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Regulatory Foundation of 505(B)(2) Application in US FDA

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ABSTRACT

Before the Hatch-Waxman Act of 1984, the concept of new drugs was different than what it is now. Old concept of a new drug had narrow scope than the modified concept of the new drug after Hatch-Waxman Act 1984. "New drugs are those drug products containing one or more APIs (Active Pharmaceutical Ingredients) that have never been part of any drug products marketed previously in the history of FDA record in the USA." This was the concept of a new drug before Hatch-Waxman Act had made the revolution in FDA rules. "New drugs are those drug products that have never been marketed under the record of FDA and in contrast if API of the drug product is same as that of other drug product marketed in history and the drug product claiming to be a new drug is not eligible under ANDA and has distinguishable difference than that the previously marketed drug product in terms of the dosage form, strength, dosage, etc., it is referred as new drug". This is the new concept to new drug and Hatch-Waxman act has introduced section 505(b)(2) to full fill new approach toward afford to decrease drug price and avoiding repetition of clinical trials as well as animal experiments to uphold ethical principles.

Keywords: Hatch-Waxman Act, New drugs, ANDA, 505(b)(2)

INTRODUCTION

This was the concept of new drug before Hatch-Waxman Act had made the revolution in FDA[1] rules. Big pharma players, like Pfizer or Eli Lilly or it can be else; have always insisted to produce a new drug containing NCE (new chemical entity). History has proven this approach as a most appropriate and new drugs have offered riotous growth to the pharmaceutical company. On the other side of the coin, human being have been benefited due to the availability of new drugs that treat diseases better way. New drugs offer alternative to existing products and also offer options to physicians while treating a patient suffering from a disease and not responding well to existing therapy. Pharmaceutical research & development is serving human being by making them available with new drugs. Pace of pharmaceutical research & development of generating new drugs containing new chemical entity has slowed down despite this it has found better alternatives to it. This alternative is to get maximum potential out of the existing drug products. Now the question is how one can drag out the maximum potential from the existing product that is treating patients. It can be understood by a hypothetical example.

In the hypothetical example (Figure 1) DEF is the innovator company. It has innovated a drug product containing XYZ active ingredient and the dosage form (DF) of the drug product is tablet. Brand name of the drug product is ABC and active ingredient XYZ is NCE (New Chemical Entity). This XYZ possess a very good pharmacological action and it treats the disease well. Now the question is that XYZ is active in the form of tablet only or activeness of XYZ lies like XYZ? It is not a brain-teaser and answer is very obvious that the activeness of XYZ is because of its nature. It is the tablet dosage form that conveys XYZ to the body system to treat the undesired pathological condition of the body. But it never means XYZ would not be effective in dosage form other than tablet.

It would also wrong to say that XYZ will not be active in combination with other active ingredients. Other possibility is also very interesting to note that does XYZ possess the potential to the extend of its use under the known indications listed under the approved label? The fact is that indications of XYZ are made based on the results obtained at the end of the clinical trials. Clinical trials are conducted based on the preliminary findings at the early stage of drug development. Approach adopted in the early stage of drug development is not always broad rather it is very specific. And it is often observed such a product would find new indications during its life cycle.

Bunch of other possibilities wait ahead on the way and each possibility is practically observed in history. In above cases, an applicant, proposing to develop a new drug product after

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making suitable modifications in existing version of new drug product, has to hold on his idea till all patents get clear related to existing new drug product. This state of affairs produced the need of 505(b) (2) application.

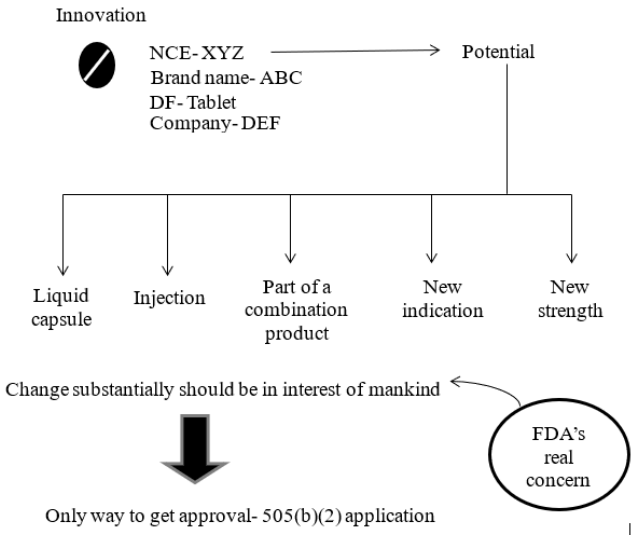

Figure 1: An hypothetical example to explain the need for the 505(b)(2) application

Hatch-Waxman Act has rightly found out an appropriate pathway by including section 505(b) (2) under FD&C Act. 505(b) (2) application has come into rescue to such applicants. While getting approval for the modified new drug product under section 505(b) (2), mere modification does not help an applicant but the applicant has to prove before FDA[2,3] that the change made to the existing new drug product is substantially in favor of mankind and at the same time modified new drug product does not infringe any patent relating to the existing new drug product and utmost safety and efficacy must be proved.

