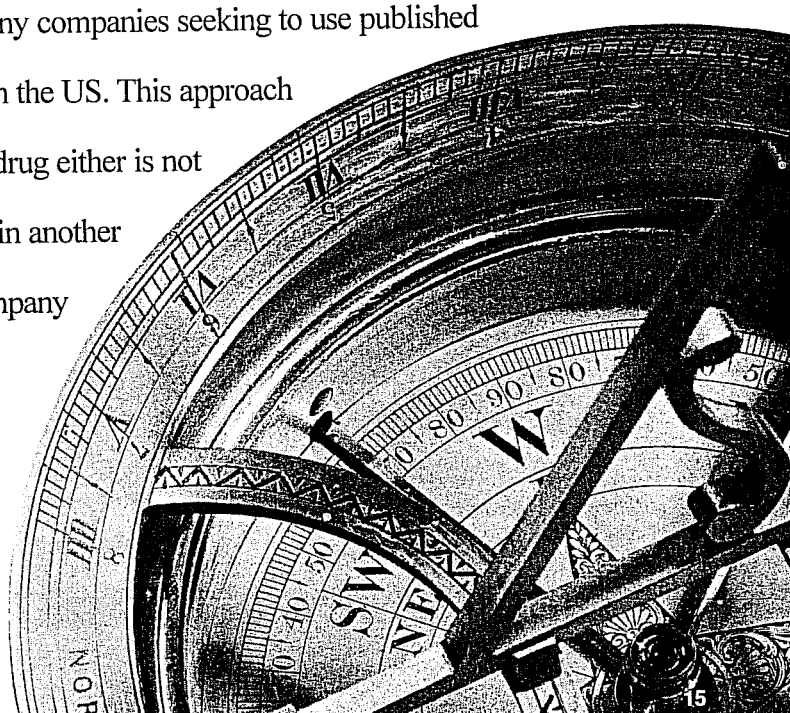
Successfully Navigating the 505(b)(2) Regulatory Maze

By Susan M. Mondabaugh, PhD

Submitting a 505(b)(2) application for a new chemical entity (NCE) or new molecular entity (NME) is an attractive strategy for many companies seeking to use published literature to support approval of new drugs in the US. This approach could be applied to situations for which the drug either is not approved anywhere globally or is approved in another region, such as Europe or Japan, but the company does not have, or cannot gain, access to the data because the marketing authorization application is held by a different company.



In the latter situation, companies may look to the use of published literature to support approval under the provisions of Section 505(b)(2) rather than perform a full nonclinical and clinical development program. In the case of an NCE that is a prodrug or active metabolite of a drug approved in the US, it may be possible to rely on the nonclinical and clinical studies conducted for this listed drug in a 505(b)(2) application. Basing a 505(b)(2) application solely on published literature presents unique challenges. This article will focus on some of the key considerations that contribute to the success of this submission strategy.

Regulatory Background

The Food and Drug Administration (FDA) issued the draft guidance document on applications covered by section 505(b)(2) in October 1999[1] to clarify situations appropriate for submission of a new drug application (NDA) as a 505(b)(2) application. This guidance discusses that a 505(b)(2) NDA can be submitted for an NCE/NME 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. The guidance states that the data are likely to be derived from published studies rather than FDA's previous finding of safety and effectiveness for a drug.

Regulatory Requirements

The submission for an NCE/NME as a 505(b)(2) application may not be as straightforward as submission of changes to an approved (listed) drug as a 505(b)(2) application. Because a 505(b)(2) application is submitted under Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act) and approved under Section 505(c) of the Act, it must meet the same statutory requirements as a full stand-alone NDA [(505(b)(1)] in terms of containing adequate data upon which FDA can base its finding of safety and effectiveness for the new drug. These requirements are set forth in 21 CFR Part 314.50[2] for the content and format of a new drug application, including those submitted under 505(b)(2).

Where Can We Go Wrong?

A successful strategy for submission of a 505(b)(2) application for an NCE/NME needs to be developed not only within the current framework of regulations but within the context of all applicable guidance documents. The draft guidance document on 505(b)(2) applications cannot be followed to the exclusion of other relevant guidance documents, especially in the case of an NCE/NME.

Examples of some of the issues that need to be addressed in new drug applications and the relevant guidance documents that should be consulted that will be discussed in the following sections are presented in **Table 1**.

