(HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. The ANPRM and the petition are available for review at the Division of Dockets Management or electronically on FDA's Web site at *http://www.fda.gov/ohrms/dockets/98fr/03–16789.pdf* (ANPRM) and *http://www.fda.gov/ohrms/dockets/98fr/00p–0685–cp00001.pdf* (petition). You also may request a copy of these documents from the Division of Dockets Management.

FOR FURTHER INFORMATION CONTACT: Ritu Nalubola, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition (HFS–820), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–2371.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of July 3, 2003 (68 FR 39873), FDA published an ANPRM announcing that a petition was filed on February 18, 2000, requesting that the agency revoke the standards of identity for lowfat yogurt and nonfat yogurt; amend the standard of identity for yogurt in numerous respects, including incorporation of provisions for lowfat and nonfat yogurt; and amend the standard of identity for cultured milk in numerous respects, including allowing for the use of the alternate term ''fermented milk.'' Interested persons were given until October 1, 2003, to comment on the ANPRM.

Following publication of the July 3, 2003, ANPRM, FDA received a request to allow interested persons additional time to comment. The requester asserted that the time period of 90 days was insufficient to respond fully to FDA's specific requests for comments and to allow potential respondents to thoroughly evaluate and address pertinent issues, including those that have emerged since the petition was filed in 2000.

FDA believes that it is sound public policy to reopen the comment period (21 CFR 10.40(b)(3)(i)), given the variety of scientific and other issues raised in the ANPRM.

II. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding the ANPRM. 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. Comments previously submitted to the Division of Dockets Management do not need to be resubmitted because all comments submitted with that docket number will be considered in any future rulemaking. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 21, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03–27188 Filed 10–28–03; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 320

[Docket No. 2003N–0341]

Requirements for Submission of In Vivo Bioequivalence Data; Proposed Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations on submission of bioequivalence data to require an abbreviated new drug application (ANDA) applicant to submit data from all bioequivalence studies (BE studies) that the applicant conducts on a drug product formulation submitted for approval. In the past, ANDA applicants have submitted BE studies demonstrating that a generic product meets bioequivalence criteria for FDA to approve the ANDA, but have not typically submitted additional BE studies conducted on the same drug product formulation, such as studies that do not show that the product meets these criteria. FDA is proposing this change because we now believe that data from additional BE studies may be important in our determination of whether the proposed formulation is bioequivalent to the reference listed drug (RLD) and are relevant to our evaluation of ANDAs in general. In addition, such data will increase our understanding of how changes in components, composition, and methods of manufacture may affect formulation performance.

DATES: Submit written or electronic comments by January 27, 2004. Submit written comments on the information collection requirements by November 28, 2003.

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. The Office of Management and Budget (OMB) is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Aida L. Sanchez, Center for Drug Evaluation and Research (HFD–650), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5847.

SUPPLEMENTARY INFORMATION:

I. Background

Section 505(j)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)(2)(A)(iv)) requires that ANDA applicants submit, among other things, information showing that the applicant's drug is bioequivalent to a drug that has previously been approved by FDA and designated as an RLD. The statutory requirement is reflected in FDA's regulations in part 314 (21 CFR part 314) at § 314.94(a)(7). Part 320 (21 CFR part 320) at § 320.24 sets forth the types of evidence acceptable to establish bioequivalence. The most common BE studies are those performed on solid oral dosage forms of drugs that are absorbed into the systemic circulation. Data from BE studies provide an estimate of the rate and extent of drug absorption for a test product compared to a reference product. These data are examined, using statistical procedures, to determine whether the test product meets bioequivalence limits.

A BE study may fail to show that a test product meets bioequivalence limits because the test product has significantly higher or lower relative bioavailability (i.e., measures of rate and extent of absorption compared to the reference product). Where the relative bioavailability of a test product is too low, the concern is that not enough of the active ingredient is reaching the site of action and therefore the product may

not be as therapeutically effective as the RLD. Where the relative bioavailability of a test product is too high, the concern with the product generally is not therapeutic efficacy but rather its safety relative to the RLD. In some cases, bioequivalence will not be demonstrated because of inadequate numbers of subjects in the study relative to the magnitude of intrasubject variability rather than either significantly high or low relative bioavailability of the product.

