The Nuts and Bolts of 505(b)(2) Applications

By Margaret E. Hurley, MD

The 505(b)(2) new drug application (NDA) has been described as a submission that shares characteristics of both NDAs and abbreviated new drug applications (ANDAs). The 505(b)(2) NDA gets its name from the section of the Federal Food, Drug and Cosmetic (FD &C) Act in which it is described. Section 505(b)(2) was added to the FD&C Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (also known as the Hatch-Waxman Amendments). Because it was not well understood, years passed before it was widely implemented.

Before 1984, the "paper NDA" was another route to appproval. The paper NDA policy was created as a means by which duplicates of post-1962 drugs could be approved because the Drug Efficacy Study Implementation (DESI) program and abbreviated route to approval did not apply to drugs approved after 1962. (1962 was the year the Kefauver Amendments, which required drugs to prove efficacy in addition to safety, were enacted.) The paper NDA policy allowed applicants to use published literature to satisfy the requirements for full reports of safety and effectiveness. The 1984 amendments eliminated the paper NDA policy because they provided a mechanism to approve duplicates of post-1962 drugs.

A 10 April 1987 "letter to industry" —written by Paul D. Parkman, MD, then the acting director for the Food and Drug Administration's (FDA) Center for Drugs and Biologics, to clarify some of the changes to reference-listed drugs that could be submitted as 505(b)(2) NDAs—is perhaps one of the most widely recognized of the letters to industry and provided FDA's interpretation of the amendments. The letter had such an impact that for years, the 505(b)(2) application became known as a Parkman supplement. Nonetheless, it was not until FDA issued *Guidance for Industry. Applications Covered by Section 505(b)(2)*[1] in October 1999 that consideration of this route as a registration strategy gained popularity.

Planning and executing successful 505(b)(2) NDA application strategies can be a confusing and frustrating experience. This article will explore the basic principles of applications, the 505(b)(2) NDA and the types of drug products that are appropriate for this submission route.

Table 1. The Three Types of NDAs Available to Seek Approval to Market a Drug

	Section of FD&C Act	Reference Listed Drug	Clinical Safety and Efficacy
NDA	Section 505(b)(1)	No	NCE: Full reports of investigations of safety and effectiveness
		Yes	Approved Indication: Full reports of investigations of safety and effectiveness because sponsor chooses not to reference the listed drug
NDA	Section 505(b)(2)	Yes	Approved Indication: Full reports of investigations of safety and effectiveness but where none of the studies required for approval of the indication were conducted by the applicant
		Yes	New Indication: Full reports of investigations of safety and effectiveness but where some of the studies required for approval were not conducted by the applicant
		No	NCE: Full reports of investigations of safety and effectiveness but where some of the studies required for approval were not conducted by the applicant
ANDA (generic)	Section 505(j)	Yes	Proposed product is shown to be identical to a previously approved product

Marketing Applications

Table 1 shows the three types of NDAs available to seek approval to market a drug, along with a reference to the Section of the FD&C Act describing the type of application and an indication of whether or not the application refers to a drug product listed in the *Orange Book*.[2]

505(b)(1) Application. An NDA submitted under Section 505(b)(1) of the FD&C Act is a complete application that contains the following:

- Administrative documents
- Chemistry, manufacturing and controls data
- Preclinical data
- Clinical data

505(j) Application (ANDA for generic products). An ANDA may be submitted for a copy of a drug that has already been approved by FDA in a 505(b)(1) application (referred to as the listed drug or reference-listed drug) as long as it is the same as the listed drug and does not meet the criteria for a 505(b)(1) or a 505(b)(2) application. The definition of the "same as" is that it is identical in active ingredient(s), dosage form, strength, route of administration and conditions of use.

505(b)(2) Application. A 505(b)(2) application is also considered a complete application, but it shares some attributes of NDAs and some of ANDAs. As with an NDA, a 505(b)(2) application is submitted under Section 505(b)(1) and approved under Section 505(c) of the act. Like ANDAs, a 505(b)(2) application may refer to FDA's previous finding of safety and effectiveness for a listed drug, and its approval is subject to patent exclusivity limitations.

One of the cornerstones of the 505(b)(2) application is that not all of the information required for approval of a 505(b)(2) is from studies conducted by or for the applicant, and the applicant has not obtained a right of reference to the original data.

