World Research Journal of
PHARMA TECHNOLOGY
ISSN: 2454-5546
Review Article

REGULATORY REQUIREMENTS FOR FILING ANDA WITH FDA

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ABSTRACT

Abbreviated New Drug Application (ANDA) stands for Abbreviated New Drug Application. Its filing is done for the generic drugs to get approval from FDA. It is for a generic duplicate product which approved by the New Drug Application (NDA). It contains data when submitted to the FDA's Centre for Drug Evaluation Research, Office of Generic Drugs, provides for generic drug product's review and final stage approval. Drugs associated with a brand name becomes expensive as the added cost is the investment which company puts into during drug development phase. Generic drugs are marketed after the patent of the relevant brand drugs gets expired in a cheap price as they don't undergo the research process. Stepwise legal procedures are fulfilled prior to the launch of generic drug product in the market, ANDA filing being one of them.

Keywords: *Abbreviated New Drug Application (ANDA), Regulatory Affairs.*

INTRODUCTION

An Abbreviated New Drug Application (ANDA) contains data which are submitted to FDA's CDER, Office of Generic Drugs, for the review and ultimate approval of a generic drug product. Once it is approved by FDA after certain long procedures, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative of branded product [1].

Approval of generic drug product requires a similar comparison between innovators drug product in terms of dosage, administration route, strength, quality, performance and the use. In 1970, the FDA established ANDA as a mechanism for review and approval of the generic versions. Before 1978, generic product applicants were required to submit complete safety and efficacy through clinical trials. Post 1978, submission of published reports of the trials assuring efficacy and safety was required. These approaches were a failure hence there was introduction of Hatch Waxman act, 1984 which was related to generic drug product approval. [2] ANDA may not be submitted for five years after the date of the approval of the New Molecular Entity (NME). ANDA filing is based on a few basic parameters viz., chemistry, manufacturing, testing, labeling, inspections, and bioequivalence [3].

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to conclude the safety and efficacy of a generic drug product. A demonstration on a scientific level that whether the product is bioequivalent or not should be established.The present article intends to review the present scenario of the process of ANDA filing with FDA and various regulatory requirements for new generic drugs [4].

GENERIC DRUG

A generic drug is a drug which is produced and distributed without patent protection.Formulation of a generic drug may have a registered patent on to it ,

active ingredient being exempted. Generics are usually cheaper than innovator drugs because there is no cost of identification and isolation of new chemical entity, zero cost of research and development, and minimizing marketing cost (because branded drug is already approved as safe and effective) [5].

FDA requirements for Approval

To gain FDA approval, a generic drug must:

Have similar active ingredient when compared with innovators drug product.

Parameters like strength, dosage and route of administration should be same.

Similar in their usage/indications.

Innovators and generic drug product should share similar batch requirements in terms of quality, safety and purity.

Standard criteria laid by FDA and GMP's should be followed by both.

ACT OF HATCH-WAXMAN

"The Hatch-Waxman act is an act dealing with the approval of generic drugs and associated conditions for getting their approval from FDA, exclusive rights for marketing, extension of patent term and listing in orange book".

The main objectives of the act were:

1. Offset the drug approval delay.

2. Bring healthy competition and to avoid price rises.

3. Make life easier for the generic.

Generic manufacturers used to face lot difficulties in doing all the pre-clinical and clinical studies as done by the brand name manufacturers to get their generic approval.

RESOURCES FOR ANDA SUBMISSION

The following resources are necessary with the legal requirements of an ANDA application, assistance from CDER to help you meet those requirements, and internal ANDA review principles, policies and procedures.

Guidance Documents for ANDAs

The FDA has numerous guidance that relate to ANDA content and format issues.

- Generics

  Procedural Draft: Applications Covered by Section 505(b) (2). Under this provision approval by NDA is the reliability criteria for FDA while data provided by the applicant is not considered.

- Biopharmaceutics

  Studies on orally administered drug products related to Bioavailability and Bioequivalence-

  This guidance should be useful for applicants planning to conduct bioavailability (BA) and bioequivalence (BE) studies during the IND period for an NDA.

  Two drugs are said to be bioequivalent if their bioavailability after administration in same dose similar to a degree that there effects, with respect to safety & efficacy can be expected to be the same.

  a) Information that shows the drug product is bioequivalent to the reference listed drug upon which the application relies.

  b) Results of bioavailaibility and bioequivalence testing required by

regulatory agency whenever an ANDA application is submitted.

- Drug Master Files: A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
- Post approval changes to ANDA or NDA: Guidance for industry.
- CDER's decision to refuse any incomplete application can be categorized into –Refusal to Receive.
- Database serving as a storehouse for all the inactive ingredients either present in approved or conditionally approved drug products – Inactive Ingredient Database.

Laws, Regulations, Policies and Procedures

Code of Federal Regulations (CFR)

The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.). is a collection under CFR which is subdivided into 50 titles representing areas as per FDA regulations.For ANDA process regulations usually applied are as followed:-

21CFR Part 314 : Submission of application to FDA for marketing a new drug or antibiotic drug.

