APP SCIENTIFIC UPDATES
AN OFFICIAL BIANNUAL MAGAZINE OF ASSOCIATION OF PHARMACY PROFESSIONALS

ASU Vol. 8, No. 1-2 (2020)

MINI REVIEW

FDA'S "505" REGULATIONS FOR PRODUCT APPROVAL: HOW 505(B) 2 IS A UNIQUE PATHWAY ?

Sunita Dahiya*

Department of Pharmaceutical Sciences, Pharmaceutical Research, Development and Processing Laboratory
School of Pharmacy, University of Puerto Rico-Medical Sciences Campus, San Juan, PR 00936, USA

Determining the right approval pathway is crucial for successful approval of a new drug or a new drug product. This article briefly discusses the types of regulatory pathways for FDA approval of the new drug or new product along with significant differences among each type.

Keywords: FDA regulatory pathways, NDA, ANDA, 505(b)2, hybrid pathway

Introduction

The "505" comes from Section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act. In 1984, 505(J) and 505(b)(2) were added to this section under Hatch-Waxman Amendments by the Drug Price Competition and Patent Term Restoration Act of 1984 in order to rectify the shortage of generic approvals in the United States (US)[1].

Applications of "505"

In Section 505 of the act, Hatch-Waxman defined a number of different types of drug applications under subsections for three types of applications[1,2] (**Figure 1**).

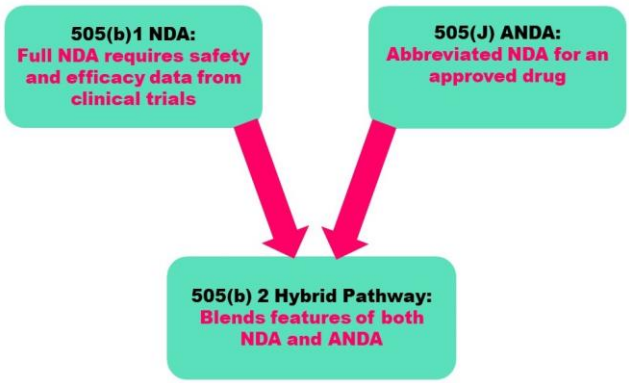

Fig 1. FDA's regulatory pathways for drug and product approvals

The 505(J) ANDA

This application is used to approve a generic version of a drug that is already on the market when the innovator drug is near to patent expiration. The main requirements for an "Abbreviated New Drug Application (ANDA) includes demonstration of bioequivalence (BE) with the innovator product as well as a food effect study if the new product is an oral dosage form.

An ANDA, as defined in section 505(J) of the act, is an application intended to demonstrate "equivalence", meaning an identical API, in the same dosage form, with identical strength, efficacy, route of administration, quality, therapeutic indication and more, to a previously approved New Drug Application (NDA) product. Thus, ANDAs are exclusively used for filing applications for those generics which essentially duplicate existing approved API.

The 505(b)(1) NDA

This application is used to file approval of new chemical entity (NCE) for which no chemical safety or efficacy data exist, that means the safety and efficacy reports have never generated or submitted before for this moiety. Therefore, a full NDA essentially contain full reports of safety and efficacy data. Studies under the 505(b)(1) pathway are conducted by and for the sponsor and are the primary sources of data used to gain FDA approval for a new drug to be available in the market for clinical use by patients in the US. The 505(b)(1) requires the longest time and highest resources among all three pathways. Thus, a 505(b)(1) NDA requires comprehensive safety and efficacy studies for a new, unapproved chemical entity demonstrated through controlled clinical trials.

The 505(b)(2) Hybrid Pathway

This pathway was created to simplify and speed up the approval process for products incorporating the already approved API. In such cases, the FDA relies on previously submitted clinical data by others and not on the applicant of the 505(b)(2) application. Not surprisingly, the European equivalent of the 505(b)(2) application is officially known as the Hybrid application. The intent of this pathway is to speed up the FDA application and review process and encourage further innovation with already approved chemical entities, which eliminates need of duplication of previously performed work.

Thus, the 505(b)(2) is a hybrid of pathway that incorporates elements of a full NDA (505(b)(1) and an ANDA (505)(J). This hybrid application is a blending of old and new drug information in the context of seeking FDA approval of a new drug product of an existing approved API. The 505(b)(2) is usually reserved for situations in which a modification, which is typically an improvement, is being made to the innovator drug resulting in the creation of a whole new "drug product" – with its own exclusivity as it essentially possesses a novelty as compared to an existing approved product. This novelty might be in form of a new therapeutic application, new delivery mechanism, a different strength, or something else, but it relies on an existing approved product and its associated studies – sometimes performed by others. A 505(b)(2) application will typically contain full safety and efficacy studies, but some portion of the data comes from an external, existing source.