The applicant submitting a 505(b)(2) application may rely on either published literature or FDA's finding of safety and effectiveness for an approved drug to support the approval of its submission. When an applicant is depending on FDA's finding of safety and effectiveness for an approved drug, the applicant may refer to specific studies in the listed drug's NDA to support approval of the 505(b)(2) application. For instance, the applicant may refer to the nonclinical toxicology and pharmacology data for the approved drug, as well as to some or all of the clinical data.

For this type of application, published literature may be used to support approval of a new indication for a listed drug submitted by an applicant other than the original NDA holder, or for a new chemical entity (NCE)/new molecular entity (NME). The extent to which published literature alone can be used to support approval of a new drug should be discussed with the reviewing division at FDA. Particularly in the case of a new indication, FDA will likely need to rely on some primary data to enhance the acceptability of the published literature.

The applicant can obtain primary data by either conducting a new clinical study demonstrating safety and effectiveness of the drug for the new indication or of the NCE/NME itself or by obtaining the rights to the raw data in the publications, such as protocols, case report forms, and electronic datasets and programs.

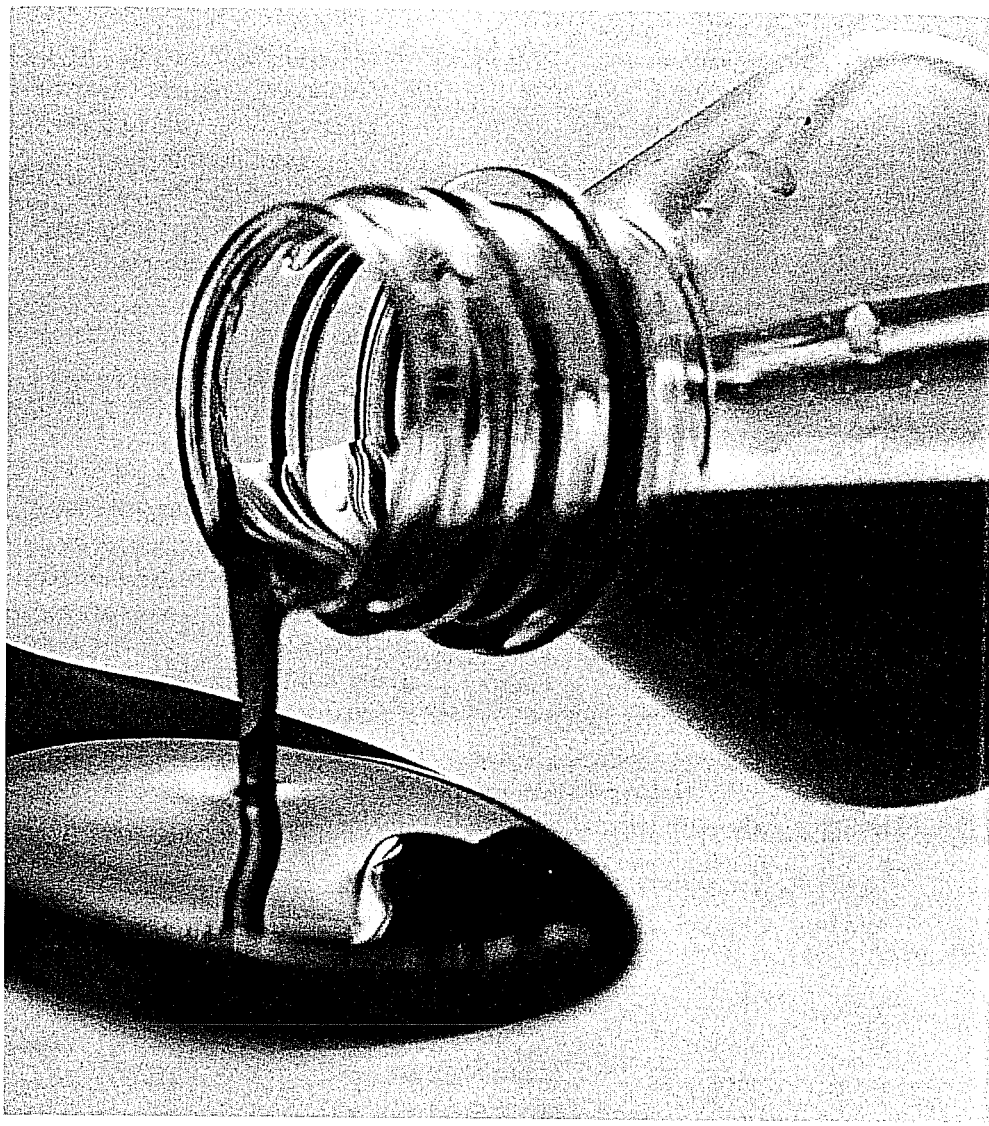
A 505(b)(2) application that relies on FDA's previous finding of safety and effectiveness for a listed drug is codified in 21 CFR Part 314.54.[3] This provision allows FDA to approve a modification of a drug under the same type of mechanism used to approve generic drugs. The applicant relies on the agency's finding of safety and effectiveness of the previously approved drug, together with additional data required to support the change from the approved drug.

