

An Approval to manufacture and sale the copy of innovator product in the US Market

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ABSTRACT

The drug designated for production has to be manufactured in compliance with Current Good Manufacturing Practices (cGMP) following USFDA requirements, EU Directive or International Conference on Harmonization (ICH) Guidelines or Regulatory Authority of respective country. Regulatory authorities bear the responsibility to conduct inspections on pharmaceutical manufacturing plants to ensure they follow cGMP guidelines so that the drug manufactured is safe and effective. A quality system has to be set up such that the drug is manufactured in accordance with approved procedures. A drug is not permitted for sale until the marketing application for the new drug has been reviewed and approved by regulatory authorities. Extensive dossiers are provided to the authorities to demonstrate the safety, potency, efficacy and purity of the drug. After the drug has been approved and marketed, there is continuous monitoring of the safety and performance of the drug to ensure that it is prescribed correctly and adverse events (side effects) are investigated. The United States Food and Drugs Administration (FDA) has one of the most comprehensive and transparent regulatory systems in the world. In US Common Technical Document (CTD) format and most recently its electronic version-the electronic Common Technical Document (eCTD) format is used for submission of dossiers. Inclusion of a paragraph IV certification permits the Applicant to file its ANDA 4 years after the approval of a new chemical entity that is 1 year before the actual expiry of the 5 years exclusivity. In case patent exists that claims the drug, drug product, or method of use, the applicant is requested to file a patent certification with regards to the patent status. The different types of patent certifications are discussed. This project work elucidates US FDA's previous interpretations of the statute regarding 180 days exclusivity and latest amendments in the current guidance. Information considered helpful in the compilation of different CTD modules 1, 2, 3, and 5 is discussed. Electronic submission in eCTD format is outlined.

Keywords: ANDA, cGMP CTD, CFR, FDA, FD&C, ICH

INTRODUCTION

Drug discovery occurs when a new compound is developed that addresses a specific disease target. After scientists identify a potentially viable drug candidate in the early drug discovery process, that compound proceeds to laboratory testing against specific targets to determine its effects. Most compounds are eliminated as they proceed from the discovery to the human development phase. When a chemical is found to impact a specific target, human testing is conducted through clinical trials to show the safety and efficacy of the chemical so that it may be approved by the FDA as a drug. The emphasis is that drugs should be safe, pure, effective and of consistent quality to ensure that they are fit to be

used for their intended functions¹. A drug is not permitted to sale until the marketing application for the new drug has been reviewed and approved by regulatory authorities. This process is performed within legislative framework which defines the requirements necessary for application to the concerned regulatory authority, details on the assessments procedure and the ground for approval or rejection of the application, and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked². The authorities in The United States, The European Union and Japan ask for the common Technical Documents format and more recently, its electronic version the Electronic Common Technical

Document. The current framework for generics in the United States is governed by the Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as Hatch-Waxman Act, and the Medicare Prescription Drug Improvement and Modernization Act (MMA)³. The Hatch-Waxman created the section 505(j) of FD&C Act which was codified under title 21 of the CFR in section 314. Section 505(j) provides the statutory basis allowing pharmaceuticals companies to file Abbreviated New Drugs Application (ANDAs) instead of providing a full new drug application comprising the whole range of preclinical and clinical studies.

At the same time Hatch-Waxman allows brand name companies to apply for up to five additional years of patent protection for new medicines to compensate for time lost while their products were going through FDA's approval process⁴.

Provisions of the Hatch-Waxman Act that protect products of innovator companies comprise:

- Market Exclusivity up to 5 years
- Patent Term Restoration

Benefits of the Hatch-Waxman Act for the generic manufacturer:

- Implementation of Abbreviated New Drugs Application.
- Establishment of Bioequivalence as the basis for approving generic drugs.
- Providing manufacturer of generics with an exemption for pre expiry development and testing including the use of brand name drug to perform studies required for the approval process.
- 180 days generic exclusivity.

