

ability to ensure sound science-based decisions.

IV. Description of the Proposed Rule

The proposed rule would amend and clarify current BE study submission requirements to specifically require applicants to submit data on all BE studies, including studies that do not meet passing bioequivalence criteria, performed on a drug product formulation submitted for approval under an ANDA or an amendment or supplement to an ANDA that contains BE studies. Applicants would also be required to submit data in an annual report on all postmarketing BE studies conducted or otherwise obtained on the approved drug product formulation during the annual reporting period. In addition to the regulatory changes and clarifications described in this rulemaking, the agency is planning to issue guidance on this subject to help ensure that all affected entities are notified of, and understand, the proposed changes.

A. Proposed Requirements for the Submission of Data From All BE Studies Conducted on the Same Drug Product Formulation Submitted for Approval in ANDAs, Supplements, and Amendments

1. Proposed Requirements for Reporting BE Studies in ANDAs Submitted Under § 314.94

Current § 314.94(a)(7)(i) states that an ANDA applicant must submit information that shows a drug product to be bioequivalent to an RLD. FDA is proposing to amend § 314.94(a)(7)(i) by adding language requiring an applicant to submit information from all BE studies, both passing and nonpassing, conducted on the same formulation of the drug product submitted for approval. The applicant would continue to be required to submit complete reports of the BE studies upon which the applicant relies for approval. For all other BE studies on the same drug product formulation, the applicant would be required to submit a summary report. FDA plans to issue guidance on the format of a summary report. If a summary report is submitted and the agency believes that there may be bioequivalence issues or concerns with the product, the agency may require that a complete report be prepared and submitted to FDA.

Section 320.21(b)(1) and (b)(2) (21 CFR 320.21(b)(1) and (b)(2)) requires that any person submitting an ANDA include in the application evidence demonstrating that the drug submitted for approval is bioequivalent to the RLD

or information to permit FDA to waive the submission of evidence to demonstrate bioequivalence as provided in § 320.21(f). FDA is proposing to amend current § 320.21(b)(1) to add language requiring an applicant to submit evidence demonstrating bioequivalence that includes information from all BE studies, both passing and nonpassing, conducted on the same formulation submitted for approval. This change is consistent with the change being proposed in § 314.94(a)(7)(i) for ANDA submissions.

2. Proposed Requirements for Reporting BE Studies in ANDA Supplements Submitted Under § 314.97 (21 CFR 314.97)

In addition to modifying the information required in ANDAs, the proposed amendment to § 320.21(b)(1) would also modify the information required to be included in certain supplements to approved ANDAs (which are submitted under § 314.97). Under § 320.21(c), any person submitting a supplement to an ANDA must include the evidence or information required by § 320.21(b) (i.e., BE studies or information permitting waiver) for certain types of changes to the drug product or labeling. For example, a change in the manufacturing process beyond the variations provided for in the ANDA would require a supplement containing BE studies or information permitting waiver of such studies. FDA is not proposing to amend the language of § 320.21(c). However, because § 320.21(c) incorporates the requirements of § 320.21(b) by reference, the proposed amendment to § 320.21(b)(1) would modify the requirements of § 320.21(c). Specifically, for ANDA supplements requiring BE studies under § 320.21(c), applicants would be required to include the information required by proposed § 320.21(b)(1) (i.e., information from all BE studies, both passing and nonpassing, conducted on the same formulation for which the supplement is being submitted).

3. Proposed Requirements for Reporting BE Studies in Amendments to ANDAs Submitted Under § 314.96

Section 314.96(a)(1) states that an ANDA applicant may amend an ANDA that has been submitted but not yet approved to revise existing information or provide additional information. FDA is proposing to amend current § 314.96(a)(1) to require that, where BE studies are submitted in an amendment, the amendment contain information from all BE studies, both passing and nonpassing, conducted by the applicant

on the same drug product formulation, unless the information has previously been submitted to FDA in the applicant's ANDA.

4. Proposed Requirements for the Format of the Reports of BE Studies Submitted in ANDAs, Supplements, and Amendments

Under the proposed rule, proposed §§ 314.94(a)(7)(i), 320.21(b)(1), and 314.96(a)(1), as well as § 320.21(c) (which incorporates the requirements of § 320.21(b)(1) by reference) would require applicants to submit full reports of BE studies upon which the applicant relies for approval and either full or summary reports of all other BE studies conducted on the same drug product formulation. If a summary BE study report is submitted and FDA believes that there may be a bioequivalence issue or concern with the product, FDA may require that a complete report be prepared and submitted to FDA.

B. Proposed Requirement for the Submission of Data From All BE Studies Conducted on the Same Drug Product Formulation Submitted for Approval Under a Petition Approved Under § 314.93

Section 314.94(a)(7)(ii) states, in relevant part, that if an ANDA is submitted under a petition approved under § 314.93, the applicant must submit the results of any bioavailability or bioequivalence testing required by the agency to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the RLD and that the proposed drug product can be expected to have the same therapeutic effect as the RLD. The agency is proposing to interpret § 314.94(a)(7)(ii) to require the submission of results from all bioavailability and BE studies conducted on the same formulation. FDA believes that the language in current § 314.94(a)(7)(ii) is sufficient to accomplish this purpose. Therefore, FDA is not amending this language, but is clarifying through this rulemaking that it intends to require applicants that submit ANDAs under petitions approved under § 314.93 to submit information from all BE studies, passing and nonpassing, conducted on the same drug product formulation. Applicants would be required to submit complete reports of the bioavailability or BE studies upon which the applicant relies for approval and either a complete or summary report for all other studies on the same drug product formulation. If a summary report is submitted for an