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A REVIEW ON THE NDA 505(B)(1) AND NDA 505(B)(2) REGULATORY PATHS FOR NEW DRUG PRODUCTS AND THEIR REGULATORY IMPLICATIONS FROM THE USFDA

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ABSTRACT

In order to develop and market a novel drug in the U.S must be cognizant of this application of the Food Drug and Administration (FDA) known as the New Drug Application (NDA). Centre for Drug Evaluation and Research (CDER) is the department in the FDA that regulates the approval and review of safe and effective drugs for the public use. In general, NDA is applicable for new drugs which are not approved earlier and ANDA is for generic drugs. NDA is further divided into two types namely., 505(b)(1) and 505(b)(2) applications. NDA 505 (b)(1) is submitted by the sponsor for drugs that are novel and are to get approval for marketing and patient use. Whereas 505 (b)(2) is another FDA regulatory pathway submitted either by sponsor or applicant for approving a new drug that contains the active ingredient(s) which is/are already approved by FDA. Therefore, choosing an appropriate regulatory pathway is important. Hence, this article serves as a concise and quick guide for the applicant to determine the appropriate regulatory pathway, requirements for obtaining approval from FDA and a clear difference between these two regulatory pathways.

Keywords: FDA, New Drug Application (NDA), Investigational New Drug (IND), Common Technical Document (CTD), 505(b)(1) pathway, 505(b)(2) pathway, Reference Listed Drug (RLD)

INTRODUCTION

The FDA is the United States (US) regulatory body which is in charge of ensuring the quality, safety, and efficacy of drug products throughout the drug lifecycle. FDA adopts stringent guidelines, which when followed appropriately fastens the approval process. The NDA [via 505(b)(1) or 505(b)(2)] and ANDA [through 505(j)] are two drug development pathways in the US, each with its own provision under the Food, Drug, and Cosmetics (FD&C) Act.

New pharmaceuticals have been approved through the submission of New Drug Applications (NDAs) comprising reports of drug's safety and its efficacy since the Kefauver-Harris Drug Amendments Act was revised in 1962. In 1984, Congress passed the Hatch-Waxman Act, that established a new regulatory procedure for approving new pharmaceuticals by requiring the filing of an ANDA. From bioequivalence studies, the ANDA pathway approves generic copies of approved products known as reference listed drugs (RLDs) [RLDs are novel/new drugs which are accepted through NDA 505(b)(1) application and serve as a reference for upcoming substitutions of the similar active ingredient]. Unlike the NDA, ANDA does not require complete date on safety and efficacy. This procedure aids in identifying which clinical and non-clinical investigations should be done and how marketing applications should be presented to regulators.

The following are the essential aspects to be considered before deciding on a regulatory path:

- Determine whether the active constituent is unique or similar to a previously approved drug product in US.
- If the active constituent is the similar then check whether a Reference Listed Drug (RLD) exits or not likewise, if the active ingredient is not same then it should follow the NDA 505(b)(1) pathway.
- Check for the differences between the proposed drug product and approved drug product, for example, dose, strength, route of administration, etc., which may have an impact on the drug product safety and efficacy.
- Check if the claimed drug product is authorized for the same indication as the existing medication product.
- Is there any data available from the approved product or published literature which supports the claimed drug development?

Above listed points are not the only considerations, but are the important things

that are to be determined to select the appropriate regulatory pathway that serves as a critical step in developing and submitting an NDA or ANDA **[1]**.

A clear discussion about NDA and its two applications [505(b)(1) & (b)(2)] will be discussed below.

NEW DRUG APPLICATION (NDA)

Before the drug product is commercialized in the United States, the sponsor must submit a NDA to the FDA for approval. Sponsor can file an NDA only when the drug which is known as Investigational New Drug (IND) passes all three phases of clinical trials along with all the human and animal studies, in-vitro studies, manufacturing and its predicted label.

All of the documents submitted with the NDA assist the FDA reviewer in determining the safety and effectiveness of drug product (and whether the drug's benefits outweigh the risks), the packaging insert's appropriateness and any additional additions that need to be made, and the manufacturing methods and controls used to maintain the drug's quality.

NDA is submitted via two regulatory pathways that are 505(b)(1) and 505(b)(2) which are discussed in detail in the further sections.