Demonstrating Safety and Effectiveness

In the case of an NCE?NME for which there is no listed drug to refer for FDA's previous finding of safety and effectiveness, FDA will need to make this judgment based on the information contained in the 505(b)(2) application. For a stand-alone NDA, FDA makes this determination based on the body of evidence of the nonclinical and clinical studies conducted by the sponsor and the manufacturing and controls information.

Traditionally, the adequate and well-controlled clinical studies (as defined in 21 CFR Part 314.126)[3] included in a new drug application formed the primary basis for the demonstration of safety and effectiveness. The issuance of the guidance document *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*[4] in May 1998 provided situations in which other evidence could be considered sufficient to support a finding of safety and effectiveness.

In addition, FDA amended its new drug and biological product regulations (21 CFR Part 314.600, subpart I,[5] and 21 CFR Part 601.90, subpart H,[6] respectively) in July 2002 to allow data from appropriate studies in animals in certain cases to provide substantial evidence of the effectiveness of new drug and bio-

Table 1. Issues in NDAs and Applicable Guidance Documents

Issues to Be Addressed	Guidance Document
Demonstration of clinical safety and efficacy	Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998
Nonclinical data required to support changes in impurity profile of drug substance	ICH Q3A(R) Impurities in Drug Substances, February 2003
Nonclinical data required to support changes in impurity profile of drug product	ICH Q3B(R) Impurities in Drug Products, November 2003

logical products used to reduce or prevent the toxicity of chemical, biological, radiological or nuclear substances. These animal studies would be accepted only in cases where adequate and well-controlled studies in humans are not considered ethical and field efficacy studies are not feasible.

The use of published literature or other reports in lieu of full study reports is discussed in FDA's guidance document, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.[4] As discussed in this guidance, unless the publications contain detailed information about the statistical plans, statistical analysis methods, study endpoints and a full accounting of all patients, it may be difficult for FDA to make a determination of effectiveness for an NCE/NME based solely on a publication of a study.

The following information, which documents the prospective nature of the study and its analysis and provides additional details about the conduct of the study, together with the publication, will enhance its acceptability:

- The protocol and any amendments used for the study;
- Prospective statistical analysis plan and any changes to the plan, including when the changes were made in relation to unblinding the study;
- Randomization codes and documented study entry dates for subjects;
- Full accounting of all study subjects, including identification of those subjects on treatment who were excluded from the analyses;
- Subject case report forms; and
- Complete information for deaths and dropouts, especially if there are safety issues with the drug.

If the published literature does not contain sufficient detail for FDA to base its finding of safety and effectiveness and additional study information as listed previously and in the guidance document cannot be obtained, it is likely that an additional clinical study (studies) will need to be performed to support approval.

