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AN OVERVIEW ON USFDA 505(B) (2) NDA AND EU HYBRID MEDICINAL PRODUCTS

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ABSTRACT

Drug development is one of the challenging processes to make profit. Number of promising molecule are wash out in preclinical and clinical studies and some are fail in last stage of marketing, out of them only one molecule is their which clear the all phases of clinical trial and get marketing approval. Pharmaceutical industry invests million of dollars on launching a new molecule and also require 12-15 year of time period for such studies from preclinical studies to marketing approval. Thus pharmaceutical companies are shifting towards the shorter and less costly ways. That can be achieved by 505(b)(2) application of the FD&C Act and Article 10(3) of the directive 2001/83/EC in EU. This pathway is cost effective and have lower risk and used by most of pharmaceutical industry. This review gives the brief overview of hybrid application in EU and US and their effectiveness, which avoids the known possible risk and launches the drug easily with lower cost.

KEYWORDS: FD&C Act (Food, Drug, and Cosmetic Act), EU (European union), 505(b)(2) application, Article 10(3), hybrid application.

1. INTRODUCTION

The process of bringing a new drug to the market after the discovery of lead compound is known as drug development which includes preclinical studies, clinical studies and finally to obtain regulatory approval to market the drug. Brining the new drug to market form drug discovery through clinical trial to approval is very costly process.

Pharmaceutical industry spends billion of dollar for launching a new molecule. The rising cost along with the failure to develop new molecule led to decrease in new drug application filing.[1] Among the thousands of promising molecule only one can reach to the market rest of them wash out during drug development phases and that one molecule successfully reach to market also takes approximately 12-15 year. The new drug development is extensive as well as expensive process. However there are some novel approaches that can be helpful for drug development with reduced period of time and cost and thus boost the drug development.

This paper dissects the regulatory framework in the U.S and Europe for the development of known drug in new therapeutic areas.

2. Legal Framework in the US

In US area 505 of section V of the Food, Drug, and Cosmetic Act (FD&C Act) present the necessities that must be satisfied by candidate for new drug application (NDA), in which subsection (b) (1) gives prerequisites for full dossier NDA and application under subsection (b) (2) are permitted to utilize considers for which the candidate has not got a privilege of reference or use.[1]

In US regulation new drug and generic drug isolates into three classifications [2]

- New medications, secured under area 505(b)(1) of the FD&C Act
- Generic medications, secured under segment 505(j) of the FD&C Act
- Similar medications, secured under segment 505(b)(2).

505(j) and 505(b)(2) pathway were included by Hatch-Waxman Act, 1984. 505(b)(2) application, frequently alluded to as a "paper NDA" that wipe out tedious and expensive duplication of clinical trials, this is the half breed pathway between 505(j) application for non

specific medication application and 505(b)(1) application for new drug application.[3]

Various 505 dossier filings.[4]

- **505(b)(1) NDA**

A 505(b)(1) application contains full reports of examinations for wellbeing and viability for which the examinations the candidate depended on for approbation were led by or for the candidate or the candidate has acquired a privilege of reference or use for the examinations.

- **505(b)(2)NDA**

A 505(b)(2) applications an application submitted under area 505(b)(1) for which the examinations the candidate depended on for support were not led by or for the candidate and the candidate has not acquired a privilege of reference or use for the examinations.

- **505(j) ANDA**

A 505(j) application is an ANDA that contains data to demonstrate that the proposed item is indistinguishable in dynamic fixing, dose structure, quality, course of organization, marking, quality, execution attributes and expected utilization, in addition to other things, to a formerly endorsed In this manner the 505(b)(2) pathway offers a practical and quicker pathway that may utilized by a large portion of producer for making so as to create product with worth full changes into existing item sanction by the USFDA. This pathway permit the inventor to utilize the prior information into its 505(b)(2) application, along these lines result in considerable funds in endorsement costs.

The normal 505(b)(2) endorsement costs $3-7 million, which is far less than the estimated $1.3 billion to bring a new drug to market under 505(b)(1), furthermore accomplish USFDA approbation in only 30 months with 3-7 year of market exclusivity relying upon the degree and kind of progress to the approved drug and the for generic medication promoted under 505(j) application gets just 180 days restrictiveness.[5]

2.1505(b)(2) application[6]