The most common changes to a listed

drug for which 505(b)(2) NDAs may be submitted include changes to the following:

- Dosage form changes, such as a change from an immediate-release to a modified-release product, that rely to some extent on FDA's finding of safety, effectiveness (or both) for the approved drug in the reference dosage form.
- Dosage strength changes including changes to a lower or higher strength.
- Dosage regimen changes, such as a change from twice-daily to once-daily dosing.
- Formulation changes where the proposed drug product contains a different quantity or quality of excipients that are beyond those that would normally be covered by demonstration of bioequivalence between the new and approved version of the drug product, i.e., under Section 505(j).
- Active ingredient changes, such as a different salt, acid or base of a listed drug containing the same active moiety, or a change in one of the active ingredients in an approved combination drug product for another active ingredient that has or has not been previously approved.
- A combination product in which the active ingredients have been approved individually.
- An indication that has not been previously approved for a listed drug.
- An application to change a prescription indication to an over-the-counter indication.

Changes to a listed drug that go beyond those that would be accepted in a suitability petition for an ANDA and require more than bioavailability/bioequivalence studies to support the change (i.e., an additional toxicology or clinical study) would be acceptable as a 505(b)(2) application rather than a 505(j).



Where the proposed drug product contains differences in the active ingredient from the listed drug, the differences in the impurity profile of the proposed drug product compared with the approved drug product will need to be determined and qualified. Typically, this is achieved with a bridging toxicology (14-to 90-day) study with toxicokinetics in an appropriate species according to International Conference on Harmonisation (ICH) guidance Q3A(R)[4] and Q3B(R).[5]

This bridging study needs to link the data in the approved application to the new formulation so that the applicant can refer to the preclinical information in the approved application of the listed drug. Additional toxicology studies such as mutagenicity and genotoxicity are likely to be needed to support approval. The ultimate toxicology package required for approval will depend on how closely related the active pharmaceutical ingredients (APIs) are in terms of their quality characteristics.

Pharmacokinetic Considerations

For applications involving drug products where the absorption rate, extent of absorbtion or both differ from the approved reference dosage form, additional clinical studies may be required to document safety and efficacy of the differences. In a 505(b)(2) application, a demonstration

of clinical superiority to the approved product is not required, but the following biopharmaceutical requirements need to be met:

- The proposed product must be at least as bioavailable as the approved reference product (unless it has some other advantage, such as a smaller peak/trough ratio); and
- The pattern of release of the proposed product, although different, must be at least as favorable as the approved reference product.

Appropriate bridging studies may be acceptable to FDA if the studies are shown to provide an adequate basis of reliance on the agency's finding of safety and effectiveness of the listed drug. Typically, changes in the dosage form or formulation will require a toxicology study to bridge the new dosage form or formulation to the listed drug's toxicology data in the innovator's NDA.

FDA's 1999 guidance[1] on 505(b)(2) applications provides additional information on the agency's current thinking about the types of documents that may be submitted under a 505(b)(2).

Since 1984, 126 drug products have been approved via 505(b)(2) applications.[6] The 505(b)(2) can be used to support approval when changes to an approved drug are not so extensive that they require a stand-alone NDA but are extensive enough that they may require additional safety or effectiveness data, making the product ineligible for approval under Section 505(j). In addition, the 505(b)(2) application can be used to support approval of an NCE/NME.