With the publication of the Generic Drugs Final Rule and Initiative in June 2003⁵, FDA revised its interpretation of the Hatch-Waxman Act by improving the implementation regulations with regards to generic drugs. The final rule facilitates the market entry of generic medicines by allowing a maximum of one 30-month stay per ANDA instead of previously possible multiple and overlapping 30 month stays. It clarifies the type of patents that must and must not be submitted to FDA for listing in Orange Book, revising the information required to be submitted on patents and consolidating all patent

information on declaration forms to make those submissions are more informative and precise.

The Medicare Prescription Drug Improvement & Modernization Act which changed provisions of the FD&C Act that were originally added by the Hatch-Waxman Act.

Regarding Generics MMA provides for:

- Single 30 month stay on a statutory basis.
- First Commercial Marketing to trigger the 180 days exclusivity.
- Forfeiture Mechanism to avoid scenarios where multiple first filers block one another to market.
- Modification to be included in a single drug application on a statutory basis.

BASIS FOR SUBMISSION

The Legal basis for the filling of an ANDA is laid down in section 505(j) of the FD&C Act, which was implemented by Hatch-Waxman Act. Regulatory action required for the submission of an ANDA by the applicant is provided in the corresponding section of CFR, that is subpart c or section 314.62 to 314.99. The content and format of and abbreviated applications described in section 314.94 of the CFR. An ANDA is usually submitted for a drug product that is the same as a drug product previously approved (Reference Listed Drug) by the FDA.

Application submission is generally substantiated by the following particulars

- A. Reference to the name of the Listed Drug, including its dosage form and strength
- B. A statement as to whether the Listed Drug is entitled to a period of marketing exclusivity
- C. However, as stipulated in § 314.92 an Abbreviated New Drug Application may only be submitted for drug products that are the same as the (Reference) Listed Drug. As further detailed in § 314.92(a) (1) the term "same as" means, the drug product and Listed Drug⁶:
 - i. Shall contain the identical active ingredients
 - ii. Shall be identical in strength, dosage form, and route of administration
 - iii. Shall have identical conditions of use

MARKET EXCLUSIVITY

New drug exclusivity is implemented by provisions under section 505(j) (5) (F) of the Act codified in 21 CFR 314.108. This section of the Act provides for specific time periods, known as new drug product exclusivity or market exclusivity, during which an ANDA cannot be submitted or the effective date of approval for an ANDA must be delayed. As per section 505(c) (3) (E) and 505(j) (5) (F) of the Act a 5-year period of exclusivity is granted for new chemical entities (NCE) not previously approved by FDA. These sections of the Act expressly state that no ANDA may be submitted during the exclusivity period and that such applications may be submitted after 4 years only if they contain a certification of patent invalidity or non-infringement. Under the same sections it is laid down that certain drugs or changes to drugs such as a change in dosage form or strength, new indications or routes of administration can receive 3 years period of exclusivity. However, approval of three-year exclusivity requires new clinical investigations (other than bioavailability studies).

PATENT PROTECTION

The patent confers "the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" Patent applications are filed with the USPTO, which is part of the US Department of Commerce. Hence, the role of the USPTO is only to grant patents or to register trademarks but not to protect the inventions. Generally, the period of validity of a new patent is 20 years from the date of filing of the patent application⁷. Patents may only be enforced via lawsuits. If a patent is infringed, the patentee may sue for relief in the appropriate federal court. The patentee may ask the court for a restriction to prevent the continuation of infringement and may also ask the court for an award of damages because of the infringement. In such an infringement suit, the defendant may raise the question of the validity of the patent, which is then decided by the court. Patent Term Restoration (PTR) enacted by the Hatch-Waxman Act in 1984 compensates patent holders for marketing time lost while developing the product and awaiting FDA

approval by extending the patent term up to five years.

According to section 505(j) (2) (vii) of the Act ANDAs are required to include certifications on the status of all patents applicable to the listed drug. Section §314.94(a)(12) of the CFR describes the patent certification requirements for ANDAs as interpreted by the FDA. Section 314.94 presents an overview on the provisions that will be discussed in turn: § 314.94(a) (12)⁶.

- A. Patents claiming drug, drug product, or method of use
- B. No relevant patents
- C. Method of use patent
- D. Method of manufacturing patent
- E. Licensing agreements.

