Review Phase Assessment for ANDA Submission in US: A Regulatory Review

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Abstract: Today, the vast majority of drugs available for patient in the United States are generics. They have gone through a rigorous system of evaluation, supervised by the United States Food and Drug Administration (FDA), to ensure the drugs are safe and efficacious. USFDA is one of the most regulated agencies, wherein the submission process is critical. Generic medicines are those where patent protection has expired of innovator drugs, and which have been placed on the market at a lesser price but with therapeutic action, safety and efficacy. The accessibility of generics made easier to the public. This study considers how to submit an ANDA application as per FDA requirements and review phase with a discussion of ANDAs, and its similarity and differences with NDAs. Applicants should submit information showing the proposed generic product and the innovator product are both pharmaceutically equivalent and bioequivalent. By law, generics must be shown to be safe and effective before they can be approved by the agency for marketing. After submission, CDER reviews the application by issuing queries within the scheduled timeline: information request (IR), discipline request letter (DRL), and complete response letter (CRL), which accelerate the approval of the ANDA application.

Key words: CDER, ANDA, information request (IR), discipline request letter (DRL), and complete response letter (CRL)

Introduction

The Food and Drug Administration (FDA) is a regulatory agency of the United States Department of Health and Human Services, a federal executive department[1]. It is composed of seven centres responsible for ensuring the safety, efficacy, oversight and security of the nation's human and veterinary drugs, tobacco products, biological products, medical devices, food, cosmetics and products that emit radiation[2]. The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. In the ANDA submission, FDA CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness[3]. The agency considers a generic drug to be "identical, or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use"[4]. The generic drug comes onto the market once the patent ends or the patent owner waives his rights, and the FDA requirements are met. Once the generic drug becomes available, the market competition is increased, hence the prices of both the generic and the original brand are lowered. Generic drugs are usually sold at a much lower price compared to the original brand drug[5]. The FDA is also responsible for advancing public health by helping with innovations that make medicines and food more effective, safer and more affordable, and helping the public to get proper, scientific information about food and medicines to improve their health[6].

Abbreviated New Drug Application (ANDA)

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower-cost alternative to the brand-name drug it references[7]. Once the ANDA is approved, the manufacturer can market the safe, effective and less expensive generic version. Generic drug applications are referred to as "abbreviated" because they are not required to submit any clinical and animal studies to prove their safety and efficacy. The generic drugs are scientifically proven to have the same properties as those of the innovator drug. To demonstrate that a generic drug is similar to the innovator drug is to measure the bioavailability of the drug in the systemic circulation of healthy volunteers. Bioavailability, the rate of absorption of the generic drug, will be evaluated by conducting a 'bioequivalence' study and is compared to the branded drug. To be approved by the FDA, the amount of active ingredients in the circulatory system of the patient should be same for both the generic and the innovator drug. Enactment of the Drug.

Price Competition and Patent Restoration Act of 1984, better known as "The Hatch-Waxman Act" is the major force for generic market development in the US. It has created opportunities for developing and marketing generics, better called an abbreviated new drug application, with 180 days. Final approval of the ANDA by the FDA takes minimum18 months. Under ANDAs, a pharmaceutical manufacturer can develop and market low-price generic versions of previously approved innovator drugs, thus providing the same product to a patient at a lower price with safety and efficacy. All approved products, both innovator and generic, are listed in FDA's orange book[8].

The USA defines a generic drug product as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use"[9].

Facts About Generic Drugs

1. The FDA requires generic drugs to have the same active ingredient, strength, dosage form, and route of administration as the brand-name drug.
2. The generic manufacturer must prove its drug is the same (bioequivalent) as the brand-name drug.
3. All manufacturing, packaging, and testing sites must pass the same quality standards as those of brand-name drugs.
4. Many generic drugs are made in the same manufacturing plants as the brand-name drugs[10].

Hatch-Waxman Act

This is also known as "Drug Price Competition and Patent Term Restoration Act of 1984". It established the approval pathway for generic drug products, under which applicants can submit an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It takes account of provisions regarding new drug applications regarding patents and exclusivities. The ANDA applicant should demonstrate the generic product is "bioequivalent" with the reference listed drug (innovator drug).

Types of Certifications Provided under the Hatch-Waxman Act

1. Paragraph I: Patent details have not been filed
2. Paragraph II: Patent(s) expired
3. Paragraph III: Patent(s) remain(s) extant
4. Paragraph IV: Patent is purported to be invalid or generic product is purported to infringe[11].