II. Not All BE Studies Are Currently Being Submitted

The act and FDA regulations require that an ANDA applicant submit information demonstrating bioequivalence of a proposed drug to the RLD, but they do not specify the type or quantity of information that must be submitted to demonstrate bioequivalence. It has been the practice of ANDA applicants to submit evidence of bioequivalence consisting of studies demonstrating that the rate and extent of absorption of the test product meets bioequivalence limits. Thus, ANDA applicants that have conducted multiple studies on a final formulation producing passing and nonpassing results have generally not submitted the results of the nonpassing study or studies to FDA. Similarly, ANDA applicants that have conducted multiple studies on a final formulation producing more than one passing result have generally not submitted the results of all of the passing studies to FDA. As a result, FDA only infrequently sees data from additional studies and is generally unaware of the existence of such studies. In rare instances, ANDA applicants have submitted additional BE studies or the agency has learned about such studies through other means. As discussed in section III of this document, information from additional BE studies conducted on a product can be important in assessing bioequivalence for that product.

III. Need for Submission of All Studies

In recent years, there have been certain cases where applicants did not submit all of the BE studies conducted on the final formulation of an ANDA product prior to approval, and FDA discovered postapproval that the submission of such studies could have been important in assessing bioequivalence. The agency is not aware of any adverse public health consequences associated with products for which studies were not submitted. Moreover, the agency is not aware of any information regarding any generic product currently on the market that would suggest that the product is not bioequivalent to a reference listed drug to which it has been designated as therapeutically equivalent. However, the agency now believes that it is necessary for the purposes of evaluating a drug product submitted for approval under an ANDA to have data obtained from all additional BE studies conducted on the final formulation. This view was supported by FDA's Advisory Committee for Pharmaceutical Science, which recommended in a recent meeting that FDA review all BE studies conducted by the applicant on the final formulation (Ref. 1). The agency is proposing that ANDA applicants submit information from all BE studies for the following reasons:

1. Data contained in additional passing and nonpassing BE studies can be important to FDA's assessment of bioequivalence for a specific product.

2. Even when additional BE studies are not critical to the agency's bioequivalence determination for the specific product being reviewed, the data provide valuable scientific information that increases the agency's knowledge and understanding of bioequivalence and generic drug development and promotes further development of science-based bioequivalence policies.

The agency's experience with evaluating additional passing and nonpassing BE studies has shown that information from such studies can be important in assessing whether a formulation is bioequivalent to the RLD. For example, in one recent case, the ANDA applicant conducted an additional BE study on the final formulation prior to submission of its ANDA, but did not submit the results of the study to FDA. The agency found out about the results of the additional study after approval of the ANDA. The additional study indicated that the bioequivalence of the approved product was questionable. Based on the information in the additional study, the agency reconsidered its decision to approve the drug and requested that the firm voluntarily withdraw the product from the market. The firm withdrew the product from the market and withdrew its ANDA. Although cases such as this may occur relatively infrequently, it is imperative that FDA be aware of the additional BE studies and have the information necessary to evaluate their significance.

When FDA receives an ANDA that contains one or more nonpassing BE studies for the final formulation, the agency will evaluate the significance of both the passing and nonpassing BE studies. As an initial matter, for each study submitted in summary report form, FDA will consider whether it is necessary to request a full report from the applicant. Regardless of the form of the report, however, FDA anticipates that a number of factors will be critical in evaluating both the passing and nonpassing BE studies. For example, FDA may consider: (1) The statistical power of each study, (2) minor differences in the formulation used in each study, (3) whether the product was administered consistent with the RLD's labeling in every study, and/or (4) various other study design issues. In addition, FDA may inspect the sites of the different studies to determine whether there were technical flaws in how the studies were conducted. For example, the reliability of a particular study's results could be undermined by flaws in: (1) Its inclusion and exclusion criteria, (2) an investigator's compliance with standard operating procedures and/or the study protocol, (3) its analytical or assay methodologies, (4) the storage of samples, (5) how between treatment washout periods were carried out, and/or (6) various other flaws in how the study was conducted. The goal of FDA's evaluation will be to determine: (1) The importance and reliability of the data collected in the different studies and (2) how the studies should be weighed in making a bioequivalence determination. Ultimately, however, the responsibility to demonstrate that the ANDA product is bioequivalent to the RLD rests with the applicant. Therefore, if conflicting BE studies are submitted, it will ultimately be the applicant's responsibility to demonstrate why the nonpassing study or studies should not undermine a determination that the ANDA product is bioequivalent to the RLD.