Types of Patent Certification and Effects on ANDA Approval

Certificate	Patent Status	Statement	Effect on ANDA Approval
Paragraph 1	Patent existing but not submitted	The patent information has not been filed	ANDA may be approved immediately
Paragraph 2	Patent listed but expired	The patent has expired	ANDA may be approved immediately
Paragraph 3	Patent listed not expired	The date on which the patent expires	ANDA may be approved on patent expiry date
Paragraph 4	Patent listed not expired	The patent is invalid Unenforceable or will not be infringed.	Possibility of law suit and 180 day exclusivity

30-MONTH STAY

The ANDA applicant who has included a Paragraph IV Certification in its application is required to send a 'Notice of certification of invalidity or non-infringement of a patent' also known as 'notice of certification' to each owner of the patent in question and to the holder of the approved NDA to which the ANDA refers. Section 314.95 of the CFR describes the current requirements with regard to the sending of the notice and the

information to be included in the notice by the applicant. According to that regulation the applicant is obliged to send the notice not on submission of the ANDA but when it receives from FDA an acknowledgement letter stating that its ANDA is sufficiently complete to permit a review of the entire dossier. If the innovator company decides to sue the generic applicant for the patent infringement, it must do so within 45 days from receipt of notice according to section 505(j)(5)(B)(iii) of the Act. In such cases, the FDA will delay the approval of the ANDA up to 30 months for pending resolution of lawsuit. FDA approval can only come into effect when the 30-months period has elapsed, or the generic applicant wins during patent litigation. As outlines in the following the MMA introduced significant improvement in the field of ANDAs, e.g. by providing a statutory basis for a single 30-month stay and benefits in terms of timing of ANDA approvals.

180 DAY EXCLUSIVITY

Section 505(j)(5)(B)(iv) of the Act provides an incentive for generic manufacturers filing a Paragraph-IV Certification to challenge patents that may be invalid, not infringed or unenforceable, thereby possibly triggering a patent action against them by the patent owner. According to this section of the Act the first generic applicant to submit an application containing a Paragraph IV Certification will enjoy 180 days of generic exclusivity, since all subsequent applications, although including a Paragraph IV Certification will be made effective on the date that is 180 days after the date of the first commercial marketing of the drug by the first applicant. In situations where

different applicants challenged different Orange Book-listed patents for the same drug product FDA adopted a complicate "shared exclusivity" approach under which the first-to-file applicants with a Paragraph IV Certification for each listed patent shared the 180 day exclusivity period based on that patent. Once the first-to-file applicant forfeits its 180-day exclusivity, no subsequent ANDA applicant will be eligible for 180- day exclusivity. Any subsequent ANDA filer may launch its generic product immediately provided that any patent issues are resolved and final FDA approval is received⁸.

SUPPLEMENTS

In case a change to the product applied for would lead to a significant difference as compared to the listed drug cited in the initial submission (e.g., different active ingredient, dosage form, route of administration) a new application should be filed for the different drug product and the new ANDA should refer to the separate listed drug with the desired characteristics (e.g., active ingredient, dosage form, route of administration) if identifiable in the Orange Book. The applicant is not allowed to submit a supplement or amendment to its pending or approved application to seek approval for such a change. Generally, a single application can be used to seek approval for different strengths of the same listed drug. Consequently, an applicant may submit an amendment or supplement to seek approval of a different strength from that for which the application was initially submitted and is not required to file a separate application for such a change. This is expressly permitted under the Act, as amended by the MMA (see section 505(j) (2) (D) (ii) of the Act).