A. 505(b)(1) regulatory pathway

This is a traditional regulatory pathway for those novel or new drugs that are not been studied or approved previously. This regulatory process necessitates the submission of all comprehensive investigation reports demonstrating the drug safety and efficacy. The sponsor, or any competent person acting on behalf of the sponsor, is responsible for conducting both non-clinical and clinical research. This is a time-consuming procedure, and these studies serve as evidence for the regulator when deciding whether to approve or reject a drug product.

Investigational New Drug Application (IND)

The IND is necessary for the start of human trials on a novel drug. Clinical trials for novel drugs are undertaken as part of the development process before they are marketed. These studies are used to see if newly produced drugs are safe and effective in humans. For the 505(b)(1) pathway IND is the key role in providing the data supporting the utilization of drug products in humans. IND application mainly includes reports from the non-clinical studies and published literature along with the initial quality parameters and manufacturing details. An IND contains data from animal pharmacology and toxicity research, manufacturing data, clinical procedures, and investigator information, among other things. All the details required for the IND application are mentioned in the 21 CFR part 312.

Title 21 Volume 5 Code of Federal Regulations (CFR) part 312 Chapter-1 of FDA includes regulations and requirements regulating the use of investigational novel drugs, including procedures and requirements for submitting and reviewing investigational new drug applications (INDs). This part contains 9 subparts (Subpart A- Subpart I) [Click on the link attached for more information https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312].

Once IND gets approval, sponsor can start the clinical trials in humans in three phases (Phase 1, 2, 3) **[tab-1]**. This data collected during the IND phase will become the foundation for NDA. When compared with IND, NDA requires well studied and complete information about the drug product. This includes all the data including in the Common Technical Document (CTD) Module 2,3,4 and 5 which includes the data about clinical and non-clinical studies, pharmacokinetic/pharmacodynamic studies, summaries of data, quality of the drug product, manufacturing details with equipment and materials used, impurities if any and in-process quality control parameters. [A clear idea about phases of clinical trials is given below and along with the CTD triangle **(Figure 1)**]

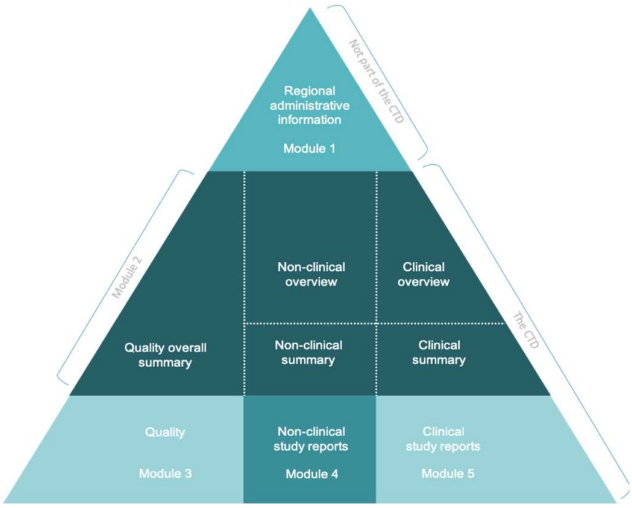

Figure 1: CTD Traingle

Table 1- Phases Of Clinical Trials

Clinical Trails Phases	Study Population	Length of Study	Purpose of Study	% Of Drugs Passed
Phase-1	**20 to 100 healthy volunteers or people with the disease/condition**	**Several months**	**Safety and dosage**	**Almost 70% of drugs move to the next phase**
Phase-2	**Up to several hundred people with the disease/condition.**	**Several months to 2 years**	**Efficacy and side effects**	**~33% of drugs move to the next phase**
Phase-3	**300 to 3,000 volunteers who have the disease or condition**	**1 to 4 years**	**Efficacy and keeping track of adverse events**	**~25-30% of drugs move to the next phase**
Phase-4 (Pharmacovigilance)	**Several thousand volunteers who have the disease/condition**	**Throughout the life cycle of drug**	**Safety and efficacy**	

B. 505(b)(2) regulatory pathway

An NDA specified in section 505(b)(2) of the Act is filed under section 505(b)(1) of the Act and authorised under section 505(c) of the Act as a 505(b)(2) application. The application contains comprehensive reports of safety and efficacy investigations in this regulatory pathway, but at least some material necessary for approval originates from studies that were not conducted by the sponsor and for such data the applicant has not secured a right of reference.

This pathway came into force after the amendment of the Drug Price Restoration Act/ Hatch-Waxman Act in 1984. As a result, the 505(b)(2) pathway helps applicants that have non-novel/new drug products that can be approved based on data previously published by the sponsor for the same active ingredient, with the applicant publishing any additional information as needed.

