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Review Article

Types of Regulatory Submission : A Review

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Abstract

The aim is to provide the basic information & understanding related to the types of regulatory submissions are in practice by pharmaceutical industries to commericalise drug product in market of perticular country. A regulatory submission includes any documentation or information submitted to a regulatory agency for review, of submitted information or in response to a request for additional information related to a healthcare product. The format for submission can be paper or electronic format like Electronic Common technical document (e-CTD) or can be filled using both way. Each regulatory agencey has its own set of rules and procedures which is important to comply and implement. Non compliance leads to the queries or refusal of submissions based on the type of problem Minor or major. FDA usually takes certain time to respond on submissions and asks submitter to reply on his queries within his required time frame. In this article different types of regulatory submissions are highlighetd with their steps

Keywords: *IND, NDA, ANDA, Regulatory Submissions, Regulatory affairs, FDA*

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Introduction

Regulatory is nothing but the regulation of particular process, in the pharmaceutical industry the regulatory requirements of the regulatory agencies are the most critical step before getting any marketing authorization. Each country in the world has its own regulatory agency which looks into the management, affairs, and approvals of various applications received by the Industry[1]. It important for the industry to comply the regulatory requirements of the agency where company (sponsor) intends to market his healthcare or drug product. In the current regulatory market of the world it seems that US & Europe has most stringent regulatory agency where compliance is required in various segment like for example Drug Master File (DMF) requirement of facility, packing material etc. regulatory requirement and fillings are vary from country to country, product which are marketed in one country can be different qualitatively as well as quantitatively in composition with each other as match the bio equivalency differs product to product, therefore it become a challenge to pharmaceutical company to file single product in all countries at one time to get approval[2]. Deep homework need to be done before starting development work to avoid any surprises after regulatory submissions.

Regulatory agency also helps sponsor in form providing guidance, information through website, OGD disso, IIG, Orange book database etc. so that pharma company should aware how to comply requirements of the agency. Getting marketing approval for the healthcare or drug product has various stages to be followed which also depend upon IP (Intellectual Property) protection and prior approval of similar kind of product. Below are the types of drug application listed of which a sponsor can file his application which contains every detail of his drug product

Following are the types of regulatory fillings or submissions
A] New Drug Application (NDA)
B] Abbreviated New Drug Application (ANDA)
C] Investigational New Drug Application (IND)
D] Biologics License Application (BLA)
E] Master files: Drug Master File (DMF) and Biologics Master File (BMF)
F] Emergency Use Authorization (EUA)

All the above submission are made through eCTD (Electronic common technical document)

A] New Drug Application (NDA)

The NDA is the application through which drug sponsors (Pharma industry) formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. for NDA it is important to have data that gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) which is the main part of the NDA

Types

1) 505 (b1) Application: full application data predominantly obtained from studies conducted by and for the sponsor
2) 505 (b2): it is the hybrid application between 505 (b1) and ANDA application (505 9j)

Regulatory equirement for NDA is given in table 1

Table 1. NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	6. Bioequivalence
7. Clinical Studies	
8. Bioavailability	

B] Abbreviated New Drug Application (ANDA)

Abbreviated New Drug Application (ANDA) is an appication made to opt approval for US Generic drug, which is already marketed. Fda Requirements For A Generic Drug Product is it should have Same active ingredient(s) i.e. Pharmaceutical equivalent, same route of administration, dosage form should be same, same strength, same conditions of use, it should be comparable to reference listed drug (RLD) – (brand name product – listed in "Orange Book), it should be bioequivalence etc[3-4]. Generic drug products are considered to be therapeutic equivalents only if they meet general criteria of safe and effectiveness, pharmaceutical equivalency, bio equivalency, adequately labeled, Manufactured in compliance with Current Good Manufacturing Practice (cGMP) regulations. FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. ANDA Marketed mostly under chemical names. This submissions costs around US $0.3 to 1.5 million and requries about 3 years timelines (including 18 months review period).

