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MINI REVIEW

THE 505 (B) (2) PATHWAY: OLD DRUG IN NEW PACKET

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Drug development process is expensive, time-consuming and risky affair. To comply with FDA approval criteria, companies need to invest enormously; even though the process does not guarantee the success. There are two main FDA approval processes for the products to reach the market, which are known as New Drug Application (NDA) and Abbreviated New Drug Application (ANDA). This mini review concisely addresses the rationale of 505 (b) (2) pathway that is hybrid between these two FDA approval approaches. The 505 (b) (2) approach has become prominent over the time for the pharmaceutical drug development companies that wish to ease the product approval with much less efforts, resources and revenue as compared to full NDA, yet meeting the unmet therapeutic needs by launching superior quality products in less time and efforts, consequently earning good business and surviving in this competition-based industry.

Keywords: Drug development, FDA, NDA, ANDA, 505 (b) (2)

Introduction

Bringing a new drug to market is a costly and time-consuming process. As per the study conducted by the Tufts Center for the Study of Drug Development, the cost of bringing a new drug to market requires an average $2.558 billion, which includes all the necessary steps to gain FDA (Unites States Food and Drug Administration) approval. For many drugs, this process takes as long as a decade or more[1]. In addition, most of the new drugs in the early stages of research restricts it to reach or never reaches the market.

The Drug Development Regulatory Pathways: A Quick Look

The major regulatory pathway for drug approvals by FDA to reach the market falls under two categories: New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA). Fundamentally, the NDAs are for new drugs that have not yet been approved, and ANDAs are for generic products. However, there is an additional pathway, which falls between these two and known as 505 (b) (2)[1]. The quick look at a difference among three pathways are depicted in **Figure 1**.

NDA, called as 505 (b) (1), is the format for the new chemical entity (NCE) or new molecular entity (NME) that the sponsor company or manufacturer uses to bring a formal proposal to the FDA. The NDA is made with an intent that a new drug should be approved and made available for use by patients in the United States. The NDA includes a great deal of information and data from study results about the drug being evaluated for approval[2]. The information includes the ingredients, how it's made, pre-clinical (animal model) study results, clinical trial study results (in humans), pharmacodynamics (what the drug

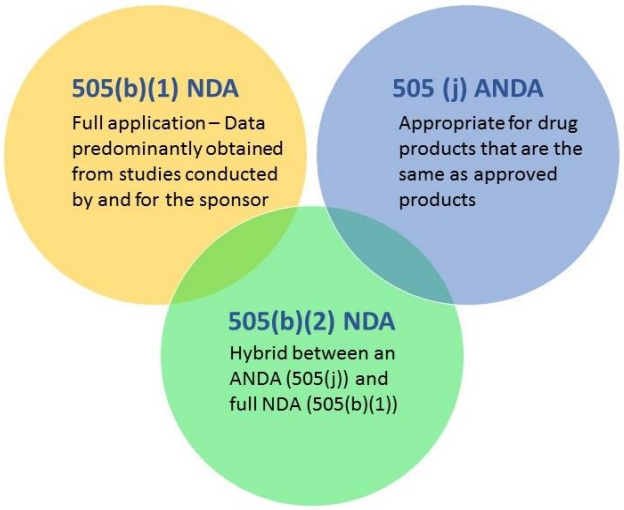

Fig. 1. Quick look to the FDA approval pathways

does to the body) and pharmacokinetics (what the body does to the drug), and how it will be packaged[2]. It takes myriad of time and resources for a manufacturer to complete all the necessary requirements to submit a successful NDA to the FDA for review. ANDA, called as 505 (j), is used to gain approval for a generic version of a drug that is already on the market. Getting approval through this pathway involves the manufacturer to provide evidence to the FDA that the generic product is comparable to the currently approved product. This includes study results obtained through the analytical chemistry and bioequivalence evaluations. It is important to note that the approved indication, route of administration, and strength for the generic will be the same as the original (or reference) product. This pathway is "abbreviated" because preclinical and clinical trials are not required as it implies to the already approved drug whose preclinical and clinical data are known and available through the studies performed by the innovator company or manufacturer of the original product and had already been reviewed by the FDA as part of the approval process[3]. Therefore, this application sets the generic manufacturer free from the extensive burden of similar trials again. This saves a great deal of time, resources and revenue for the manufacturer as compared to that of NDA.