UNDERSTANDING OF 505(b) (2) APPLICATION

Drug products that may be submitted under section 505(b)(2) are not completely new products, yet they are not generics. These medications have both similarities and some differences from an innovator or brand drug. For example, a product may have the same active ingredient as a previously approved product, but now it is formulated in a different delivery mechanism or with different indications. The basis for the 505(b)(2) application is that there already is a certain amount of information that is known about the active ingredient. As such, repeating all the clinical studies required for a 505(b)(1) application would be expensive and time-consuming. So, under the rules in section 505(b)(2), the applicant can rely on information from studies it did not conduct and for which it does not have the right of reference. These include full reports of investigations of safety and effectiveness where at least some portion of the information submitted for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained the right of reference for the information.

The types of information an applicant can rely on include published literature describing study results and the FDA's findings of safety and effectiveness from a previously approved medication. Although the manufacturer may not have performed some of the studies, it must submit clinical and non-clinical data to demonstrate the medication is safe and effective. It also must be able to provide data and information, including bioavailability or comparative bioavailability studies, to establish sufficiently the appropriateness of relying on material without the right of reference[4].

Application can be submitted as a 505(b)(2) application

1. New chemical entity (NCE)/New molecular entity (NME)

A 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For an NCE, this data is likely to be derived from published studies, rather than the FDA's previous finding of safety and effectiveness of a drug. If the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be considered a 505(b)(1) application.

Changes to previously approved drugs[5]

For changes to a previously approved drug product, an application may rely on the Agency's finding of the safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data. This use of section 505(b)(2), described in the regulations at 21 CFR 314.54, was intended to encourage innovation without creating duplicate work and reflects the same principle as the 505(j) application: it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug.

An applicant should file a 505(b)(2) application if it is seeking approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data. However, section 505(b)(2) applications should not be submitted for duplicates of approved products that are eligible for approval under 505(j)[5].

In addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration according to a suitability petition under Section 505(j)(2)(C) of the Act. In the preamble to the implementing regulations for the Hatch-Waxman amendments to the Act, the Agency noted that an application submitted pursuant to section 505(b)(2) of the Act is appropriate even when it could also be

submitted following a suitability petition as defined at section 505(j)(2)(C) of the Act.

Examples of 505(b)(2) applications[6]

Following are examples of changes to approved drugs for which 505(b)(2) applications should be submitted. Please note that in particular cases, changes of the type described immediately below may not require a review of information other than BA or BE studies or data from limited confirmatory testing.

In those particular cases, approval of the drug may also be sought in a 505(j) application based on an approved suitability petition as described in section 505(j)(2)(C) of the Act. The descriptions below address the situation in which the application should be filed as a 505(b)(2) application because approval of the application will require a review of studies beyond those that can be considered under section 505(j). Some or all of the additional information could be provided by literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based upon studies conducted by or for the applicant or to which it has obtained a right of reference.

- Dosage form: An application for a change of dosage form, such as a change from a solid oral dosage form to a transdermal patch that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug.

- Strength: An application for a change to a lower or higher strength.

- Route of administration: An application for a change in the route of administration, such as a change from an intravenous to an intrathecal route.

- Substitution of an active ingredient in a combination product: An application for a change in one of the active ingredients of an approved combination product for another active ingredient that has or has not been previously approved.

Following are additional examples of applications that may be accepted according to section 505(b)(2)[7-10] of the Act. Some or all of the additional information could be provided by the literature or reference to past FDA findings of safety and effectiveness for approved drugs, or it could be based on studies conducted by or for the applicant or to which it has obtained a right of reference.

- Formulation: An application for a proposed drug product that contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application.

- Dosing regimen: An application for a new dosing regimen, such as a change from twice daily to once daily.

- Active ingredient: An application for a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety.

- New molecular entity: In some cases, a new molecular entity may have been studied by parties other than the applicant and published information may be pertinent to the new application. This is particularly likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, data on a drug with similar pharmacologic effects could be considered critical to approval.

- Combination product: An application for a new combination product in which the active ingredients have been previously approved individually.

- Indication: An application for a not previously approved indication for a listed drug.

- Rx/OTC switch: An application to change a prescription (Rx) indication to an OTC indication.

- OTC monograph: An application for a drug product that differs from a product described in an OTC monograph (21 CFR 330.11), such as a non-monograph indication or a new dosage form.