International Council of Harmonisation

This is a unique initiative taken to achieve harmonisation of regulatory authorities and pharmaceutical industry. Since its inception in 1990, it has had well-defined objectives as follows:

i. To encourage the global registration process
ii. To accelerate the new drug development
iii. To develop the harmonised guidelines[12].

Common Technical Document (CTD)

This is a harmonised specification developed and maintained by ICH. It is a globally accepted model to submit one single application to a country or multiple countries at the same time for the registration of a human pharmaceutical product (innovator or generic drug product). Initially it was developed by the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Ministry of Health Labour and Welfare (Japan).

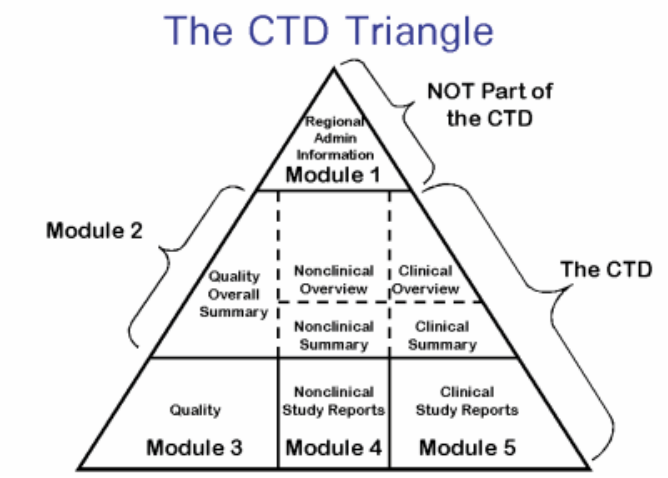

Figure 1: CTD triangle

The CTD outline is divided into five modules:

Module 1. Administrative Information and Prescribing Information

This module contains country-specific official papers and it will be detailed by the respective regulatory agency. (Ex: application forms, label text).

1.1 Forms
- Form [form-type]

1.2 Cover letters

1.3 Administrative information
- 1.3.1 Contact/sponsor/applicant information
  - 1.3.1.1 Change of address or corporate name
  - 1.3.1.2 Change in contact/agent
  - 1.3.1.3 Change in sponsor
  - 1.3.1.4 Transfer of obligation
  - 1.3.1.5 Change in ownership of an application or reissuance of license
- 1.3.2 Field copy certification
- 1.3.3 Debarment certification
- 1.3.4 Financial certification and disclosure
- 1.3.5 Patent and exclusivity
  - 1.3.5.1 Patent information
  - 1.3.5.2 Patent certification
  - 1.3.5.3 Exclusivity claim
- 1.3.6 Tropical disease priority review voucher

1.4 References
- 1.4.1 Letter of authorisation
- 1.4.2 Statement of right of reference
- 1.4.3 List of authorized persons to incorporate by reference
- 1.4.4 Cross-reference to previously submitted information

1.5 Application status
- 1.5.1 Withdrawal of an IND
- 1.5.2 Inactivation request
- 1.5.3 Reactivation request
- 1.5.4 Reinstatement request
- 1.5.5 Withdrawal of an unapproved BLA, NDA, ANDA, or Supplement
- 1.5.6 Withdrawal of listed drug
- 1.5.7 Withdrawal of approval of an application or revocation of license

1.6 Meetings
- 1.6.1 Meeting request
- 1.6.2 Meeting background materials
- 1.6.3 Correspondence regarding meetings

1.7 Fast track
- 1.7.1 Fast track designation request
- 1.7.2 Fast track designation withdrawal request
- 1.7.3 Rolling review request
- 1.7.4 Correspondence regarding fast track/rolling review

1.8 Special protocol assessment request
- 1.8.1 Clinical study
- 1.8.2 Carcinogenicity study
- 1.8.3 Stability study
- 1.8.4 Animal efficacy study for approval under the animal rule

1.9 Pediatric administrative information
- 1.9.1 Request for waiver of pediatric studies
- 1.9.2 Request for deferral of pediatric studies
- 1.9.3 Request for pediatric exclusivity determination
- 1.9.4 Proposed pediatric study request and amendments
- 1.9.5 Proposal for written agreement (no longer applicable)
- 1.9.6 Other correspondence regarding pediatric exclusivity or study plans

1.10 Dispute resolution
- 1.10.1 Request for dispute resolution
- 1.10.2 Correspondence related to dispute resolution

1.11 Information amendment: Information not covered under modules 2 to 5
- 1.11.1 Quality information amendment
- 1.11.2 Nonclinical information amendment
- 1.11.3 Clinical information amendment
- 1.11.4 Multiple module information amendment