The Role of Nonclinical Data in Establishing Safety

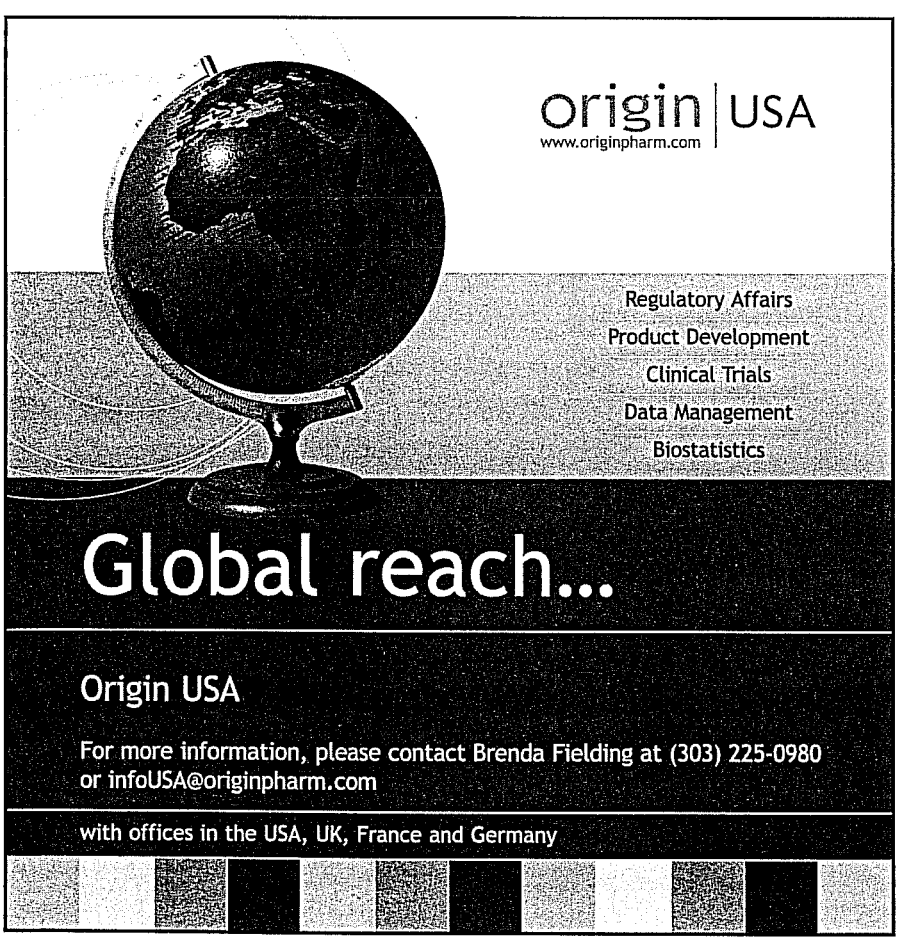
If an NCE/NME is a prodrug or active metabolite of a listed drug, it may be possible to refer to the nonclinical studies of the approved drug product to support the nonclinical safety of the NCE/NME. If the drug has been approved outside the US and the toxicology studies have been published, it may be possible to rely on the publications for nonclinical safety. In either

case, it can be expected that bridging toxicology studies will be required to link the toxicology profile of the NCE/NME to the toxicology profile of either the listed drug or the drug in the published literature.

Two International Conference on Harmonisation guidance documents, *Q3A(R): Impurities in New Drug Substances*[7] and *Q3B(R): Impurities in New Drug Products*,[8] provide decision trees for the types of bridging studies that should be conducted to qualify differences in both the impurity profile and degradation products of drug substances and drug products. Typically, the studies to be conducted include genotoxicity and a bridging toxicology study with toxicokinetics of 14 to 90 days' duration in an appropriate species.

If an applicant cannot refer to the toxicology studies of a listed drug or rely on published literature, a full toxicology program may need to be conducted for FDA to support the finding of nonclinical safety.

Successful 505(b)(2) submission strategies can be achieved for NCEs. The interpretation and interrelatedness of the regulations and various guidance documents need to be considered to determine whether published literature alone or in conjunction with additional study documentation is sufficient to support approval of an NCENME, or whether additional studies will likely be needed for approval.



NOTES

1. Food and Drug Administration. Guidance for Industry. *Applications Covered by Section 505(b)(2).* October 1999. Available at: www.fda.gov/cder/guidance/2853dft.htm. Accessed 24 March 2004.
2. 21 CFR Part 314.50 Application for FDA Approval to Market a New Drug—Content and format of an application.
3. 21 CFR Part 314.126 Application for FDA Approval to Market a New Drug—Adequate and well-controlled studies. Available at: www.fda.gov/cber/ind/21cfr314.pdf. Accessed 24 March 2004.
4. Food and Drug Administration. *Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.* Available at: www.fda.gov/cder/guidance/1397fnl.pdf. Accessed 24 March 2004.
5. 21 CFR Part 314 Subpart I. Approval of new drug when human efficacy studies are not ethical or feasible.
6. 21 CFR Part 601 Subpart H. Approval of new drug when human efficacy studies are not ethical or feasible.
7. International Conference on Harmonisation. *Guidance Q3A(R): Impurities in New Drug Substances.* Available at: www.fda.gov/cber/gdlns/ichq3a.pdf. Accessed 24 March 2004.
8. International Conference on Harmonisation. *Guidance Q3B(R): Impurities in New Drug Products.* Available at: www.fda.gov/cber/gdlns/ichq3br.pdf. Accessed 24 March 2004.

Susan M. Mondabaugh, PhD, is vice president of regulatory affairs at Hurley Consulting Associates Ltd., Chatham, NJ. Before her current position, she held various regulatory positions at Pharmacia, Upjohn and Marion Merrell Dow Inc.