- 21CFR Part 320 : Bioavailability and Bioequivalence Requirements.
- 21CFR Part 310 : New Drugs

MaPPs

CDER's Manual of Policies and Procedures (MaPPs) provide official instructions for internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, available for public review for better knowledge in office policies, definitions, procedures and staff responsibilities both at an internal and external level.

ANDA Forms and Electronic Submissions

- ANDA Filing Checklist (PDF)
- FDA Form 356h. Application to Market a New Drug for Human Use/Antibiotic Drug for Human Use
- Providing Regulatory Submissions in Electronic Format - assist applicants making regulatory submissions in electronic format of abbreviated new drug applications. Guidance should be used in linkage with the following guidance.

  Regulatory submissions in electronic format : Guidance for industry.

  Regulatory Submissions in Electronic Format: New Drug Applications.

ANDA CERTIFICATIONS

Filing an ANDA application requires the manufacturer of generic drug product to file one of the certifications as well, on the subject of the reference brand name patents listed in the Orange Book.

- **Paragraph I**- there is no patent for the drug listed in the Orange Book.
- **Paragraph II**- patent is listed but has expired.
- **Paragraph III**- patent is listed, is valid but the generic wants approval to market the drug once the pertinent patent expired.
- **Paragraph IV**- the generic manufacturer either challenges the validity of the brand name listed patent assering it to be invalid or

fake, or it affirms not to cross the fringe of the brand name patent claims.

CONTENTS OF ANDA

- Application Form 356h
- Application copies
- Cover letter
- Table of contents
- Tabs
- Pagination
- Field copies-additional information

APPLICATION COPIES

1. Archival copy
2. Review copy
3. Field copy

COVER LETTER

- Purpose of application
- Type of submission
- Name, title, signature and address of the applicant.
- Drug products established name and its proprietary name.
- Number of volume submitted
- Approved methods validation process, if identified with any issues later - commitment to resolve it.
- A statement issuing that a part of submission or application is in electronic format.
- Clearly identify submission that contains sterility assurance data.

COMMON TECHNICAL DOCUMENT (CTD)

The **Common Technical Document (CTD)** is a format set by ICH which was passed by the regulatory agencies of Europe, Japan & the USA.

CTD is organized into 5 modules.

Module 1: Information on administrative and prescribing region (related to specific region)

- Information on patent on already patented product.
- Certification of patent.
- Debarent certification.

Module 2: Overview and CTD summaries-

- M4Q: The CTD-quality
- M4S: The CTD-safety
- M4E: The CTD-efficacy

Module 3: Quality (CMC)

Module 4:

Preclinical (Pharmacology/Toxicology)- Not required in ANDA filing

Module 5: Clinical – efficacy (Clinical Trials).

REFERENCES

1.www.fda.gov

2.www.phorum.com

3.Guidance for Industry ANDAs: Impurities in Drug Products (Issued by CDER, November 2010).

4.Draft Guidance for Industry ANDA Submissions: Refuse-to-Receive Standards (Issued by CDER, October 2013).

5.Draft Guidance for Industry Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules (Issued by CDER, December 2013).

6.Guidance for Industry Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (Issued jointly by CDER and CVM, November 1994).

7.Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (Issued jointly by CDER and CBER, September 2004).

8.Draft Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics (Issued jointly by CDER and CBER, February 2014).

9.Guidance for Industry ANDAs: Impurities in Drug Substances (Issued by CDER, June 2009).

10.Guidance for Industry Abbreviated New Drug Applications: Stability Testing of Drug Substances and Products (Issued by CDER, June 2013).

11. Draft Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (Issued by CDER, December 2008).

12. Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (Issued by CDER, March 2013).

13. Guidance for Industry Size of Beads in Drug Products Labeled for Sprinkle (Issued by CDER, May 2012 Rev. 1).

14. Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products Questions and Answers (Issued by CDER, May 2014).

15. Guidance for Industry Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (Issued by CDER, February 1987).

16. Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics (Issued jointly by CDER and CBER, May 1999).

17. Guidance for Industry ICH Q8 (R2) Pharmaceutical Development (Issued jointly by CDER and CBER, November 2009).

18. Guidance for Industry Process Validation: General Principles and Practices (Issued jointly by CDER, CBER and CVM, January 2011 Rev. 1).

19. Draft Guidance for Industry Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (Issued jointly by CDER and CBER, January 2013 Rev. 3).

20. Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application (Issued by CDER, CBER, CDRH, CFSAN, CVM, ORA, August 2003).

21. Draft Guidance for Industry Submitting Debarment Certification Statements (Issued by CDER, CBER, and CVM, September 1998).

22. Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (Issued jointly by CDER and CBER, February 2010).

23. Guidance for Industry Variations in Drug Products that May Be Included in a Single ANDA (Issued by CDER, December 1998).