1.12 Other correspondence
- 1.12.1 Pre IND correspondence
- 1.12.2 Request to charge for clinical trial
- 1.12.3 Request to charge for expanded access
- 1.12.4 Request for comments and advice
- 1.12.5 Request for a waiver
- 1.12.6 Exception from informed consent for emergency research
- 1.12.7 Public disclosure statement for exception from informed consent for emergency research
- 1.12.8 Correspondence regarding exception from informed consent for emergency research
- 1.12.9 Notification of discontinuation of clinical trial
- 1.12.10 Generic drug enforcement act statement
- 1.12.11 ANDA basis for submission statement
- 1.12.12 Comparison of generic drug and reference listed drug

- 1.12.13 Request for waiver for *in vivo* studies
- 1.12.14 Environmental analysis
- 1.12.15 Request for waiver of *in vivo* bioavailability studies
- 1.12.16 Field alert reports
- 1.12.17 Orphan drug designation

1.13 Annual report

- 1.13.1 Summary for nonclinical studies
- 1.13.2 Summary of clinical pharmacology information
- 1.13.3 Summary of safety information
- 1.13.4 Summary of labeling changes
- 1.13.5 Summary of manufacturing changes
- 1.13.6 Summary of microbiological changes
- 1.13.7 Summary of other significant new information
- 1.13.8 Individual study information
- 1.13.9 General investigational plan
- 1.13.10 Foreign marketing
- 1.13.11 Distribution data
- 1.13.12 Status of postmarketing study commitments and requirements
- 1.13.13 Status of other postmarketing studies and requirements
- 1.13.14 Log of outstanding regulatory business
- 1.13.15 Development safety update report (DSUR)

1.14 Labeling

- 1.14.1 Draft labeling
  - 1.14.1.1 Draft carton and container labels
  - 1.14.1.2 Annotated draft labeling text
  - 1.14.1.3 Draft labeling text
  - 1.14.1.4 Label comprehension studies
  - 1.14.1.5 Labeling history
- 1.14.2 Final labeling
  - 1.14.2.1 Final carton or container labels
  - 1.14.2.2 Final package insert (package inserts, patient information, medication guides)
  - 1.14.2.3 Final labeling text
- 1.14.3 Listed drug labeling
  - 1.14.3.1 Annotated comparison with listed drug
  - 1.14.3.2 Approved labeling text for listed drug
  - 1.14.3.3 Labeling text for reference listed drug
- 1.14.4 Investigational drug labeling
  - 1.14.4.1 Investigational brochure
  - 1.14.4.2 Investigational drug labeling
- 1.14.5 Foreign labeling
- 1.14.6 Product labeling for 2253 submissions

1.15 Promotional material [promotional-material-audience-type]

- 1.15.1 Correspondence relating to promotional materials
  - 1.15.1.1 Request for advisory comments on launch materials
  - 1.15.1.2 Request for advisory comments on non-launch materials
  - 1.15.1.3 Presubmission of launch promotional materials for accelerated approval products
  - 1.15.1.4 Presubmission of non-launch promotional materials for accelerated approval products
  - 1.15.1.5 Pre-dissemination review of television ads
  - 1.15.1.6 Response to untitled letter or warning letter
  - 1.15.1.7 Response to information request
  - 1.15.1.8 Correspondence accompanying materials previously missing or rejected
  - 1.15.1.9 Withdrawal request
  - 1.15.1.10 Submission of annotated references
  - 1.15.1.11 General correspondence
- 1.15.2 Materials attribute = [promotional-material-doc-type]
  - 1.15.2.1 Material [promotional-material-type, material-id, issue- date]
  - 1.15.2.1.1 Clean version
  - 1.15.2.1.2 Annotated version
  - 1.15.2.1.3 Annotated labeling version
  - 1.15.2.1.4 Annotated references

1.16 Risk management plan

- 1.16.1 Risk Management (Non-R EMS)
- 1.16.2 Risk Evaluation and Mitigation Strategy (REMS)
  - 1.16.2.1 Final REMS
  - 1.16.2.2 Draft REMS
  - 1.16.2.3 REMS Assessment
  - 1.16.2.4 REMS Assessment Methodology
  - 1.16.2.5 REMS Correspondence
- 1.6.2.6 REMS Modification History

1.17 Postmarketing studies

- 1.17.1 Correspondence regarding postmarketing commitments
- 1.17.2 Correspondence regarding postmarketing requirements

1.18 Proprietary names

1.19 Pre-EUA and EUA

1.20 General investigational plan for initial IND

Module 2. Common Technical Document Summaries

This Module comprises of seven sections as specified below:

2.1 Table of contents
2.2 Introduction
2.3 Quality Overall Summary
2.4 Non-clinical Overview
2.5 Clinical Overview
2.6 Non-clinical Written and Tabulated Summaries
2.7 Clinical Summary

Module 3. Quality

This module comprises the information regarding chemistry manufacturing and control (CMC). It gives an overview regarding drug product composition, formulation development and quality attributes.