What is 505 (b) (2)?

The 505 (b) (2) NDA is one of the three FDA drug approval pathways and represents a fascinating hybrid regulatory strategy for many clients. This pathway was created by the Hatch-Waxman Amendments of 1984, with 505 (b) (2) referring to a section of the Federal Food, Drug, and Cosmetic Act. The provisions of 505 (b) (2) help to avoid unnecessary duplication of studies already performed on a previously approved ("reference" or "listed") drug. This provision provides FDA the permission to rely on data not developed by the NDA applicant. Therefore, the 505 (b) (2) pathway provides manufacturers an opportunity to acquire FDA approval for some drugs without performing all the studies which are required with an NDA. These drugs are neither strictly generics nor entirely novel new molecular entities. The 505 (b) (2) can be an option for drugs with a new aspect related to indication, dosage form or regimen, strength, combination with other products, or other unique traits[1]. Although the 505 (b) (2) NDA contains full safety and effectiveness reports, some of the information required for NDA for safety and efficacy of the drug itself, is allowed to come from studies originally not carried out by the applicant; thereby making the approval process much less costly and much faster as compare to the traditional 505 (b) (1).

Key Features of 505 (b) (2) Pathway

As discussed in previous section, a key feature of the 505 (b) (2) pathway is that it allows a manufacturer to submit their product for FDA review by including data and/or study results originally collected by another manufacturer or researcher. To do so, the manufacturer of the 505 (b) (2) eligible product requires to build a correlation between their version of the product, or the drug in it with the reference product. This could include data and results of bioanalytical testing, preclinical studies, or even clinical trial results. If the manufacturer of eligible 505 (b) (2) becomes successful in their effort to include supporting evidence from other researchers in their submission, the manufacturer won't have to redo these studies themselves. While the 505 (b) (2) path allows for using the research of others as a component of their FDA submission, the manufacturer of the 505 (b) (2) product may still need to complete some of their own research in other areas to help fulfil all the various requirements of the FDA to earn approval. Another fascinating aspect of gaining approval through the 505 (b) (2) is that the approved product is eligible for 3-5 years of market exclusivity, which is 5-years in case of full-NDA and six months in case of ANDA[3]. Market exclusivity period allows the product to be protected from competitors and benefits the manufacturer/innovator. In addition, as the 505 (b) (2) approval is not granted for a simple generic of a previously approved product, it may reach additional patients or offer advantages over existing products for the currently available treatment. The summary of stepwise process toward 505 (b) (2) approval pathway is depicted in **Figure 2**. Manufacturers have recognized the potential benefits of 505 (b) (2) This is done with creating new, distinguished products with huge market value offering a value addition to company's product line extension and contribute in its economic health and status. Manufacturers have recognized the potential of 505 (b) (2) pathway as evidenced from the approvals granted in last few years[4] (**Figure 3**).

