CONCEPT OF 505 (b) (2) APPLICATION: BENEFITS AND CHALLENGES

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REVIEW ARTICLE

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ABSTRACT

A 505(b) (2) application is a new drug application (NDA) delineated in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.505(b)(2) application is one that one or a lot of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and has not obtained a right of reference or use from the person by or for whom the investigations were conducted. Section 505(b) (2) was added to FFDC Act by the Drug price competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). The applicant will depend on either revealed literature or agency's findings of an antecedent approved drug. This approval route was designed to encourage innovation and to eliminate expensive and long duplicative clinical studies.

Keywords: ANDA; Clinical Trials; CFR; Exclusivity; FFDC Act; Hatch Waxman Act; 505 (b) (1); NDA; NME.

INTRODUCTION

A 505(b)(2) application is a new drug application (NDA) delineated in section 505(b)(2) of the FFDC Act. It is submitted under section 505(b)(1) of Federal Food, Drug, and Cosmetic Act and approved under section 505(c) of the Act.

Section 505 of the FFDC Act describes three types of new drug applications: 1) An application that contains full reports of investigations of safety and effectiveness {section 505(b)(1)} to which they has 'right to reference' and raw information. 2) An application that contains full reports of investigations of safety and effectiveness, but where a minimum of some of the data required for approval comes from studies not conducted by or for the applicant and that the applicant has not obtained a right of reference (section 505(b)(2));3) an application that contains information to indicate that the projected product is identical in active constituent, dosage form, strength, route of administration, labeling, quality, performance characteristics, and proposed use, among other things, to a antecedently approved product(section 505(j)).

505 (b) (2) was added to FFDC act by Hatch Waxman amendment 1984.This amendment allows FDA to depend, for approval of an NDA on data not developed by the applicant. This pathway requires careful consideration and planning. Important issues to consider include intellectual property concerns, the amount and quality of supporting information available from reference products or the literature.

APPLICATION APPROVAL PATHWAYS

505 (b) (1) approval pathway:

A 505(b)(1) application is an application which contains the entire data about safety and effectiveness. (1) The investigations the applicant submitted for approval were conducted by or for the applicant or the applicant have obtained a right of reference or use for the investigations. In order to prove safety and efficacy, manufacturers are required to complete extensive clinical trials, consisting of three phases (Phase I, Phase II, and Phase III). Phase I trial is conducted in tiny range of healthy volunteers starting from 25-100 to determine dose ranging. Phase II trial includes testing of drug on patients to assess efficaciousness and safety, conducted in patients starting from 100-300. Phase III trial determines a drug's therapeutic effect and conducted in patients starting from 1000-3000. When all three phases are over, the

manufacturer submits an NDA containing results from these studies to the FDA. The NDA is reviewed by FDA scientists to assess whether the trials demonstrate the product's benefit, compared with its risks. Information submitted may include not only the results of the various clinical trials, but also the raw data that was used to generate the conclusions. The drug company is able to do this because it either conducted the studies itself or paid for the studies. This is called the "right of reference."

By the time an NDA is approved, the manufacturer has invested numerous years and many millions of dollars for development, clinical trials and regulatory approval. As compensation, the FDA grants the company the exclusive right to manufacture the product for a period of time under patent protection. Manufacturers are granted patent protection for 20 years from the date of the first filing of the patent application.

505 (b) (2) approval pathway:

Type of Information Can Applicant Rely:

Type of information can an applicant relies on in an application that is based upon studies not conducted by applicant.

1. Published literature: One should submit a 505(b)(2) application if approval of an application will rely to any extent on published literature {i.e. literature type 505(b)(2)}. If the applicant has not obtained a right of reference to the raw data underlying the published study or studies, the application is a 505(b)(2) application (2); if the applicant owned a right of reference to the raw data, the application may be a full NDA {i.e., one submitted beneath section 505(b)(1)}. An NDA will be a 505(b)(2) application if any of the specific information necessary for approval is obtained from literature or from another source to which the applicant does not have a right of reference, even if the applicant also conducted clinical studies to support approval.
Nevertheless, that this does not mean any reference to published general information (e.g., Information related to disease etiology, information for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application. Reference should be to specific information (clinical trials, animal investigational data) necessary to the approval of the application.