3.1 Comprehensive Table of Contents for Module 3
3.2. S Drug Substance
3.2. P Drug Product
3.2. A Appendices
3.2. R Regional Information
3.3 Key Literature References

Module 4. Nonclinical Study Reports

It comprises the complete pharmacological and toxicological study reports and information equivalent to the quality of the drug to provide the evidence of the safety of the drug product.

4.1 Comprehensive Table of Contents
4.2 Study Reports
4.3 Literature References

ANDAs generally do not contain data required for Module 4.

Module 5. Clinical Study Reports

These generally comprise the human study reports, bioequivalence and study tagging file studies in the ANDA submission.

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

Review Phase Assessment

- The ANDA review process commences with submission of the ANDA to the Office of Generic Drugs (OGD) within the Center of Drug Evaluation and Research (CDER).
- An ANDA pre-assigned application number will be assigned within three working days upon request through secure email to cderappnumrequest@fda.hhs.gov[14].
- OGD and OPQ simultaneously review ANDA on key elements, like:

i. Pharmaceutical Quality
ii. Bioequivalence
iii. Labelling

FDA Commitment Towards ANDA Review Process

- The FDA introduced Generic Drug User Fee Amendments (GDUFA) to enhance the efficiency and effectiveness of the review process.
- GDUFA I was introduced in 2012 as part of the Food and Drug Administration's Safety and Innovation Act. It was introduced to facilitate the appropriate resources to review ANDA applications, which were received in large numbers.
- GDUFA I has been reauthorized (GDUFA II) on August 18, 2017 and it will remain effective until September 30, 2022.
- GDUFA II set a goal of a standard 10-month review cycle time.
- GDUFA II derived two terms, i.e. standard and priority submissions.
- **Standard:** The submissions not affirmatively identified as eligible for expedited review pursuant to the CDER (Center for Drug Evaluation and Research) prioritisation MAPP (Manual of Policies & Procedures).
- **Priority:** The submissions affirmatively identified as eligible for expedited review pursuant to CDER's MAPP 5240.3, prioritisation of the review of original ANDAs, amendments and supplements[15].
- GDUFA II enriches the communication between agency and applicant by issuing of IR(s) and DRL(s) at an appropriate mid-point of the review.
- GDUFA II fiscal fees for years 2018 and 2019 are detailed below in Figure 2[16]:

User Fee Type		FY 2019	FY 2018
ANDA		$ 178,799	$ 171,823
DMF		$ 55,013	$ 47,829
Program	Large Size	$ 1,862,167	$ 1,590,792
	Medium Size	$ 744,867	$ 636,317
	Small Size	$ 186,217	$ 159,079
Facility	Domestic API	$ 44,226	$ 45,367
	Foreign API	$ 59,226	$ 60,367
	Domestic FDF	$ 211,305	$ 211,087
	Foreign FDF	$ 226,305	$ 226,087
	Domestic CMO	$ 70,435	$ 70,362
	Foreign CMO	$ 85,435	$ 85,362
Backlog		$ 17,434	$ 17,434
PAS			

Figure 2: GDUFA fee comparison of FY 2019 and FY 2018

GDUFA II Role in Review Phase:

- Two programme enhancements centred on improving communications during a review cycle:
  1. Discipline Review Letters (DRLs).
  2. Information Request (IR) Letters.
  - ECDs are no longer used.
  - Multiple DRLs and IRs can be issued in one GDUFA cycle.
- Impact of GDUFA II:
  - Reviews of ANDAs will begin earlier in the review cycle
  - Applicants will receive preliminary thoughts on their application at about the mid-point of the review period
  - Applicants may have an opportunity to resolve issues during the review cycle
  - The goal is to improve review efficiency and reduce review cycles (get generics to market faster).

Information Request (IR):

- "A letter that is sent to an applicant during a review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review."[17]
- It will be issued for clarification or additional information required to complete a discipline review with a specified response date.
- It will be issued early in the review cycle by the discipline or sub-discipline through teleconference, e-mail, facsimile or letter.
- In case of no response or partial response by agency, then it may be included in a further issued DRL or CRL.
- An extension may be requested when unable to respond by the requested response date in an IR.