Types of ANDA

Para I: Para I filing for the launch of generic drug is made when the innovator has not made the required information in the Orange book.
Para II: Para II filing is made when patent is expired
Para III: A Para III filing is made when the applicant does not have any plans to sell the generic drug until the original drug is off patent. It means the patent of drug product is active.
Para IV: Para IV filling is made by considering the drug product is not infringing current patent i.e. by bypassing the active patent current filling can be done.

Reference Listed Drug (RLD)

The RLD is the reference drug product upon which and an applicant relies when seeking approval of an *abbreviated new drug application* (ANDA). RLD is generally the brand-name drug that has a full *new drug application* (NDA). FDA designates a single references listed drug as the standard to which all generic versions must be shown to be bioequivalent. FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs

Table 2: Innovator & Generic Companies

Top Innovator companies with their markets values (in billions)	Top Generic companies
Pfizer (US $21	Abbott
Merck & Co.(US $19)	Andrx
GSK (US $18.9)	Alpharam
AstraZeneca (US $14)	Barr
BMS (US $11.3)	Mylan
J & J (US $10.2)	Teva
Eli Lilly (US 9.3)	Ranbaxy (Now merged with Sun Pharma)
Novartis (US $7.7)	Watson
Wyeth (US $6 l)	Ivax

Hatch – Waxman Act

This act was created for a framework for patent term extensions and non-patent exclusivity periods for brand name drug product it is established for the first time an *abbreviated new drug application* (ANDA) approval process also provided for pre-patent expiration testing (Bolar Provision) and generic drug exclusivity. The ANDA is based on bioequivalence to the brand name product, appropriate chemistry and manufacturing information, and appropriate labelling. Generic drug sponsors do not have to duplicate the non-clinical animal toxicity studies nor expensive clinical efficacy and safety studies that are included in the new drug application, NDA which is submitted to the FDA for market approval of the brand name drug product.

Table 3: Drug approval History in Us

Year	Act/ Amendments
1862	Chemist in US Department of Agriculture.
1906	Federal Food and Drug Act. Established Purity std & labeling requirements.
1927	Food, Drug and Insecticide Administration, Later changed to FDA in 1930.
1938	Food, Drug and Cosmetic Act. New drug to be shown as “Safe”. Notify FDA and wait for objection.
1962	Thalidomide tragedy. Affirmative approval required before marketing. FDA reviewed all drugs marketed between 1938 and 1962.
1970	‘Drug Efficacy Study Implementation’ Act (DESI). Generics were filed on basis of ‘DESI’ study, comprised of manufacturing data, labelling information & in some cases, PK study.
1975	‘Paper NDA policy’ - Approvals on basis of review of published literature labelling information and bioequivalence study. NDA blocked publication, only one ANDA approved in year.
1980	Innovator – Erosion of patent protection due to long approval process. Generics – No approval of Generics.
1984	Drug Price Competition And Term Restoration Act (Hatch – Waxman Act)
1987	Generic Drug Scandal FDA Started preapproval scheme.

Generic Drug Review Process (ANDA)

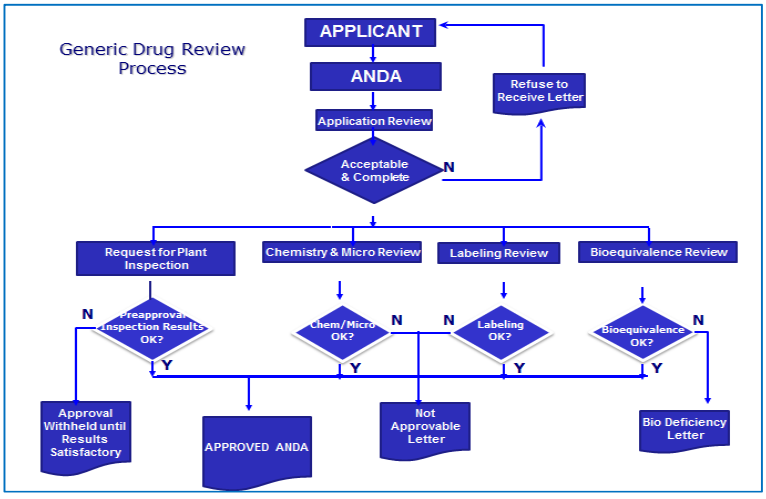

Fig.1 Generic Drug Review Process (ANDA)