2. The FDA's finding of safety and effectiveness for an antecedently approved drug:

One should submit a 505(b)(2) application for a modification in a drug, when approval of the application relies on the Agency's antecedent finding of safety and/or effectiveness of a drug.

Section 21 CFR 314.101 allows a 505(b)(2) applicant to rely on the Agency's finding of safety and effectiveness for an approved drug. This approach is meant to encourage innovation in drug development without requiring duplicate clinical studies to demonstrate what is already known about approved drug.

Categories of 505(b)(2) Application (3):

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 review of studies beyond those that can be considered under section 505(j)(ANDA).

1. Dosage form: An application for a change of dosage form, such as a shift from a solid oral dosage form to a liquid oral or parenteral that relies to some extent upon the Agency's finding of safety and/or effectiveness for an approved drug.
2. Strength: An application where a change in strength of already approved compound .After changing strength it should show significant improvement in its therapeutic indication to be eligible for 505 (b) (2) application.
3. Route of administration: An application for a change in the route of administration, Ex: Shifting from oral route to parenteral route.
4. Substitution of an active ingredient in a combination product: An application for a change in one of the active constituents of an approved combination product for another

active ingredient that bears or has not been previously approved.

5. 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.

6. Dosing Regimen. An application for a new dosing regimen Ex: A dose change from thrice daily to once in a day.

7. Changes in Active ingredient. An application for a change in an active ingredient such as a different salt, chelate, complex, racemate, clathrate, ester or an enantiomer of an active ingredient in a listed drug containing the same active moiety. eg. S-Omeprazole & E-Omeprazole.

8. New molecular entity (NME): 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 significantly possible if the NME is the prodrug of an approved drug or the active metabolite of an approved drug. In some cases, information on a drug with similar pharmacological effects could be considered critical to approval.

9. Combination product. An application for a new combination of active constituents, where two of them are already approved individually.

10. Indication: An application where a new therapeutic indication was identified for an already approved drug (RLD).

11. Rx/OTC switch: An application where a drug is switched from a prescription category to OTC (over the counter) indication.

12. Naturally derived ingredient: An application for a drug product containing an active pharmaceutical ingredient obtained from animal or plant sources where clinical trials are necessary to indicate that the active ingredient is the same as an active constituent in a listed drug.

13. Non monograph Indication: An application for a drug product that is not described in OTC monograph, Assigned as new dosage form.

Which Can't Be Submitted As 505(b)(2) Applications:

An application that's a reproduction of a listed drug and eligible for approval beneath section 505(j) (i.e. ANDA) isn't eligible for applying beneath 505 (b) (2) application. An application in which the only difference from the reference listed drug is that the extent & rate to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than the listed drug.

Patented and Non patented Market Exclusivities for 505 (b) (2) applications(4):

Exclusivity based on patents provides the patent owner the right to exclude others from specific uses of their products for a specified period. To obtain product approval, the sponsor must provide patent certification, i.e., authenticating statements claiming the drug or a method of using the drug that is submitted in the NDA. 505(b)(1) drugs may have patents on both the active ingredient and formulation/method of use, whereas 505 (b)(2) and 505 (j) drugs may patent the formulation/method of use, but not often the active ingredient. Listed patents have the potential to delay subsequent 505(b)(2) and ANDA approvals. A 505(b)(2) application may also be granted 5 years of exclusivity if it is for a new chemical entity. And it may also be eligible for orphan drug exclusivity or pediatric exclusivity. (5)

Strategies for Developing 505 (b) (2) Products:

For smaller drug companies, the 505(b)(2) pathway for a new product could prove an attractive business model for the simple reason that it takes much less time, cost and risk get the product onto the market compared to innovator drugs, and could yield considerably higher returns on investment compared to generic medicine.

The following are few strategic issues for a 505(b)(2) product:

1. Extent of innovation/modification made to the innovator product: these modifications decide whether the product is applicable for a 505(b)(2) review or not, and facilitate verify

the quantity of years of market exclusivity granted.

2. Development strategy: careful analysis of data should lead to a list of the additional studies that may be required for a given 505(b)(2) product; bridging studies are required to show that changes to the innovator product lead to the desired impact on safety, efficacy and tolerance of the proposed drug product.

3. As 505(b) (2) products are generally more expensive than generic versions of the innovator drug, the manufacturer ought to have a strong selling arrangement.

