

(which references the requirements of § 320.21(b)(1)) and § 314.94(a)(7)(ii) (as interpreted in section IV.B of this document), would apply only to ANDAs, amendments, or supplements submitted on or after the effective date of the final rule. Thus, applicants who have submitted these applications prior to the effective date of the final rule would not be required to report additional BE studies that were conducted in conjunction with their applications. However, where an ANDA has been approved or submitted prior to the effective date of the final rule, and a supplement or amendment to the ANDA containing a BE study or studies is submitted on or after the effective date of the final rule, the applicant would be required under proposed §§ 314.96(a)(1) and 320.21(b)(1), as well as § 320.21(c) (which refers to the requirements of § 320.21(b)(1), to submit all BE studies, both passing and nonpassing, conducted in conjunction with the supplement or amendment. In addition, on and after the effective date of the final rule, all applicants with approved ANDAs, including ANDAs that have been approved or submitted for approval prior to the effective date of the final rule, would be required to comply with § 314.81(b)(2)(vi), as interpreted by FDA in section IV.C of this document. However, the agency is proposing to use its discretion in the enforcement of § 314.81(b)(2)(vi) such that it would apply only to those additional BE studies conducted after the effective date of the final rule. Thus, applicants with approved ANDAs would be required to provide information in an annual report on additional passing or nonpassing BE studies conducted or obtained by the applicant on the approved drug product formulation after the effective date of the final rule.

VII. Comments on the Proposed Rule

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type

that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Analysis of Economic Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612 (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121))), and the Unfunded Mandates Reform Act (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866. With respect to the Regulatory Flexibility Act, the agency does not believe that the proposed rule is likely to have a significant economic impact on a substantial number of small entities. Nevertheless, because our projections are uncertain, the analysis presented below also constitutes the agency's Initial Regulatory Flexibility Analysis. Because the rule does not impose mandates on State, local, or tribal governments, or the private sector, that will result in an expenditure in any one year of \$100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

A. Background

Under current regulations, ANDA applicants are required to submit information demonstrating that a generic product is bioequivalent to an RLD. In the past, firms have submitted

only the results of those BE studies that demonstrate that the rate and extent of absorption of the test product meets bioequivalence limits. Firms have not typically submitted the results of any additional BE studies that were conducted on the same product formulation submitted for approval. As discussed in section III of this document, the agency now believes that data and information from additional BE studies, both passing and nonpassing, are important for determining whether the proposed formulation is bioequivalent to the RLD. Therefore, FDA is proposing to require ANDA applicants to submit all BE studies, passing and nonpassing, on a drug product formulation submitted for approval under an ANDA, amendment or supplement.

As discussed in section IV.C of this document, the agency also believes that it is important to clarify that the responsibility to submit all BE studies, passing and nonpassing, continues after approval under the annual report submission requirements. However, the agency 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.

B. Affected Entities

The proposed rule would affect establishments that submit ANDAs containing BE studies. FDA does not know the precise number of entities, either large or small, that will submit ANDAs in the future. In the year 2000, there were 346 BE studies submitted by 57 applicants in 197 ANDAs, amendments, and supplements. FDA estimates that this proposed rule would result in a 10 percent increase in the number of BE studies submitted annually, or 35 (346 x 0.10) additional studies. This estimate is based on information suggesting that approximately 20 percent of all BE studies conducted produce results that do not meet bioequivalence limits and that approximately 50 percent of these studies are conducted on formulations that are not submitted for approval.

C. Compliance Requirements and Costs

The main cost of complying with this proposed rule would be staff time. This analysis assumes a weighted average wage rate of \$40 per hour (Ref. 2). FDA estimates it would require approximately 120 hours of staff time to prepare and submit each additional complete BE study report, and approximately 60 hours of staff time for