Since 2001, FDA has received several challenges to its interpretation of Section 505(b)(2), including a 2001 citizen's petition submitted on behalf of Pfizer Inc. and Pharmacia Corp.; a 2002 petition submitted on behalf of Pfizer Inc.; a 2001 petition submitted by the Biotechnology Industry Organization (BIO); and a 2003 petition submitted on behalf of TorPharm (2003P-0408/CP1).[7]

In essence, petitioners argue that the FD&C Act does not permit approval of a Section 505(b)(2) submission that relies, without the innovator's authorization, on that company's proprietary data.

The petitioners in the Pfizer/Pharmacia case argue that Section 505(b)(2) does not allow "FDA's unauthorized reliance on or use of an innovator's proprietary data to approve" 505(b)(2) NDAs; that any such reliance by FDA is an unconstitutional "taking" in violation of the Fifth Amendment; and that assignment of "A" therapeutic ratings in the *Orange Book* for any drugs approved under Section 505(b)(2) is unlawful. The Pfizer/Pharmacia petition requests FDA to:

- Cease approval of all 505(b)(2) NDAs;
- Rescind the agency's regulations implementing section 505(b)(2); and
- Refuse to grant "A" substitutability ratings to such products.

According to a 14 October 2003 response by FDA to the four petitions, the agency "is considering whether to commence a public process to examine the narrow question of whether to change our interpretation of Section 505(b)(2) as it applies to applications for which the only change from the listed drug is a change in active ingredient."[8]

If the Section 505(b)(2) procedure and the district court's ruling on the scope of patents extended under Hatch-Waxman are upheld, generic drug manufacturers will increasingly be able to use Section 505(b)(2) to obtain quick approval of new forms of drugs based on the innovator's data.

NOTES

1. Food and Drug Administration. *Guidance for Industry. Applications Covered by Section 505(b)(2).* Available at: www.fda.gov/cder/guidance/2853dft.htm. Accessed 12 March 2004.
2. Food and Drug Administration. *The Orange Book. Approved Drug Products with Therapeutic Equivalence Evaluations.* Available at: www.fda.gov /cder/ob /default.htm. Accessed 12 March 2004.
3. Food and Drug Administration. 21 CFR Part 314. 54 Procedure for submission of an application requiring investigation for approval of a new indication for, or other change from, a listed drug.
4. International Conference on Harmonisation. Q3A(R): Impurities in New Drug Substances. Available at: www.fda.gov/cber/gdlns/ichq3a.pdf. Accessed 12 March 2004.
5. International Conference on Harmonisation. Q3B(R): Impurities in New Drug Products. Available at: www.fda.gov/cber/gdlns/ichq3br.pdf. Accessed 12 March 2004.
6. Food and Drug Administration. CDER New and Generic Drug Approvals: 1998-2004. Available at: www.fda.gov /cder/approval/index.htm. Accessed 24 March 2004.
7. These petitions were submitted under 21 CFR Part 10.30, the agency's citizen petition regulation. The number preceding the petition indicates the document number. They are Doc. No. 2001P-0323/CPI, submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer Inc. and Pharmacia Corporation; Doc. No. 2001CP-0323/C5, submitted by the Biotechnology Industry Organization; Doc. No. 2002P-0447/CPI submitted by Morgan, Lewis & Bockius, LLP on behalf of Pfizer Inc.; Doc. No. 2003P-0408/CP1, submitted by Lord, Bissell & Brook LLP on behalf of TorPharm.
8. Parkman, PD. Re: Dockets Nos. 2001P-O323/CPI & C5, 2002P-O447/CPI, and 2003P-O408/CPI. 14 October 2003 FDA response to citizen petitions filed by Pfizer/Pharmacia and the Biotechnology Industry Association and TorPharm challenging the Section 505(b)(2) NDA. Available at: www.fda .gov/cder/ogd /505b2-cpresponse.pdf. Accessed 12 March 2004.

Margaret E. Hurley, MD, has been president of Hurley Consulting Associates Ltd. for 16 years. Before founding the company, she was director of cardiovascular research at Ciba-Geigy Corporation.