Segment 505(b)(2) of FD&C act depend on non-proprietary studies as it not indicate the source from where the examinations can utilized yet any distributed study can be referenced to support a 505(b)(2) application. For Reference Listed Drug (RLD) that contains exhibition of bioavailability or bioequivalence and bioequivalence of a generic drug falls purposefully or unexpectedly short of that of the RLD. In such circumstance application may not submitted as Abbreviated New Drug Applications (ANDA) normally utilized for generics and must be submitted under Section 505(b) (2) of the FD&C Act FD&C Act require that 505(b) (2) applications contain pediatric information because of Pediatric Research Equity Act (PREA). Along these lines, any medication or biologics application for a new active ingredient, new dosage form, new dosing regimen, new indication, or new route of administration must contain the pediatric examination appraisal. In this manner holders of 505(b)(2) promoting approbations seem, by all accounts, to be excluded from composed solicitations by the FDA to direct pediatric studies as these are issued to supporters of clinical trials. Orphan drug applications are absolved from the prerequisite to contain pediatric information paying little respect to whether the application is documented under Section 505(b)(1) or 505(b)(2) of the FD&C Act.

2.2 Type of Changes Applicable Under 505(b)(2) NDA[7]

- New dosage formulation e.g., the approved drug is a tablet and the 505(b)(2) application is for tablet to capsule
- Changes in route of administration e.g., approved drug is oral and the 505(b)(2) application is for a iv injection
- Changes in strength of the drug substance e.g., approved drug is a 5% solution and the 505(b)(2) applications is for a 10% solution
- Changes in indication e.g., a new indication
- Changes in dosing regimen e.g., existing drug is twice daily but the 505(b)(2) application is for once daily
- Change to an active ingredient e.g., different salt, ester, racemate, enantiomers or Chelate
- Substitution and combination of one active ingredient to another e.g., existing Drug is in combination of x + y and the 505(b)(2) application is for y + z)
- Change from an Rx indication to an OTC indication
- Changes in bioequivalence for drug products where the extent and rate of absorption is different from the standards for bioequivalence of already approved drug.

2.3 Type of Changes Not Applicable Under 505(b)(2) NDA

- An application that is a copy of a recorded medication and qualified for support under area 505(j).
- For which the rate and extent of absorption is lower than the reference drug.

2.4 Information on which applicant can rely

- Already distributed data, e.g., literature examining the clinical trials directed effectively, creature studies led before, and so on. The data depended on must be particular and not summed up.

- FDA's finding of past security and viability, however candidate now needs a change from that past finding. The motivation behind this is to give the candidate the best approach to "prove up" the item however not need to do duplicative clinical study.

2.5 Patent and Exclusivity criteria [8]

505(b) (2) applications for beforehand endorsed medications are compensated with a 3-year market restrictiveness in the event that they contain considers other than bioequivalence studies. product under 505(b) (2) applications to be entitled in exclusivity period, the application more likely than not been endorsed after the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act). New molecular entity (NME) recorded under 505(b)(2) candidate may be allowed 5 years of exclusivity. Protection is largely based on data exclusivity rather than true market exclusivity.

Pediatric exclusivity is set up by the BPCA (Best Pharmaceuticals for Children Act). 6-month protection period is conceded to applications containing NME's or known active ingredient for 505(b) (2) applications. Orphan drug get exclusivity of 7years for the application recorded under 505(b) (2).

New and already marketed drugs effectively produced for rare diseases including the pediatric populace would profit by 7-year and 6-month exclusivity.

Table I: Market exclusivities through 505(b) (2) pathway

Code	Extension Protection Period	Protection Period
NCE	New Chemical Entity	5 years
NC	New Combination	3 years
NDF	New Dosage Form	3 years
NP	New Product	3 years
NPP	New Patient Population	3 years
ODE	Orphan Drug Exclusivity	7 years
PDE	Pediatric Drug Exclusivity	+ 6 months

2.6 Advantages of 505(b)(2) type NDA [9]

- Marketed as branded products rather than generic.
- Relatively low risk because of existing safety and efficacy information.
- Lower cost due to smaller scope and number of potential studies.
- Increased speed due to fewer studies
- Wide range of drug substance with better market possibilities are made available for fast approval of drug under 505(b)(2) pathway.
- Unlike ANDA not affected by discontinuation of RLD.
- Earns patent and exclusivity.
- Insulated from high market competition.
- An opportunity in Drug efficacy Study Implementation (DESI) drugs.

3. Legal Framework in the Europe

In Europe Drug improvement of known medication in new restorative range is like that of US and incorporated into Directive 2001/83/EC in the Regulation (EC) No 726/2004.