There are a number of situations in which the 505(b)(2) stands out as great decision. Companies with a novel device, delivery system, or delivery technology can take advantage of the pathway to use it for existing approved therapeutics. Projects involving a modified mode of drug delivery are excellent candidates for the 505(b)(2) regulatory route. For example, a new transdermal system can be introduced for a compound that has only been previously used via inhalation. The new drug uses the same therapeutic compound – and perhaps even targets the same indication – but it also solves a problem. In this case, the transdermal delivery system could replace a complex inhalation device which delivered poor efficacy due to dosing inaccuracies. Likewise, a new delivery coating that allows a compound to survive the intestine can enable an oral dosage form, improving patient compliance and efficacy.

How to Identify Potential 505(b)(2) Drug Candidates ?

When considering the feasibility of pursuing the 505(b)(2) pathway, it is essential to identify if the intended drug product has documented market differentiation, low risk of development, and high profit-potential. The types of products listed below are ideal 505(b)(2) candidates[1-4]:

- Drug with different form of the drug substance
- Prodrugs of an existing drug (as they do not meet the 505(J) ANDA requirements)
- Drugs with changes in dosage form, strength, formulation, dosing regimen or route of administration
- Drugs with new indications
- New combination products

Which Candidates are Not Suitable for 505(b)(2) ?

Biological therapeutics, also known as biosimilars, are not suitable for approval under the 505(b)(2) pathway. Such biosimilar products can be approved via a Biologics License Application (BLA), via Section 351(K) of the PHS Act (42 U.S.C. 262(K), added by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). A 505(b)(2) product requires an NDA submission to the FDA's Center for Drug Evaluation and Research (CDER), whereas biosimilars require submission of a 351(K) BLA to the Center for Biologics Evaluation and Research (CBER).

What are Benefits of the 505(b)(2) ?

The 505(b)(2) pathway can be valuable to pharmaceutical companies for a variety of reasons as follows. Major objective of this pathway is to ease the cost and time associated with the traditional full NDA up to certain extent.

- Eliminate the need for most nonclinical studies and extensive safety and efficacy tests
- Reduce the potential risk due to previous drug approval
- Reduce the cost as fewer studies are required
- Accelerate the development and commercialization
- Potential to qualify for 3-7 years of market exclusivity

ANDA versus 505(b)(2): What About Cost Consideration and Market Exclusivity ?

A 505(b)(2) is more expensive than a typical ANDA, but it is still vastly cheaper than an NDA. This higher cost accounts for some clinical studies that must be conducted to bridge the difference between its proposed product and the reference brand product. At the same time, this higher cost confers benefit such as a period of post-launch exclusivity and the duration of exclusivity depends on the compound and the indication. For example, a drug compound requiring only phase I studies will not receive any marketing exclusivity period while orphan indications can receive exclusivity up to 7 years.

How to Streamline 505(b)(2) Development ?

The 505(b)(2) pathway is becoming increasingly popular for approval of repurposed, reformulated, or unapproved marketed products. It is to be noted that suitability of the 505(b)(2) regulatory pathway include those drug products for which existing information can be leveraged to reduce the time and cost for approval. Despite its tremendous potential to sustain product's life cycle with revenue generation for a blockbuster drug, the 505(b)(2) development can be challenging for sponsors. When planning to create a 505(b)(2) development program, it is essential to determine how the new drug product is different and similar to the innovator drug, especially in relation to its pharmacokinetic (PK) characteristics. From there, all information relevant to the new drug product can be leveraged by creating a "PK bridge" linking the in vivo performance of the new drug product to that of the innovator drug product. It is essential to understand how the two products can be linked in the best way for maximizing the full streamlining capability of the 505(b)(2) approach. Therefore, a robust PK development plan in 505(b)(2) strategy enable rapid advancement of the regulatory approval process at minimal cost. Typically, when considering oral products, PK studies that address bioequivalence, bioavailability, multiple-dose PK, and food effect can often meet the minimum PK requirements. FDA's final guidance for industry "Determining Whether to Submit an ANDA or 505(b)(2) Application" provides foundational guidance to assist prospective applicants and provides direction in determining which one of these pathways is more appropriate. Interested readers can further refer to reference number 4 for detailed information on this guidance.

Conclusion

The 505(b)(2) pathway combines benefits of both ANDA and full NDA including short development span, relatively lower development cost, lower risk and potential of market exclusivity. The company should carefully select and monitor a 505(b) 2 pathway development program.

References

1. https://camargopharma.com/resources/what-is-505b2
2. https://www.nuventra.com/resources/blog/what-is-505b2
3. https://www.pharmacytimes.com/view/505-b2-regulatory-pathway-for-new-drug-approvals-
4. https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/abbreviated-approval-pathways-drug-product-505b2-or-anda-september-19-2019-issuetps

asu013
(Received: 7th Dec, 2020)
*sunita.dahiya@upr.edu
https://www.appconnect.in/magazine/asu-2020