- Naturally derived or recombinant active ingredient: An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

- Bioinequivalence: Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101(d)(9)). Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted according to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the differences in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically better than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the

proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101(d)(9)).

For example, a 505(b)(2) application would be appropriate for a controlled-release product that is bioequivalent to a reference listed drug where:

1. The proposed product is at least as bioavailable as the approved pharmaceutically equivalent product (unless it has some other advantage, such as smaller peak/trough ratio); or

2. The pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product.

Application can't be submitted as 505(b)(2) applications[11]

- An application that is a duplicate of a listed drug and eligible for approval under section 505(j) (see 21 CFR 314.101(d)(9)); or

- An application in which the only difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than the listed drug (21 CFR 314.54(b)(1)); or

- An application in which the only difference from the reference listed drug is that the rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is unintentionally less than that of the listed drug (21 CFR 314.54(b)(2)).

Information that should be included in 505(b)(2) applications

The Act (sections 505(b)(1) and (b)(2)) and FDA regulations (21 CFR 314.54) distinguish between 505(b)(1) and (b)(2) applications. Although the two types of applications must meet the same standards for approval, they differ in source of information to support safety and effectiveness, the patent certification requirements, BA/BE evidence, exclusivity bars, and processing within the FDA. The requirements for 505(b)(1) and 505(b)(2) applications are described at 21 CFR 314.50. Additional requirements for certain 505(b) (2) applications are described at 21 CFR 314.54.

A 505(b) (2) application should include the following:

- Identification of those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies).

- If the 505(b)(2) seeks to rely on the Agency's previous finding of safety or efficacy for a listed drug or drugs, identification of any listed drugs by established name, proprietary name (if any), dosage form, strength, route of administration, name of the listed drug's sponsor, and the application number (21 CFR 314.54(a)(1)(iii)). Even if the 505(b) (2) application is based solely upon literature and does not rely expressly on an Agency finding of safety and effectiveness for a listed drug, the applicant must identify the listed drug(s) on which the studies were conducted, if there are any. If the 505(b)(2) application is for an NCE and the 505(b)(2) applicant is not relying on literature derived from studies of an approved drug, there may not be a listed drug. If there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, that drug should be identified as the listed drug.

- Information with respect to any patents that claim the drug or the use of the drug for which approval is sought (21 CFR 314.50(h)). This patent information will be published in the orange book when the application is approved.

- Unlike a full NDA for which the sponsor has conducted or obtained a right of reference to all the data essential to approval, the filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include patent certifications described at 21 CFR 314.50(i) and must provide notice of certain patent certifications to the NDA holder and patent owner under 21 CFR 314.52.

- Information required under 314.50(j) if the applicant believes it is entitled to marketing exclusivity (21 CFR 314.54(a)(1)(vii)).

- A patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or another drug (21 CFR 314.54(a)(1)(vi)). If there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) applicant should provide patent certifications for the patents listed for the pharmaceutically equivalent drug. Patent certifications should specify the exact patent number (s), and the exact name of the listed drug or other drug even if all relevant patents have expired.

- If an application is for approval of a new indication, and not for the indications approved for the listed drug, a certification so stated (21 CFR 314.54(a)(1)(iv).

- A statement as to whether the listed drug(s) identified above have received a period of marketing exclusivity (21 CFR 314.108(b)). If a listed drug is protected by exclusivity, filing or approval of the 505(b)(2) application may be delayed.

- A Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any).

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- Studies necessary to support the change or modification from the listed drug or drugs (if any). Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s).

Before applying, the applicant should submit a plan to the appropriate new drug evaluation division identifying the types of bridging studies that should be conducted. The applicant should also identify those components of its application for which it expects to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The division will critique the plan and provide guidance.

A detailed regulatory approval process is given in the dissertation after going through statistical observation on 505(b) (2) application approval in last few years.

STATISTICAL ANALYSIS OF 505(b) (2) APPLICATION

Understanding the present status of 505(b) (2) application is based on its history. To elucidate the history of 505(b) (2) application, statistical tool is been used in the study. Figure 5 represents graphical presentation of numbers of approved 505(b)(1) applications, 505(b)(2) applications and difference between these two approved applications during 2004 to 2012.

Number of approval of 505(b) (2) application has been increasing year by year and the graphical presentation (Figure 2) proves it true. In 2004, percentage of number of 505(b)(2) approval out of total NDA approval is around 30% and it has been raised more than 50% in 2011. 505(b)(2) application includes different NDA chemical types as listed out in following table 2.

In table 1, as per these different NDA chemical types, the distribution of 505(b)(2) applications is done and number of 505(b)(2) applications approval under each type per year is tabulated.