Table 1: Comparison of NDA, 505 (b) (2), and 505 (j)

	NDA	505 (b) (2)	505 (j) ANDA
User Fee	Yes	Yes/No	Yes
Studies	Full	Partial	BA/BE
NCE	Yes	No	No
New Ingredients	Yes	Yes	No
New Formulation	Yes	Yes	No
Patented	Yes	Yes	No
Market Exclusivity	5 Years	3-5 Years	6 months

BENEFITS AND CHALLENGES:

There are important potential business advantages in using a 505(b)(2) regulatory strategy. The 505(b) (2) applicant may be eligible for 3 or 5 years of market exclusivity, depending on the extent of the change in the antecedently approved drug and the type of clinical data included in the NDA. This differs a 505(b)(2) from an ANDA, where exclusivity can be availed for only 180 days. A product approved via the 505(b)(2) route of approval may receive an "AB" substitutability rating in the Orange Book. Therefore, from a therapeutic substitution perspective and under state formulary laws, the 505(b)(2) applicant is not deprived relative to a generic (ANDA) drug.

There are, nevertheless, some regulatory challenges that are unique to 505(b)(2) applications. Unlike a 505(b)(1) NDA, where by the sponsor owns all the data necessary for approval (or has obtained the right to reference), the filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protection on the reference drug. Sponsors filing 505(b)(2) applications must include patent certifications in their applications and must also provide notice of certain patent certifications to the NDA and patent holders of the reference drug. A major challenge with 505(b)(2) applications is determining what additional information is needed to support the proposed change of the previously approved drug. As noted in 21 CFR 314.54, the application need contain only that information needed to support the proposed modification of the reference listed drug.

Future of 505 (b) (2) application:

The 505(b)(2) strategy has been underutilized within the sixteen years since it had been legislated. One reason could be the recent conflict over its constitutionality, as Pfizer and different massive pharmaceutical corporations have petitioned against approvals of 505(b)(2) NDAs. They argue that it is illegitimate for the FDA to rely on the innovator's proprietary data and that this application. Violates Fifth Amendment rights. No court decision has yet been rendered on the constitutionality.

The more abiding reason for the underutilization of the 505(b)(2) process might be a past low market demand for drugs that would qualify for this route of approval. This climate, however, seems to be changing. Among different approaches to rising quality for life, Nowadays healthcare providers are looking for routes of administration that produce less adverse effects due to systemic absorption of drugs. For example, sustained

release techniques and oral to transdermal modification are typical drug changes that have fallen beneath the 505(b)(2) strategy. These alterations have improved the profiles of antecedently approved drugs, reducing peril, increasing the consistency and effectiveness of the drug and enhancing compliance. In addition, more companies with proprietary drug delivery technologies are entering the market. Based on these and different prevailing factors in the pharmaceutical industry, possibly the time for the 505(b)(2) NDA to be better utilized has come.

Drugs Approved under 505 (b) (2) Pathway (6):

Table 2: Drugs approved via 505 (b) (2) pathway

TRADE NAME	FORMULATION & DRUG	COMPANY	TYPE
Canasa®	Suppositories Mesalamine	Axcan	New delivery mechanism
Luxiq®	Foam Betamethasone Valerate	Connectics	New delivery mechanism
Altocor®	Extended-release tablets Lovastatin	Andrx	New dosage form
Avinza®	Extended release Morphine	Elan	New dosage form
Doxil®	liposomal injectionDoxorubicin	Janssen	New dosage form
Zyrtec D®	Certirizine and pseudoephedrine	Pfizer	New Combination
Stalevo®	carbidopa/levodopa/entacapone,	Orion	New formulation
Thalomid®	Thalidomide	Celgene	New indication
Rid®	Piperonyl butoxide and pyrethins	Pfizer	New dosage form

(Source: Computed from CDER novel new drugs summery)

CONCLUSION

505 (b) (2) application is meant to promote innovation by eliminating spare repetition of clinical trials. Exploitation of this pathway drug will simply enter into market with less value on investment. This 505 (b) (2) pathway may be a higher thanks to all sizes of pharmaceutical companies that can't afford the Brobdingnagian capital for investment.

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CONFLICT OF INTEREST

Authors declares that there are no conflicts of interest.

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