Like FDA's 505(b) (1) class for new drug application Europe has article 8(3), 10a, 10b or 10c of Directive 2001/83/EC which include marketing authorization by part state on premise complete dossier field under the procurement's of Articles 6 and 8(3) of Directive 2001/83/EC. Also Article 10(2) and Article 10(3) of the Directive 2001/83/EC are looking like to FDA's ANDA pathway and 505(b)(2) pathway respectively [10]

3.1 Article 10(3) [11]

The product which is different to reference medicinal product with respect to the active ingredient, dosage form, dose strength or rout of administration is considered as hybrid medicinal products, such product falls under the Article 10(3).

In hybrid drug application applicant has to provide in addition to reference data, result on particular non-clinical test and clinical studies.
Appropriate preclinical and clinical trial will b necessary in following condition

- The strict meaning of a “generic medicinal product” is not met;
- Bioavailability study can't be utilized to exhibit bioequivalence study; and
- There are changes in the active pharmaceutical ingredient, indications, dose strength, and pharmaceutical dosage form of the generic product contrasted with the reference drug.

Article 10(3) of the Directive 2001/83/EC does not utilized for non-proprietary studies where as area 505(b)(2) of the FD&C demonstration, which concentrates on the utilization of non-exclusive studies in backing of any piece of the application.

Applications utilizing non-proprietary studies are characterized in Annex I to Directive 2001/83/EC. Which depicts the substance of Mixed Marketing Authorization Applications (MMAA's) as any application that depending on both own and bibliographical information and requires accommodation of a full dossier according to Article 8(3).

In Europe Pediatric studies is defined by the Pediatric Investigation Plan (PIP) and require marketing authorization applications submitted under the provisions of Article 6 and 8(3) of Directive 2001/83/EC. Thus pediatric studies is not require in article 10(3) submission but it is included in section 505(b)(2) of the FD&C act.
In contrast to the US regulations the significant difference being that, once the product is approved there is no provision for 3 years of exclusivity for the hybrid medicinal product.

3.2 Data Exclusivity [12]

For orphan drugs, market protection of 10 years is granted. Regulation EC/726/2004 that is for orphan drugs permits the use of Article 10(3) of Directive 2001/83/EC for repurposed drugs or use of

bibliographical data in MMAA. The 10-year protection period for orphan drugs is extended to 12 years if pediatric studies were conducted in compliance with a PIP. For Pediatric Use Marketing Authorization (PUMA) 8-year data exclusivity and a 10-year market protection period is given.

At the time of accommodation of the generic/hybrid application, the protection time of the reference drug ought to have terminated in order to permit the candidate to depend on the reference medicinal product dossier which is depicted below

- 8 years - Applications for generic/hybrid drugs cannot be submitted until expiry of 8 years of first marketing authorization. However, applicants have been permitted to utilize a reference drug product's information in ordering their own dossiers to acquire their own regulatory endorsements following 8 years.
- 10 years (8 + 2) - Generic/hybrid drugs may not be sold in EU until 10 years have elapsed from the granting of the initial marketing authorization.
- (8+2+1) - Further one year extension if original authorization holder obtains additional authorization for a new therapeutic use of the product resulting in clinical benefits.

Table II: U.S. FDA 505(b)(2) NDA vs. EU hybrid medicinal Products

Sr. No.	Parameters	505(b)(2) NDA	EU hybrid medicinal products
1	Legal basis	Sec. 505(b)(2) of the FD&C Act	Art. 10(3) of Directive 2001/83/EC
2	Pediatric developmen t plan	Required	Not required
3	Data exclusivity	3 years and 5 years for NME's	1 year
4	Incentives for pediatric studies	6-month exclusivity	10-year market protection
5	Incentives for orphan drugs	7-year market protection	10-year market protection
6	Combined orphan/pedi atric Incentives	7-year and 6-month market protection	12-year market protection
7	Fees	Less fees than 505(b)(1) NDA	Reduced fees than full MAA

4. CONCLUSION

Medicinal services expense is expanding day by day and also there is higher drug development risk because of tight regulatory and cost benefit scrutiny, the pharmaceutical organizations are under weight to build R&D efficiency with shorter and less excessive way i.e. fast track approaches for medication development. Consequently this challenge is tackle by creating qualified medication in new therapeutic area. 505(b)(2) NDA handle especially utilized by pharmaceutical industry in light of the fact that the item separation can give fundamentally better market potential, lower cost and lower risk. 505(b)(2) NDA procedure offers numerous advantages, additionally postures numerous difficulties like what kind of "bridging" information expected to study the proposed change of the already endorsed drug is still under inquiry. US administrators ought to build their endeavors to encourage such improvements. In this paper, current US and EU regulations are inspected and looked at for their viability. EU regulation is not as viable as US regulation furthermore less steady along these lines it ought to additionally be creating. Moreover this kind of regulation ought to be fit over the world to beat the duplication of work in distinctive locale.

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