A 505(b)(2) application is a new drug application that includes comprehensive reports of research conducted to demonstrate the safety and efficacy of the product. Some information required for approval is taken from studies conducted previously by the listed drug's sponsor and for which the applicant has not obtained a right of reference or use, such as the Agency's finding of safety and/or effectiveness for a listed drug or published literature, in these 505(b)(2) applications. The other form of NDAs, known as "stand-alone" NDAs, are submitted under section 505(b)(1) of the FD&C Act and need comprehensive records of studies undertaken on safety and efficacy that are done by the applicant and have a right of reference or use **[2-3].**

Changes that are acceptable for submitting 505(b)(2) application

- Someone other than the claimed person studies a novel chemical entity (NCE) and publishes the necessary data. The NCE can be a prodrug or active metabolite of the already published active ingredient.
- Change of active constituent in its different salt or ester or amide or chelate or isomer or racemic mixture of the active ingredient that is listed in RLD containing same active molecule.
- Combination products in which already approved drug product is combined with a medical device or biological.
- Changes in dosage type, strength of dose, route through which drug is administration (oral, intravenous, intramuscular etc.,), indication, dosage regimen and formulation can be applied through this pathway
- Naturally derived either from the plant or animal or marine sources or

those active ingredients which are developed from the recombinant technology of an already approved active ingredient can get its approval through this pathway.

- Bioequivalent drug products are generally accepted through the 505(j) pathway (ANDA submission) but when the bioequivalence of that drug product is not within the standards of 505(j) rules then its approval can be made through the 505(b)(2) pathway.

Claims that are ineligible through 505(b)(2) regulatory pathway

- A novel active constituent that hasn't been approved before, hasn't been investigated, or doesn't have any relevant published literature on medication safe use in humans and its efficacy.
- Application for a duplicate listed product which is acceptable through 505(j) application.
- Application for any drugs that have relatively less bioavailability than the RLD or having more expected risks/adverse effects/side effects over the benefits than the drug listed.

Content necessary for 505(b)(2) application

- Sections of the application which uses the information to which the applicant will have no right of reference are indicated.
- If the application is based on existing data from the Agency, the applicant must identify any relevant published safety and effectiveness data.
- Information related to patent over the RLD that the Orange Book published in it.
- More information is required if the applicant believes it is entitled to marketing exclusivity.
- Section 505(b)(2) of the Act requires a certification of patent or declaration which is to be submitted by the applicant.
- Certification of the indication change. If the proposed medication's indication is different from the RLD, the proposed drug product shall be accompanied with a certificate explaining the change in indication.
- Statement on the exclusivity of the drug. Suppose there is any exclusivity then that may impact the filing and approval of the drug through 505(b)(2).
- A detailed list of bioavailability and bioequivalence studies trying to

compare the proposed medication to the RLD.

- Additional studies if necessary is to be submitted to support the changes made in the proposed drug.

Before the submission of the application, the candidate should make sure to submit a plan of work to the FDA's novel drug evaluation division, detailing the types of studies that will be conducted and the initially published data of the active ingredient on which the applicant will rely, and the FDA will provide guidance **[3]**

505(b)(2) Application Benefits

- The 505(b)(2) application will be beneficial to pharmaceutical corporations who seek to decrease competition in the pharmaceutical industry and shorten the time it takes to produce a new medicinal product by omitting most non-clinical research and safety and efficacy testing.
- Relatively low risk since the drug product is previously accepted.
- Because the applicant must undertake fewer research, the cost and time for development will be reduced.
- Can reduce the time of approval when compared to the 505(b)(1) application.
- Three, five, or seven years of market exclusivity may be available **[4].**

The flow of developing a drug product and submission criteria of 505(b)(2) application (Fig-2)

- *Start*

When preparing a 505(b)(2) development programme, consider how the new drug product differs from and is distinguished from the innovator drug, particularly in case of pharmacokinetic (PK) characteristics. Having a solid PK development strategy enables you to get through the regulatory clearance process quickly and at a cheap cost. Therefore, the first step is to identify which drugs are appropriate for the 505(b)(2) pathway and can be authorised.