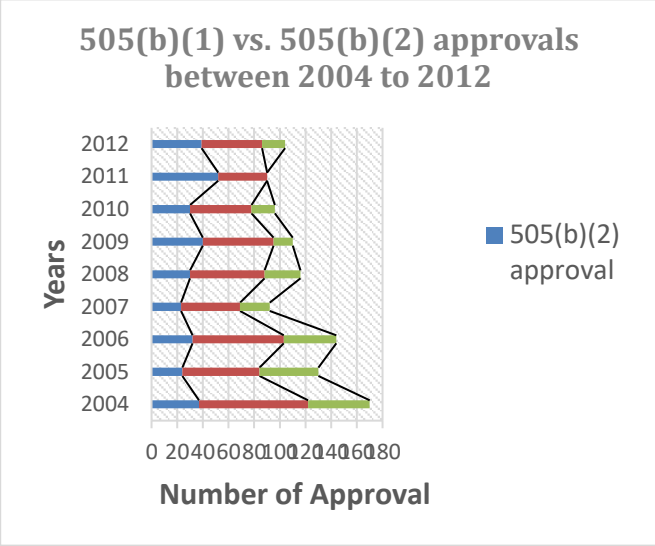

Figure 2: Graphical presentation of numbers of 505(b)(1) and 505(b)(2)[12] approvals

Source: Data are collected from Drug information (Drugs@FDA)[29]

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Table 1: 505(b)(2) applications' approval under each chemical type per year

NDA chemical type**	Years								
	2004	2005	2006	2007	2008	2009	2010	2011	2012
New molecular entity (NME)	5	2	2	0	1	1	0	1	3
New active ingredient	1	0	1	1	3	0	0	0	1
New dosage form	19	13	14	11	10	15	9	16	14
New combination	3	3	9	3	6	7	9	7	6
New formulation or new manufacturer	6	6	9	7	8	7	7	21	11
New indication	3	0	0	1	0	0	0	0	0
Drug already marketed without an approved NDA	1	0	0	0	2	6	3	2	5
OTC (over-the-counter) switch	0	0	0	0	0	1	0	0	0
New indication submitted as distinct NDA - not consolidated	0	0	0	0	0	0	0	0	0

** The Chemical Type represents the newness of a drug formulation or a new indication for an existing drug formulation. For example, Chemical Type 1 is assigned to an active ingredient that has never before been marketed in the United States in any form[13].

The meaning of each chemical type is presented in the following table (Table 2).

Table 2: Meaning of Chemical types

Type	Meaning
1	New molecular entity (NME)
2	New active ingredient
3	New dosage form
4	New combination
5	New formulation or new manufacturer
6	New Indication
7	Drug already marketed without an approved NDA
8	OTC (over-the-counter) switch
10	New indication submitted as distinct NDA - not consolidated

SUMMARY AND CONCLUSION

Summary of the major review process steps

CDER's NDA review process involves a total of six major steps, two of which occur outside the actual review time frame namely, pre-submission activities and post-action feedback to the applicant. Monitoring the progress of the review occurs continuously throughout the review process. The timelines to take action for applications that are not in the PDUFA V "Program" are 6-months from receipt for a priority review and 10 months for a standard review. The timelines for NMEs and s that fall under PDUFA V's "Program" Review Model are 10 months for standard applications and 6-months for priority reviews from the 60-day filing date (or 12 months and 8 months respectively from the date of submission of the application).

Six major steps involved in CDER's NDA review process are summarized below.

1. **Ensure readiness for application through pre-submission activities:** The first step in the process is composed of activities that applicants can take advantage of to improve the quality and content of their NDA application before submitting it to FDA.

2. **Process Submission:** Applications are received and processed by document control room staff and then distributed to the appropriate review division. The RPM conducts an initial assessment of the NDA to assure that certain regulatory requirements are met and that a user fee has

either been paid, the fee waived, or the application exempted. Reviewer assignments are made at this time.

3. **Plan Review of the Application:** The review team conducts an initial assessment of the NDA and associated labeling. Each discipline makes a recommendation on filterability of the application at the filing meeting that is held by day 45 of the review (day 30 for priority reviews). If the application is found fileable a planning meeting is held to further discuss timelines and review activities.

4. **Conduct scientific/regulatory review of the application:** During the review phase, the primary reviewers analyze their assigned portion of the application and write their reviews; team leaders interact with reviewers and guide regularly. For PDUFA V "Program" reviews, a late-cycle meeting is held between the review team and the applicant. An additional two months is available for PDUFA V "Program" applications to address complex review issues and attempt to remedy minor problems with the application.

5. **Take official action on the application:** Based on the signatory authority's review of the action package and discussions with the review team, the signatory authority determines the action to be taken on the application. The final action decision is conveyed to all team members.

Provide post-action feedback to the applicant: The focus of this activity is on learning from the review experience. This optional meeting can take place as either an end-of-review conference, typically held following an action other than an approval and/or a post-action feedback/lessons learned meeting. These two meetings can be combined into a single meeting if appropriate.

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