C] Investigational New Drug Application (IND)
IND is nothing but the kind of submission filled at US FDA to opt permission so that sponsor can ship the experimental drug in the country for its clinical studies. This activity is done before making any marketing application for the drug has been approved. IND submissions intention is to assure safety and rights of subjects in all phases of investigation and to help assure quality of scientific evaluation of drug is adequate to permit an evaluation of the drug's effectiveness and safety. USFDA has issued guidance document on IND submission which contains details about IND procedures. The IND application contains the information intended to support the initiation of clinical trials, including a description of the manufacturing processes of the drug, the effects of the drug in animals, and any data that supports the proposed indication, such as by showing antiviral activity in cell culture for a drug that is being developed as an antiviral product. Collectively, these data are used to select the starting dose, or perhaps a range of doses, that will be tested in the initial trials. The IND application also includes a protocol for the first-in-human trial that describes the procedures that will be used to safely evaluate the drug in people

Clinical Study Situations where IND Application is Not Required If the Drug is legally marketed for indicated use the IND application not required also if study not intended to support new indication or significant labeling change and/or study not intended to support significant change in advertising and/or study doesn't involve change in route of admin, dosage, or use that significantly increases patient risks.

IND application not required even if it is IVD biological for confirmatory diagnostic procedure, if it is intended for tests of in vitro or lab research animals also for placebo products

Types of IND Application
1) Treatment in IND
This type is submitted for drug intended to treat or diagnose serious or life-threatening condition, also when there is no satisfactory alternative available, while in case if any controlled clinical trials in progress under IND then also this application is made to FDA, if any drug shows promising clinical studies then also application can be filled before FDA

2) "Emergency Use" IND
This type of application allows FDA to authorize use of experimental drug in emergency situation

Pre IND Meeting
FDA pre IND Meeting allows early communications between sponsors and new drug review divisions to provide guidance on the data necessary to facilitate IND submission. Here sponsors and representative from new drug review division meets and review the clinical data, studies conducted available for new drug, this meeting allows exchange of thoughts between sponsor and reviewer, which facilitate sponsor to convey the concept to agency.

Content of IND
IND mainly content three broad areas
1) Animal pharmacology and toxicological studies
This is an assessment as whether product is reasonably safe for initial testing in humans
2) Manufacturing information like compositions, manufacturer, stability studies and controls used for manufacturing of drug substance
3) Clinical protocol and investigator information like inform consent commitment from research subject & its review by IRB and to adhere to investigational new drug regulations.

D] Biologics License Application (BLA) [7, 8, 9]
Biological products includes virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or vaccine, also it can be composed of sugars, proteins, or nucleic acids, or a combination of these substances. This are the products which can be produce using various biotechnology methods as the source of biological product may vary from animal, human to microorganism. These products may even consist of living organism like cells and tissues, which can be utilized for prevention, treatment, cure of disease of human being.

This type of submission is applied to get permission for introducing a biological product in the commercial market. The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by sponsor / manufacturer or an applicant for a license who takes responsibility for compliance with product and establishment standards. The requirements for a BLA includes a) Applicant information, b) Product/Manufacturing information, c) Pre-clinical studies, d) Clinical studies, e) Labeling

Centre of Biological Evaluation and Research (CBER) and Centre of Drug Evaluation and Research (CDER) both division share responsibility of filling biological application, therefore before filling an applicant must evaluate the type of product and its respective division of filling CBER deals with biological products like : Allergenic, Blood, Device, Gene Therapy, Human tissue and cellular product, vaccines, xenotransplantation product while CDER deals with biological product like: Monoclonal Antibodies, Proteins, Immune modulators, Growth factors and cytokines. IND application approval by agency is necessary before filling biological license application, application can be file using form 356h for BLA and if the form is lacking with some information then FDA replies within 74 days of application

A BLA assures that the biological product is "safe, pure, and potent", all the biological product manufacturing facilities are inspect able and inspected by FDA, in case of biological product it is compulsory to have license number on each package of the biological product. After approval of application it's compulsory

to sponsor/ manufacturer to submit annual reports, reports on adverse events, manufacturing changes, and labeling changes (if any)