Discipline Review Letter (DRL)

- "A letter used to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of the discipline review. FDA does not consider a DRL to be a CRL because it does not represent a complete review of the entire submission (and, therefore, does not complete the review cycle for an ANDA)."
- It will be issued based on possible deficiencies found by a discipline reviewer and/or review team with a specified response date through teleconference, e-mail, facsimile or letter.
- If the review team finds no deficiencies, then the particular discipline will issue a DRL that states no deficiencies are identified at the current time.
- A discipline will reach the conclusion of their review and issue a DRL no later than about the mid-point of the review (i.e., mid-cycle date (MCD), meaning the mid-point of the GDUFA goal date plus 30 days).
  a. Eight-month GDUFA clock – five-month MCD (four-month mid-point + 30 days)
  b. 10-month GDUFA clock – six-month MCD (five-month mid-point + 30 days)
- An extension may be requested when unable to respond by the requested response date in a DRL.
- Mid-review cycle meeting via teleconference with the applicant to discuss current concerns with the application and next steps. CDER will schedule a mid-review cycle meeting after the last key discipline has issued its IR and/or DRL for ANDAs that were the subject of prior product development meetings or pre-submission meetings.

Complete Response Letter (CRL)

- "A written communication to an applicant from FDA usually describing all of the deficiencies that the Agency has identified in an ANDA that must be satisfactorily addressed before it can be approved. Issuance of a CRL completes the review cycle for an ANDA."
- It was introduced in 2008 to replace the old "approved", "approvable", and "not approvable" letters.
- CRLs are important documents to a drug application's success or failure.
- It must be dealt with in a timely fashion to maximise the chance for an application's approval.
- Most successful drug applications receive only one CRL.
- A CRL may be issued on multiple deficiencies like manufacturing sites, safety, efficacy, bioequivalence, faulty statistics, product quality and stability, and proposed labelling.

Office of Pharmaceutical Quality

- This is organised around discipline and expertise. It streamlined the FDA to assess and monitor drug quality.
- It enhances the interactions, communication and consistency among sub-disciplines.
- Office of Pharmaceutical Quality developed a 10-month

process timeline for original ANDAs and a review flow described in the figure below.

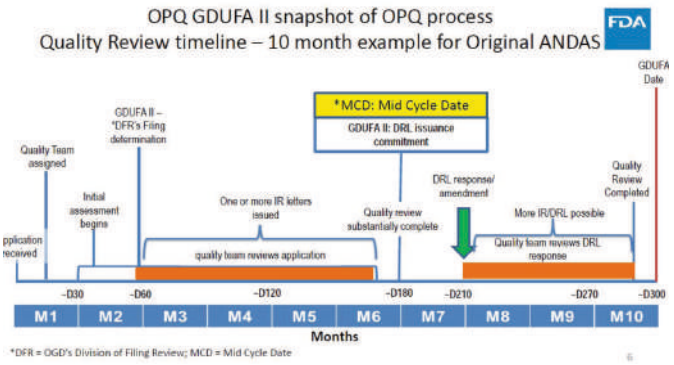

Figure 3: OPQ GDUFA ll snapshot of OPQ process quality review timeline.

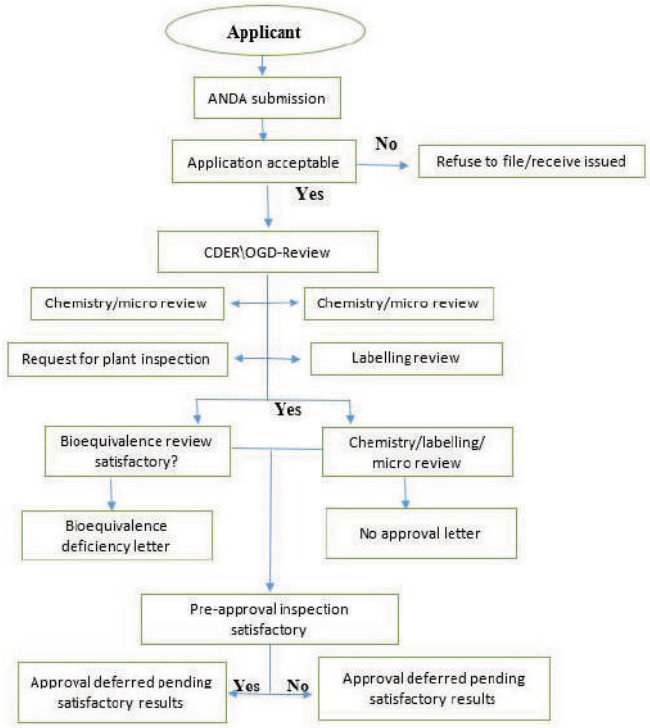

Figure 4: Review flow of ANDA application

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