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The 505(b)(2) New Drug Application – A Rapid Approval Route

The 505(b)(2) application is one of three established types of new drug application (NDA), and it is a pathway to approval that can potentially save pharmaceutical sponsors both time and money. However, many sponsors are unsure how to evaluate the possible benefits of using this type of application.

The 505(b)(2) regulatory pathway is defined in The Federal Food Drug and Cosmetics Act as an NDA containing investigations of safety and effectiveness that are being relied upon for approval and were not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. These applications differ from the typical NDA (described under Section 505(b)(1) of the Act), in that they allow a sponsor to rely, at least in part, on the FDA's findings of safety and/or effectiveness for a previously approved drug (the "reference drug"). Section 505(b)(2) was added to the Act in 1984 with the goal of avoiding unnecessary duplication of preclinical and certain human studies. However, the sponsor must still provide any additional preclinical or clinical data necessary to ensure that differences from the reference drug do not compromise safety and effectiveness. The 505(b)(2) NDA also differs from an abbreviated NDA (ANDA; described under Section 505(j) of the Act), which is an application containing information to demonstrate that the proposed product is identical to a previously approved product. Identity is proven in an ANDA simply through chemistry and bioequivalence data, without the need for preclinical and clinical trials assessing safety and efficacy. In a sense, a 505(b)(2) application can be thought of as a hybrid that contains more data than an ANDA, but less data than an NDA.

The 505(b)(2) approval route can be utilized for a wide range of products, especially for those that represent a limited change from a previously approved drug. The following are examples of changes to approved drugs which would be appropriate to submit as 505(b)(2) applications:

- Changes in dosage form, strength, route of administration, formulation, dosing regimen, or indication
- A new combination product where the active ingredients have been previously approved
- Change to an active ingredient (e.g., different salt, ester complex, chelate, etc)
- New molecular entity when studies have been conducted by other sponsors and published information is pertinent to the application (e.g., a pro-drug or active metabolite of an approved drug)
- Change from an Rx indication to an OTC indication
- Change to an OTC monograph drug (e.g., non-monograph indication, new dosage form)
- Drugs with naturally derived or recombinant (i.e, biological) active ingredients where additional limited clinical data is necessary to show the ingredient is the same as the ingredient in the reference drug



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- Bioinequivalence for drug products where the rate and or extent of absorption exceed or are otherwise different from the standards for bioequivalence compared to a listed drug. Additional studies might be required to document the safety and efficacy at the different rate and extend of delivery.

The 505(b)(2) applications are not appropriate for products:

- That are covered under Section 505(j)
- For which the only difference is lower extent of absorption than reference drug
- For which the only difference is an unintended lower rate of absorption than reference drug

Benefits and Challenges

There are important potential commercial benefits to employing a 505(b)(2) regulatory strategy. As previously stated, this approval route was designed to encourage innovation and to eliminate costly and time-consuming duplicative clinical studies. For some products, the reference drug can be relied upon for essentially all safety and efficacy information (nonclinical and clinical), with the only a small amount of new work required to establish comparability to the reference drug.

The 505(b)(2) applicant may qualify for 3 or 5 years of market exclusivity, depending on the extent of the change to the previously approved drug and the type of clinical data included in the NDA. This distinguishes a 505(b)(2) from an ANDA, where exclusivity can be held for only 180 days. A 505(b)(2) application may also be eligible for orphan drug or pediatric exclusivity.

A product approved via the 505(b)(2) pathway may receive an “AB” substitutability rating in the Orange Book. Thus, from a therapeutic substitution perspective and under state formulary laws, the 505(b)(2) applicant is not disadvantaged relative to a generic (ANDA) drug.

There are, however, some regulatory challenges that are unique to 505(b)(2) applications. Unlike a 505(b)(1) NDA, wherein 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(s) of the listed drug.” This will usually be a case-by-case determination. FDA guidance document and discussions with regulatory professionals



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experienced in the 505(b)(2) approval route, as well as the involved FDA review division, are helpful in understanding what data is necessary and adequate.

Resources on 505(b)(2) applications are:

Federal Food Drug and Cosmetic Act—Chapter V, Section 505(b)(2)

21 USC 355(b)(2)

21 CFR 314.50 – NDAs

21 CFR 314.54 – 505(b)(2) applications

21 CFR 314.108 – Exclusivity

DRAFT Guidance for Industry: Applications covered by section 505(b)(2).