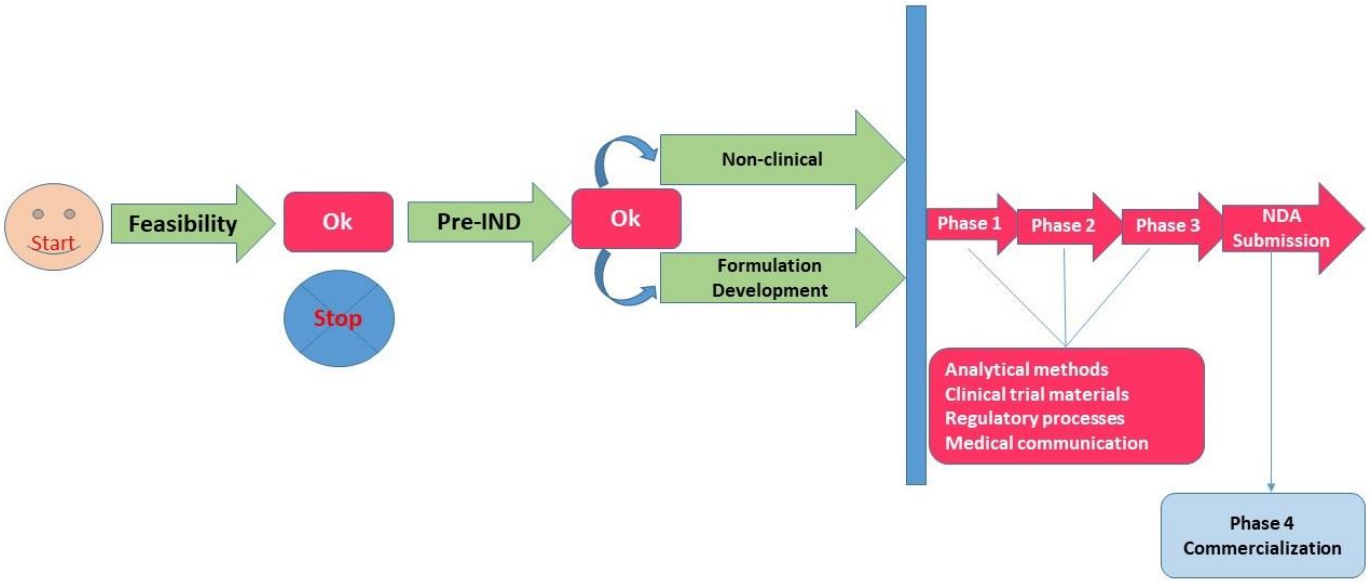

Fig 2. Stages of 505 (b) (2) approval pathway

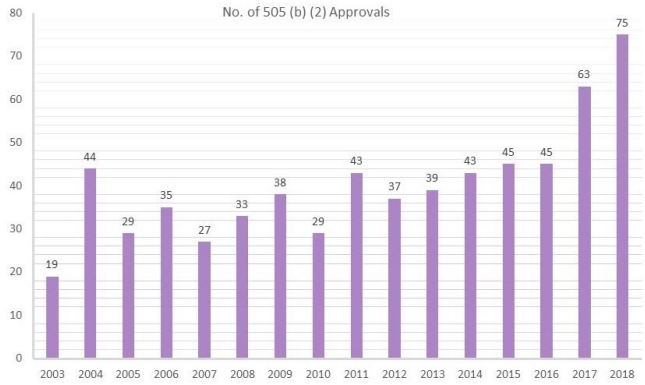

Fig. 3. Drugs approved through 505 (b) (2) pathways

Major Advantages of 505 (b) (2)

The 505 (b) (2) is specifically profitable for pharmaceutical and generics companies looking to ease competitive forces in their business environments. Major advantages of the 505 (b) (2) pathway include:

- Relatively lower risk because of previous drug approval
- Lower cost, accelerated development due to fewer studies
- May qualify for 3, 5 or 7 years of market exclusivity

Which are Ideal Drug Candidates for 505 (b) (2)?

The 505 (b) (2) is useful when a company wants: (i) to create a new dosage form that is faster acting; (ii) to combine two active ingredients in a novel way; (iii) to provide a route of administration or mechanism of drug delivery that enhance patience compliance or physician's preference over existing product; (iv) to seek approval for a new indication for an already-approved drug; (v) to carry out an Rx-to-OTC switch. This sort of new products usually contains well-understood drug candidate that are present in existing, approved drug products (so called reference drugs). Therefore, companies must need only to create a bridge between what is already known about the previously approved reference drug and the novel drug product or indication to proceed for and acquire the 505 (b) (2) NDA approval. In Europe, a regulatory approval route similar to the 505 (b) (2) pathway is the hybrid procedure based on Article 10 of Directive 2001/83/EC1. **Table 1** enlists the ideal candidates for the 505 (b) (2). Biological therapeutics, so-called biosimilars, are not suitable for approval under the 505 (b) (2) pathway.

Table 1. Ideal 505 (b) (2) candidates

Drugs with new indications
Drugs with changes in dosage form, strength, formulation, dosing regimen or route of administration
New combination products
Prodrugs of an existing drug
Branded generics
Orphan drugs
Drug-device combinations
Drug-device combinations (in rare case)

Summary

Over the last few years, the 505 (b) (2) hybrid pathway has become prominent in the pharmaceutical development industry. Although there is no specific guidance on 505 (b) (2) drug development programs, most FDA guidance documents referring to NDAs are relevant in understanding the rationale of the studies that were previously conducted. The manufacturer must be able to bridge the gap or identifying the better-over-existing to rationalize the need for acquiring an approval via the 505 (b) (2) pathway.

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