CONTENT AND FORMAT OF ANDA⁶

Archival Copy -Requirement/ Title acc. to 21 CFR § 314.94(a)	Review Copy		Field Copy	Location within CTD***
	Chem.*	Bio.**		
(1) Application form.	X	X	X	Module 1
(2) Table of contents.	X			Module 1
(3) Basis for Abbreviated New Drug Application submission	X	X		Module 1
(4) Conditions of use	X			Module 1
(5) Active ingredients.	X			Module 1
(6) Route of administration, Dosage form, and strength.	X			Module 1&5
(7) Bioequivalence.		X		Module 2&5
(8) Labelling.	X	X		Module 1

(9) Chemistry, manufacturing, and controls.	X		X	Module 2&3
(10) Sample statement required under §314.50(e) (1) and methods validation package as per (e) (2) (i).				Sample on request
(11) Other information as described in §314.50(g), e.g. reference to information submitted previously.				Module 2 &3 as applicable
(12) Patent certification	X			Module 1

* Chemistry/microbiology **, Bioequivalence, *** Common Technical Document

When paper format is submitted, the applicant is requested to submit three copies of the application according to §314.94(d).

- A. **Archival Copy:** The archival copy is a complete copy of an application and is intended to serve as the official reference source for the Agency. The archival copy is maintained during the review of the application to permit individual reviewers to refer to information that is not contained in their particular technical sections of the application.
- B. **Review Copy:** The review copy is used to evaluate the application. It is usually divided into two parts containing the scientific information needed for chemistry/microbiology review and bioequivalence review conducted by different scientific reviewers.
- C. **Field Copy:** The field copy is used to enable pre-approval inspection by the FDA. The field copy should hence contain the technical section of the chemistry, manufacturing and controls part for drug substance and drug product according to section 314.50(d)(1) as required in section 314.94(a)(9) of the CFR.

FDA encourages applicants to submit their ANDAs in the CTD format and preferably as electronic CTD. The Common Technical Document is divided into four separate sections. The four sections address the application organization (M4), the Quality section (M4Q), the Safety section (M4S) and the Efficacy section (M4E) of an application⁹.

Module 1 - Regional Requirements:

The content and format to be followed in the preparation of individual documents of Module 1 can be obtained from current FDA presentations published on the homepage of FDA or the Generic Pharmaceutical Association (GPhA).

Module 2-Overview and Summaries:

Module 2 contains the Summary of Module 3 as well as the Overview and Summary of Module 5. Non-clinical, toxicological information and non-clinical study reports located in Module 4 can be omitted for ANDAs.

Module 3-Chemistry, Manufacturing and Control:

The content and format of the chemistry, manufacturing and controls part mainly is subject to ICH Guidelines. The format follows the ICH-CTD standard for Module 3 as described in the M4Q (R1) Guideline. The majority of ICH Quality guidelines have meanwhile been adopted by FDA. Despite this common basis a few regional aspects specific to FDA are to be considered for the compilation of Module3.

Module 4- Non Clinical Part: Module 4 can be omitted for ANDAs.

Module 5-Clinical Part:

The format of the clinical part follows the ICH-CTD standard for Module 5 as described in the M4E (R1) Guideline. ICH efficacy guidelines regulate general aspects on clinical trials such as

