

additional study and the agency believes that there may be bioequivalence issues or concerns with the product, the agency may request that a complete study report be submitted to FDA.

C. Proposed Requirement for the Submission of Data From All Postmarketing BE Studies Conducted or Otherwise Obtained by the Applicant on the Same Drug Product Formulation That Has Been Approved

Under § 314.81(b)(2)(vi), an ANDA applicant is required to submit, in an annual report, the results of “biopharmaceutic, pharmacokinetic, and clinical pharmacology studies * * * conducted by or otherwise obtained by the applicant” during the annual reporting period. All BE studies would fall into one or more of the categories of studies (i.e., biopharmaceutic, pharmacokinetic, and clinical pharmacology) required to be submitted under this section. As a result, the agency is proposing to interpret this section to require ANDA applicants with approved ANDAs to submit postmarketing reports of all BE studies, both passing and nonpassing, conducted or obtained by the applicant during the annual reporting period on the same drug product formulation that has been approved. FDA believes that the language in current § 314.81(b)(2)(vi) is sufficient to accomplish this purpose. Therefore, FDA is not amending this language, but is clarifying through this rulemaking that it intends to interpret the section to require submission of postmarketing reports of all BE studies conducted or otherwise obtained by ANDA applicants. Under this section, applicants may submit either complete or summary reports of the BE studies conducted or otherwise obtained during the annual reporting period. If a summary report is submitted for a BE study and FDA believes that there may be bioequivalence issues or concerns with the product, the agency may require that a complete study report be prepared and submitted to FDA.

FDA believes that clarifying its interpretation of § 314.81(b)(2)(vi) is important for ensuring consistency in its premarketing and postmarketing requirements regarding the submission of BE studies. However, the agency also believes that it would be highly unusual for an ANDA applicant to conduct a postmarketing BE study. In particular, the agency believes that an applicant would rarely, if ever, conduct a postmarketing BE study other than one required for an ANDA supplement.

D. What Constitutes the “Same Drug Product Formulation” for the Purposes of Required BE Study Submissions

FDA is proposing to require ANDA applicants to submit information from all BE studies, both passing and nonpassing, conducted on the same drug product formulation in conjunction with the submission of ANDAs, amendments, and supplements containing BE studies. FDA intends that the terminology “same drug product formulation” would include formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the agency’s determination of bioequivalence. For example, where an applicant makes formulation or manufacturing changes of the type that qualify as level 1 or level 2 changes in FDA’s current guidances on scale up and postapproval changes (SUPAC) listed below, the agency would consider the original and modified products to be similar enough to constitute the same drug product formulation for the purposes of the proposed rule. The SUPAC guidances include:

1. “SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation” (November 1995);
2. “SUPAC-IR: Questions and Answers about the SUPAC-IR Guidance” (February 1997);
3. “SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation” (September 1997);
4. “SUPAC-IR/MR: Immediate-Release and Modified Release Solid Oral Dosage Forms: Manufacturing Equipment Addendum” (January 1999);
5. “SUPAC-SS: Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation” (May 1997); and
6. “SUPAC-SS: Nonsterile Semisolid Dosage Forms: Manufacturing Equipment Addendum” (Draft Guidance, December 1998).

Persons interested in a full discussion of level 1 and level 2 changes should consult the SUPAC guidances listed previously in section IV.D of this document. The guidances may be

obtained upon request from the Center for Drug Evaluation and Research, Office of Training and Communications, Division of Drug Information (HFD-240), 5600 Fishers Lane, Rockville, MD, 20857, 301-827-4573. The guidances are also available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the Chemistry heading.

V. Legal Authority

Under section 505(j)(2)(A)(iv) of the act, an ANDA applicant must submit “information to show that the new drug is bioequivalent to the [reference] listed drug * * *.” If this requirement is not met because information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application, FDA may deny approval of an ANDA (section 505(j)(4)(F) of the act; § 314.127(a)(6)(i) and (ii)). FDA believes that an application may not be complete if a BE study that is conducted by an applicant on the same drug product formulation is not submitted for review because the agency is being asked to make a bioequivalence determination based on a review of only part of the available bioequivalence data. As discussed in section III of this document, the agency’s experience with additional bioequivalence data on the same drug product formulation has shown that such data can be important, and even critical, to the agency’s bioequivalence determination.

Requiring the reporting of all BE studies is consistent with the act’s requirement that applications must not contain untrue statements of material fact (section 505(j)(4)(K) of the act, § 314.127(a)(13)). FDA believes that failure to report all BE studies conducted on the same formulation of a drug product submitted for approval in an ANDA, amendment, or supplement may constitute selective reporting of a material fact, which can result in withdrawal of approval of an application under § 314.150(b)(6). Selective reporting refers to reports that contain certain passing results only. Selective reporting does not consistently contain nonpassing results and does not consistently contain a scientific justification for rejecting the nonpassing data (see FDA’s notice describing selective reporting of stability tests (60 FR 32982 at 32983, June 26, 1995)).

VI. Implementation

FDA proposes that any final rule that may issue based on this proposal become effective 6 months after its date of publication in the **Federal Register**. Proposed §§ 314.94(a)(7)(i), 314.96(a)(1), and 320.21(b)(1), as well as § 320.21(c)