- *Feasibility*

Once the suitable drug product is identified, by assessing the pre-development evaluation of the claimed product there should be a clear statement whether the changes made are acceptable and beneficial, whether the manufacturing is scalable or not and the ingredients in the drug product are economical or not (falls under *Scientific Viability*). There should be a clear consideration over the risks/benefits ratio and the applicant should make sure that the benefits should always outweigh the risks (According to the Declaration of

Helsinki), applicant should also make sure that the benefits should not be less significant than the RLD (falls under *Medical Viability*).

Another duty of the applicant is to check and collect all the relevant data on clinical trials, non-clinical studies which are already been published on RLD previously. Finding out a unique label information that helps in the boosting of the proposed drug (falls under *Regulatory Viability*). The next step is to find out the capacity of the proposed drug in the US market. For successful marketing and distribution of drug products, the key points to be remembered are the demand of the proposed product, level competition, chances of substitution, population density for whom this will be useful (falls under *Commercial Viability*).

- *Pre-IND meeting:*

The pre-IND meeting with the FDA starts off the 505(b)(2) procedure. Following a successful pre-IND meeting, formulation development starts with necessary non-clinical investigations, followed by IND filing. The building blocks for *formula development* in the 505(b)(2) process is comparing the proposed molecule to the RLD, looking over the modifications made, and then generating a new formulation that is safe to human use with good efficacy.

In nonclinical research, public data can be used instead of new trial data, and safety and effectiveness testing aren't necessary for most nonclinical studies to gain 505(b)(2) approval. Because 505(b)(2) applicants collect the data over safety and efficacy profiles from the already published reports. Coming to Phase-I studies, the applicant should undergo a Phase I bridging study to compare the drug's pharmacokinetic characteristics to those of the RLD. The type of Phase I bridging study for a 505(b)(2) drug is determined by the dosage form and the reference product. Phase II or Phase III studies are not required in some 505(b)(2) petitions (for example, changes in some dosages may depend only pharmacokinetic studies of phase-1 alone). Phase II and Phase III studies can be interconnected in some 505(b)(2) NDAs to make a clearer statement about the safety of drug and also the effectiveness of drug used for human use. In the case of prodrugs or rDNA technology products, Phase III studies may be undertaken, albeit in smaller populations than Phase III of the 505(b)(1) procedure.

Existing data for a 505(b)(2) application origin either from the already accepted data by the FDA during a marketing application or from the data in the public domain (which may include data for indications not previously authorized by the FDA), or data from overseas clinical trials. The next step

in 505(b)(2) process is *NDA submission.* Compared to 505(b)(1) the time necessary for the drug development and reaching the approval phase by FDA is less in 505(b)(2). After NDA approval now the proposed drug product can be commercialized into the market (*Phase IV).* The factors to be mentioned during commercialization are already notified in the Feasibility stage, and pricing and marketing strategies are developed based on those parameters to decide how to well we can promote physician preference, consumer requests, and drug product sales **[12]**.

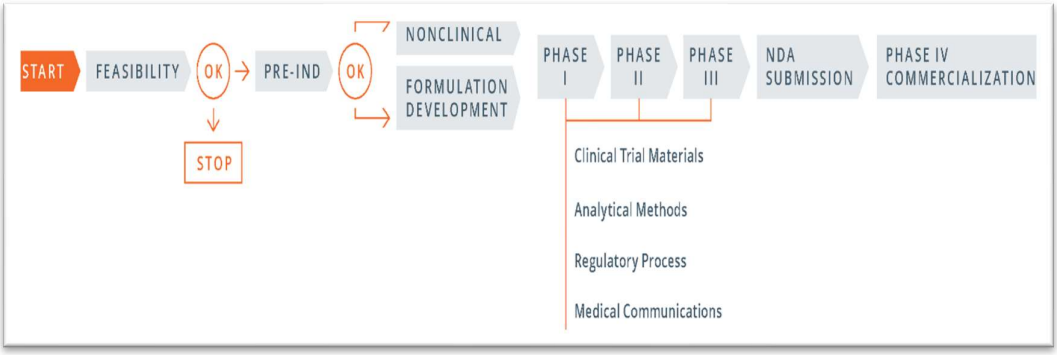

Figure 2-505(b)(2) Pathway

Patent and marketing exclusivity for 505(b)(1) and 505(b)(2)

The US Patent and Trade Office grants patent rights based on intellectual property. Even if a patent is valid for 20 years, it might be contested and declared invalid.

Marketing exclusivity refers to the period of time when a generic version of a drug cannot be created. It is given by the FDA as a financial incentive to do research. The period can last anywhere from 3 to 7 years, with paediatric trials allowing for a 6-month extension in some circumstances.