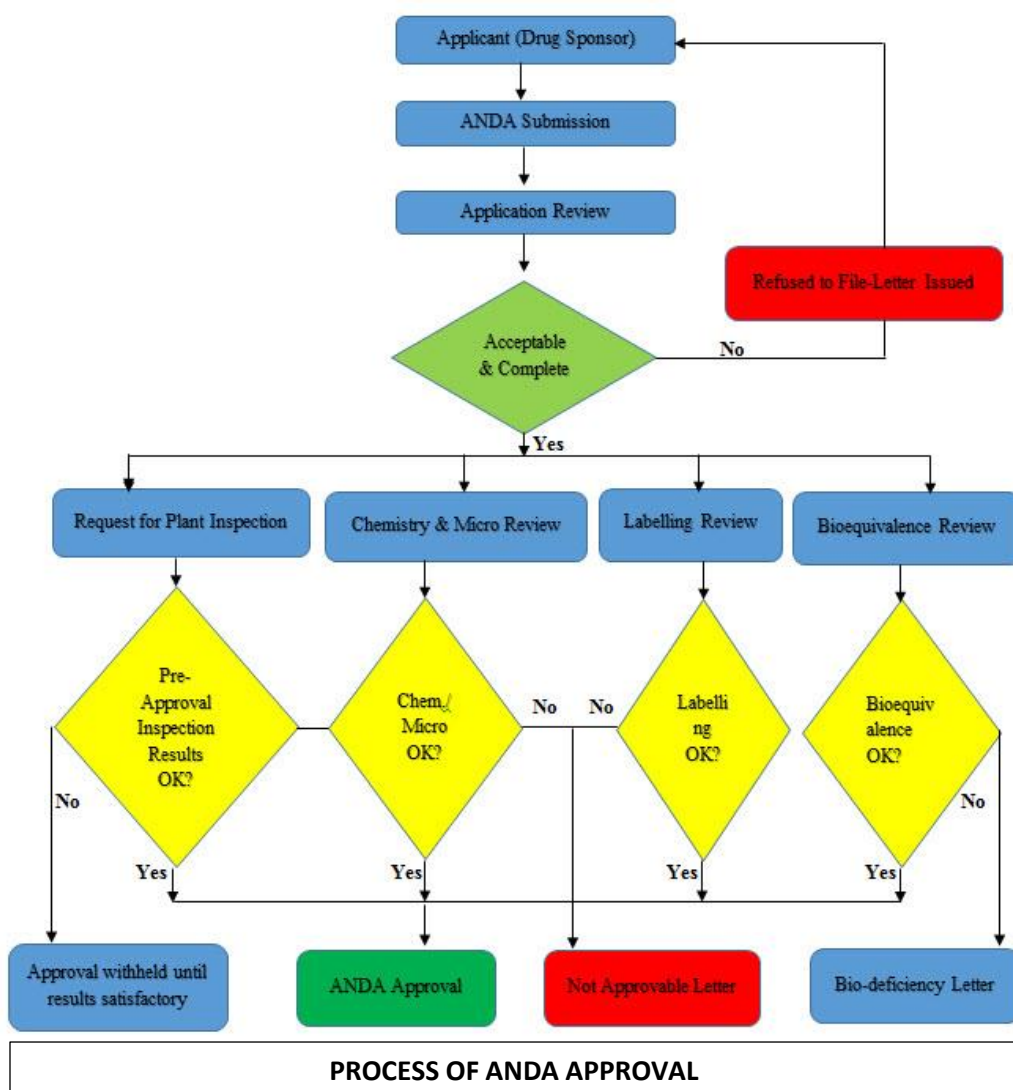
- E3 Structure and Content of Clinical Study Reports
- E6 (R1) Good Clinical Practice
- E8 General Consideration of Clinical Trials
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group and Related Issues in Clinical Trials
- E11 Clinical Investigation of Medicinal Products in the Pediatric Population
- E12 Guidelines for Clinical Evaluation by Therapeutic Category

Specific bioavailability (BA) / bioequivalence (BE) requirements are subject to national regulations in the US. According to section 314.94(a)(7)(i) the ANDA applicant is obliged to submit information showing that the proposed drug product is bioequivalent to the Reference Listed Drug to which reference is made. Regulatory requirements for documentation of bioequivalence are provided in part 320 of the CFR.

Submission in Electronic Format-eCTD:

The eCTD format is an electronic standard that provides a harmonized technical solution for the transfer of regulatory information contained in the Common Technical Document from Industry to Agencies across ICH region. The information to be included in the technical sections of Modules 1 to 5 follows the provisions laid down in the ICH M4 Guidelines. The focus of the specification is to provide the ability to transfer the registration

application electronically from industry to a regulatory authority while at the same time also facilitating the creation, review, lifecycle management and archival of the electronic submission. The specification developed by the ICH M2 EWG was the Electronic Common Technical Document Specification, which is based on Extensible Mark-up Language (XML) technology and lists the criteria that will make a electronic submission technically valid. Based on ICH CTD and eCTD specifications the FDA has published Guidance on "Providing Regulatory Submissions in Electronic Format -Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" which provides recommendations on how to organize electronic applications to FDA¹⁰. This



guidance refers to a series of technical specifications which should be followed for the preparation of an electronic application in accordance with the eCTD format. Applicants may make a sample submission reviewed by FDA to resolve any technical issues with the eCTD submission prior to the actual submission. The sample submission is however not considered an official eCTD submission. Before submission of the actual ANDA the applicant should request a "Pre-Assigned Application number". A step-by-step description of the procedure to be followed is provided on the web site of the FDA. Applicants who would like to submit electronically, but who are unable to submit in eCTD format by the official start-date, can ask for an eCTD waiver.

