.2. P.2.2 Drug Product:

3.2. P.2.2.1 Formulation Development:

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage.

3.2. P.2.2.2 Overages:

Any overages in the formulations described in P1 should be justified. The calculations of the overages is being provided under this heading.

3.2. P.2.2.3 Physicochemical and Biological Properties: (As indicated in section 3.2.P.2.2.1 Formulation development)

3.2. P.2.3 Manufacturing Process Development:

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

3.2. P.2.4 Container Closure System:

- The suitability of the container closure system for the storage, transportation (shipping), and use of the drug product should be discussed.
- Container closure system including primary and secondary packaging components and equipment for packing operations are selected.

3.2. P.2.5 Microbiological Studies:

- Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile

products, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2. P.2.6 Compatibility:

- The compatibility of the drug product with reconstitution diluents or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.
- The compatibility studies of the drug with the reconstitution diluents are to be provided.

3.2. P.3 Manufacture:

3.2. P.3.1 Drug Product:

Contains information about the manufacture of the drug product including:

1. Name and Full Address (es) of the Facility (ies)
2. Contact name, phone and fax numbers, email address
3. U.S Agent's name (if applicable)
4. Specify Function or Responsibility
5. CGMP Certification (from both applicant and drug product manufacturer if different entities)
6. CFN, FEI or DUNS numbers (if available)

3.2. P.3.2 Batch formula:

Manufacturing Formula of Product

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

1) Description of manufacturing process: A brief description of the manufacturing process of product in a stepwise process is to be provided along with a Process Flow Chart.

3.2. P.3.4 Controls of Critical Steps and Intermediates:

Contains the controls of critical steps and intermediates including:

(1) Acceptance criteria and test results for the exhibit batch (es)

(2) Comparison of controls and equipment between the pilot and commercial-batch manufacture

(3) Information about holding periods.

It comprises of the In-process Specifications and Test Procedures

3.2. P.3.5 Process Validation and/or Evaluation:

Contains process validation information to demonstrate that the manufacturing process produces a dosage form that meets product specifications including evaluation of data generated for the critical material attributes and critical process parameters that were found to meet the established scale-up guideline and/or acceptance criteria.

3.2. P.4 Control of Excipients:

3.2. P.4.1 Specifications:

Contains information on the controls of excipients including the identity of the source of inactive ingredients and the grades.

Contains the testing specifications including retest schedule and the excipient manufacturer's or supplier's COA.

3.2. P.4.2 Analytical Procedures:

The analytical procedures used for testing the excipients should be provided. A detailed description of the tests specified in the excipients specification is to be provided.

3.2. P.4.3 Validation of Analytical Procedures:

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

COA's are to be provided.

3.2. P.4.4 Justification of Specifications:

Justification for the proposed excipient specifications should be provided including:

1. Applicant COA
2. Residual solvents statement(s) from manufacturer(s)
3. Bovine Spongiform Encephalopathy (BSE) statement (as applicable)
4. Transmissible Spongiform Encephalopathy (TSE) statement (as applicable)
5. Melamine Certifications statement (as applicable)

3.2. P.5 Controls of Drug Product:

Contains information supporting the controls of the drug product.

3.2. P.5.1 Specifications:

The specifications for the drug product should be provided. These specifications include the tests, acceptance criteria, and references to methods in a tabular form. For sterile products, this section will contain the release specifications for the drug product (sterility, bacterial endotoxins, etc.).

3.2. P.5.2 Analytical Procedures:

Contains the description of analytical procedures (compendial and/or in-house). For sterile products, this section will contain methods for product release tests (sterility, bacterial endotoxins (if applicable), etc.,

3.2. P.5.3 Validation of Analytical Procedures:

Contains the validation of the analytical procedure including:

(1) Full validation reports for in-house methods and their equivalence to USP procedures if available for the drug product.

(2) Verification of USP <1226> procedures, when referenced.

3.2. P.5.4 Batch Analysis:

Contains the batch analysis including the executed COAs for all presentations and/or strengths of the finished dosage form. A tabulated summary of batches discussed in the submission to support safety, efficacy, product development, process validation and stability should be provided.

3.2. P.5.6 Justification of Specifications:

Justification for the proposed drug product specification(s) should be provided including but not limited to references to compendia (e.g., USP, JP), ICH, and/or RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Products.

3.2. P.6 Reference or Materials:

Information on the reference standards or reference materials used for testing of the drug product should be provided if not previously provided.

3.2. P.7 Container Closure System:

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and

critical dimensions, with drawings where appropriate). Contains information on the container closure system

3.2. P.8 Stability:

The following existing ICH guidelines address stability for new drug substances and products and for ANDA's:

1. Q1A (R2) Stability Testing of New Drug Substances and Products.
2. Q1B Photo stability Testing of New Drug Substances and products.
3. Q1C Stability Testing for New Dosage Forms.
4. Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and products.

3.2. P.8.1 Stability and Conclusions (Finished Dosage Form):

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions regarding storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

1. Stability Protocol submitted
2. Expiration Dating Period for Marketed Packaging.

CONCLUSION

The applicant of an ANDA has to be precise in providing all the necessary information in all the sections and areas specified by the concerned regulatory authorities, so as to minimize the delay in approval. Being precise helps in getting an faster approval of the applications, which can save time, money, work burden to the personnel. Regulatory requirements in the generic development hasten the drug approval process, which causes a delay in launching the drug in the market.

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