In 505(b)(2) some applications will not get exclusivity if clinical studies are not conducted and are accepted based on bioavailability studies. For example, if the claimed drug is sustained release and the RLD is immediate release then exclusivity is not granted **[13].**

Supplemental New Drug Applications (sNDA)

Documentation submitted to the FDA on a drug ingredient or product that is already the subject of an authorised NDA is known as a supplementary NDA (SNDA). Labelling revisions, a new or extended therapeutic indication, or a different dosage form are all reasons for supplements to be filed. For example, for labelling changes, the sponsor may want to add a new specification or test method or changes in the methods, facility, or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, and purity that it purports to

possess. The sponsor may desire to modify the limitations for a specification, create a new regulatory analytical technique, or remove a specification or regulatory analytical method for drug substance and/or drug product. Furthermore, the sponsor may desire to extend the medicinal product's expiry date based on data acquired under a new or updated stability testing technique not approved in the application, or design a new mechanism for reprocessing a batch of the drug product that fails to meet specification. However, the sponsor must thoroughly detail the modification in each condition specified in an authorised application in an SNDA, in addition to the variation previously given for in the application.

Note: SNDA is submitted by the sponsor itself. Sponsor after submitting the 505(b)(1) application can make changes in the drug substance based on the FDA reviews or market requirements or consumer requirements or for better marketing approach.

Table 2: 505(b)(1) vs 505(b)(2)

505(b)(1)	505(b)(2)
Standard full NDA application submitted by sponsor with the reports of pivotal studies on safety and effectiveness	Variable application, where most data is taken from the 505(b)(1) which is already published by sponsor
New Chemical Entity (NCE) which is not approved by FDA before and protected by patents	Not an NCE, already approved by FDA and protected by patents
Includes new active constituent, new ingredients, new formulation.	Includes same active constituent but the ingredients, formulation strength, dosage form, route of administration, manufacturing process varies.
All the non-clinical and with all the phases of clinical trials are required	All the studies are not always required. Can rely on the data already published by sponsor.
Takes around 8-15 years for drug development and getting approval from FDA	Takes 2-5 years for the development and getting approval from FDA

FDA Drug Review Process (Simplified Version)

1. Preclinical (animal) testing/ Laboratory testing.
2. An investigational new drug application (IND) which gives information regarding what the new drug proposes for human testing in clinical trials.
3. Phase 1, Phase 2 and Phase 3 clinical trials.
4. The pre-NDA period is just before a new drug application (NDA) is submitted which is the common time for the FDA and drug sponsors to meet.
5. An NDA is a standard procedure for the FDA to examine a drug product for marketing clearance.
6. After an NDA is received, the FDA reviews the application and takes a decision in 60days.

7. An FDA review panel reviews the sponsor's research on the drug's safety and efficacy if the FDA approves the NDA.
8. The FDA examines the information on a drug's professional labelling (like drug usage, formulation, shelf life etc.).
9. FDA also inspects the facilities where the drug will be manufactured and it is part of the approval process.
10. The FDA's reviewers will either approve the application or provide a detailed response letter to the applicant. Then based on the response drug can be marketed if it is approved **[16]**.

CONCLUSION

Anyone needs to understand clearly all the regulations made by the regulatory agencies to maintain a safe supply of medicine in benefiting public health. Developing a new product puts a great responsibility on the shoulder of the sponsor since it requires great efforts in researching the data, conducting trials and getting FDA approval. This review article aims to help not just applicants, but also students who are facing trouble in understanding the differences between 505(b)(1) and 505(b)(2) and their requirements. One of the departments in FDA called Centre for Drug Evaluation and Research (CDER) is in charge of NDA approval. 505(b)(1) pathway is for the novel or new drugs and for those drugs that are not accepted through 505(b)(2) pathway. This pathway requires all the investigation reports, non-clinical data and clinical data for getting approval. 505(b)(2) pathway is for those drug products which have the similar active ingredient which is previously approved (RLD) and relevant information necessary for approval can be taken from the previously published data or literature on the similar active ingredient. This paper also gives a clear view of the flow of the 505(b)(2) process stepwise. This paper also highlights a clear description of the USFDA, NDA and its 2 main regulatory pathways i.e., 505(b)(1) and 505(b)(2) including the data that is to be collected and submitted during filing NDA and information regarding patent and marketing exclusivity.

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