RESULTS

The CTD is organized into five modules. Module 1 is designed to contain region-specific information such as application forms and other administrative provisions that may apply. As such, it is not harmonized and is not considered part of the CTD. The other four modules present the technical data in a harmonized format. Module 2 should contain critical overview assessments of the quality, non-clinical and clinical data, together with summaries of the non-clinical and clinical data. The objective of this section is to provide reviewers with an introduction to the submission, and to orient them as to how the applicant believes the data support the granting of a marketing authorization. Modules 3 provide detailed quality data. Module 4 which, is for Nonclinical Study Report is not required for ANDAs. Module 5 provide the detailed clinical data.

Hatch-Waxman provides that an applicant for an ANDA or a 505(b)(2) applicant must make an appropriate certification respecting marketing of the generic drug. In an effort to encourage generic drug entry into the pharmaceutical market, the Hatch-Waxman Act provides a commercial incentive to those generic companies who are the first to file ANDAs incorporating Paragraph IV Certifications challenging infringement or validity of Orange Book-listed brand-name pharmaceutical patents. Thus, in the event the listed brand-name patent(s) are adjudged to be invalid or not infringed prior to their normal expiration date(s), the first generic filer entitled to approval of its ANDA receives a 180-day exclusivity period, during which no other ANDA can be approved for the same product. In such circumstances, the first entity to file an ANDA can be the only generic marketer for 180 days.

CONCLUSION

In the United State, applications to market a generic are filed by so called "Abbreviated New Drug Applications (ANDA)". The application is called abbreviated because results from (pre) clinical safety and efficacy studies are usually not required. Instead, reference is made to the data on file for an already approved reference drug. The legal basis for the filing of an ANDA is laid down in section 505(j) of the Food, Drugs & Cosmetics Act which is codified in 21 CFR 314. An ANDA usually is submitted for a drug product that is the same as a drug product previously approved by the FDA. The approved drug product, usually an innovator drug, when referred to in a generic application, is called the Reference Listed Drug. In case a patent exists that claims the drug, drug product, or method of use the applicant is requested to file a patent certification with regard to the patent status. The different types of patent certifications are available. Inclusion of a Paragraph IV Certification permits the Applicant to file its ANDA 4 years after approval of a new chemical entity that is 1 year before actual expiry of the 5 year exclusivity. The submission of an ANDA containing a Paragraph IV Certification is an infringing act and, therefore, may be followed by a patent infringement litigation. In such cases, the FDA will delay the approval of the ANDA up to 30 months for pending resolution of lawsuit. As provided by the Food, Drugs & Cosmetics Act, the first generic applicant to submit an application containing a Paragraph IV Certification is eligible to an incentive of 180 days of generic exclusivity. This exclusivity, commonly known as "180-day exclusivity", protects the first- to-file applicant, whose ANDA contains a Paragraph IV Certification, from competition by subsequent generic applicants referring to the same Reference Listed Drug.

↓ REFERENCES

1. Rick Ng. *Drugs From Discovery To Approval*, A John Wiley & Sons Inc. Publication, Hoboken, New Jersey, 2004.

2. http://en.wikipedia.org/wiki/Marketing_authorization
3. www.regulatoryone.com/2012/01/anda.html
4. CDER, Office of Generic Drugs web site,
<https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm119100.htm>
5. Generic Drugs Final Rule and Initiative, June 2003
6. 21 CFR 314 at the U.S. Government Printing Office web site
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314>
7. Frequently Asked Questions on the Patent Term Restoration Program on FDA web site,
<https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069959.htm>
8. 180-Day Generic Drug Exclusivity on FDA web site,
<https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069964.htm>
9. CTD on ICH web site
<http://www.ich.org/products/ctd.html>
10. ICH- eCTD Specification and Related Files,
<http://estri.ich.org/eCTD/index.htm>