E] Drug Master File Submission[5]

Apart from submissions related to healthcare product approval from FDA is also sought for manufacturing facility, drug substance, packing material, excipients etc. it is called as Drug Master File (DMF). DMFs Submitted to the FDA's Center for Drug Evaluation and Research (CDER) for evaluation and approval. FDA has given all set of instruction in form of guidance document; Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application. Data in a DMF can be cross referenced to any other DMF; following are the 5 types of DMF

Types of DMF Submissions

Type I: Manufacturing Site, Facilities, Operating Procedures, and Personnel
Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
Type III: Packaging Material
Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
Type V: FDA Accepted Reference Information

Each DMF submission should contain a transmittal letter, administrative information about the submission, and the specific information to be included in the DMF. The DMF must be in the English language. Whenever a submission contains information in another language, an accurate certified English translation is required by the agency[1]. While submitting application for DMS information required like Names and addresses of the DMF holder, Corporate headquarters, Manufacturing/processing facility, Contact for FDA correspondence, Agent(s), if any, Statement of commitment, a signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it etc.

F] Emergency Use Authorization (EUA)

An emergency use authorization (EUA), is the type of submission approved by the agency when emergency situation is declared in the United States. EUA is a legal means for the Food and Drug Administration (FDA) to approve new drugs or new indications for previously approved drugs during a declared emergency.[10] Following are the examples of EUA

Table 4: Year wise emergency use authorization

Sr. No	Year	Emergency Use Authorization (EUA)
1	2009	Use of Influenza Medicines, Diagnostic Test in Response to Swine Flu Outbreak in Humans [11]
2	2016	Zika Virus Emergency Use Authorization[12]
3	2015	Enterovirus D68 (EV-D68) Emergency Use Authorization[12]
4	2014	Ebola Virus Emergency Use Authorization[12]
5	2013	Coronavirus Emergency Use Authorization (Potential Emergency) [12]
6	2013	H7N9 Influenza Emergency Use Authorization (Potential Emergency) [12]

References

1. Kumar S., Panwar R., Singh U., A review on "Regulatory affairs in the pharmacy curriculum ", Int. J. Res. Dev. Pharm. L. Sci., 2013, 2(6), pp. 690-698
2. S. Handoo, V. Arora, D. Khera, P. Nandi, S. Sahu "A comprehensive study on regulatory requirements for development and filling of genric drugs globally" Int. J Pharma Investig 2012 Jul-Sep:"2 (3): 99-105
3. Guidance for Industry, ANDA Submissions — Content and Format of Abbreviated New Drug Applications, U.S. Department of Health and Human Services Food and Drug Administration- June 2014 (http://www.fda.gov/downloads/drugs/guidances/ucm400630.pdf)
4. Abbreviated New Drug Application (ANDA): Generics - Page Last Updated: 11/16/2016 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/)
5. Drug Master Files: Guidelines, U.S. Department of Health and Human Services Food and Drug Administration- Date updated: March 11, 2005 (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm)
6. Douglas J Pisano and David S. Mantus" 'Text book of FDA Regulatory Affairs A Guide for Prescription Drugs, Medical Devices, and Biologics'.2nd edition , August 2008
7. "Biologics License Applications (BLA) Process (CBER)". FDA. 2015. Retrieved July 9, 2016.
8. http://www.fda.gov/downloads/drugs/newsevents/ucm182539.pdf
9.http://www.thefdagroup.com/thefdgroup-blog/2014/07/test-the-biologics-license-application-bla-process
10. U.S. Department of Health and Human Services, Food and Drug Administration, Office of the Commissioner, Office of Counterterrorism Policy and Planning Guidance: Emergency Use Authorization of Medical Products. July 2007
11. FDA Authorizes Emergency Use of Influenza Medicines, Diagnostic Test in Response to Swine Flu Outbreak in Humans. FDA News, April 27, 2009.
12. *Emergency Situations Page retrive on 15th Aug 2016.(http://www.fda.gov/medicaldevices/safety/emergencysituations/ucm161496.htm)*