Even in cases where information from additional BE studies is not critical to the agency's bioequivalence determination for a specific product, the data will provide valuable scientific information that increases our knowledge and understanding of bioequivalence and generic drug development issues. Data from additional BE studies also provide FDA with useful and relevant information about drug products submitted for approval, including how minor formulation or composition changes, or changes in study design, affect the performance of a formulation. FDA anticipates that further experience with data from additional passing and nonpassing BE studies will facilitate a more focused and efficient ANDA review process and enhance FDA's

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

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)

(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

each additional BE study summary report. The agency believes that a complete report would be required approximately 20 percent of the time, while a summary would suffice approximately 80 percent of the time.

Based on a weighted-average calculation using the information presented above, the submission of each additional BE study is expected to cost $2,880 ([120 x $40 x 0.2] + [60 x $40 x 0.8]). Thus, the overall impact on the industry of reporting an additional 35 BE studies per year would be $100,800 ($2,880 x 35).

Assuming it is equally likely that each of the 35 additional BE studies would be conducted by any of the 57 applicants, a binomial distribution can be used to predict how many firms would submit additional studies. Based on this distribution, 19 firms would incur costs of $2,880 for 1 additional BE study, 6 firms would incur costs of $5,760 (2 x $2,880) for two additional studies, and 1 firm would incur costs of $8,640 (3 x $2,880) for 3 additional studies (the total number of studies in the calculation does not equal 35 because of rounding). Thus, the maximum expected annual cost burden for any one firm would be $8,640. More than half (31 of 57, or 54 percent) of all firms would be expected to incur no additional annual costs under the proposed rule.

D. Impact on Small Entities

FDA recognizes that some of the establishments that would be required to submit additional BE study reports would be small entities with limited resources. As shown in the following paragraphs, the agency estimates that the maximum expected cost of the proposed rule for any one small entity would be between 0.58 percent and 1.9 percent of the total cost of preparing and submitting an ANDA, and that the maximum expected burden for any one of these small entities would be 0.005 percent of average revenues. Although FDA does not believe it likely that the proposed rule would have a significant economic impact on a substantial number of small entities, the agency acknowledges the uncertainty of its estimates with respect to the number of additional BE studies that would be submitted, their distribution among large and small entities, and the number of small entities affected. As a result, the agency has prepared this Initial Regulatory Flexibility Analysis and requests detailed public comment regarding the number of small entities affected by the proposed rule as well as its economic impact.

FDA also recognizes that requiring submission of all BE study results may result in a longer total application review time if these additional BE study results suggest that a generic product is not bioequivalent to the RLD. In these situations, firms would be required to submit additional data that demonstrate bioequivalence in order to obtain marketing approval. Marketing approval may be denied if evidence from the additional BE studies fails to establish bioequivalence. The agency does not know how frequently these situations might occur.

According to standards established by the Small Business Administration (SBA), a small pharmaceutical preparation manufacturer (NAICS Code 325412) employs fewer than 750 employees (Ref. 3). An FDA review of ANDAs submitted during the 3–year period from October 1996 to September 1999 found that 32 percent of the applications (322 of 1,007) were from small entities and that 39 percent of ANDA sponsors (64 of 164) were small entities. Thus, the majority of ANDAs are neither submitted nor sponsored by small entities. Assuming these proportions continue to hold, there would be 22 small entities (0.39 x 57) submitting ANDAs annually. FDA also assumes that this group of small entities would submit 11 of the additional 35 BE studies (0.10 x 0.32 x 346) per year.

Assuming it equally likely that each of the 11 additional BE studies would be reported by any of the 22 small entities, a binomial distribution can be used to predict how many firms would submit additional studies. Based on this distribution, seven small entities would incur costs of $2,880 for one additional BE study, and two firms would incur costs of $5,760 (2 x $2,880) for two additional BE studies. Thus, the maximum expected burden for any one small entity would be $5,760. More than half (13 of 22, or 59 percent) of all small entities would be expected to incur no additional annual costs under the proposed rule.

The cost of preparing and submitting an ANDA is believed to be between $300,000 (Ref. 4) and $1 million (Ref. 5). Based on this information, the maximum expected cost burden of the proposed rule on any one firm would be between 0.86 percent and 2.9 percent of the total cost of preparing and submitting an ANDA. The maximum expected cost burden for any one small entity would be between 0.58 percent and 1.9 percent of the total cost of preparing and submitting an ANDA.

A year 2000 survey of 26 public generic drug companies revealed 15 firms with fewer than 750 employees (Ref. 5). These 15 small entities had an average of 331 employees and average annual revenues of $115 million. The maximum expected burden of this proposed rule for any one of these small entities therefore would be only 0.005 percent of average revenues. The agency believes this cost could be recovered through drug sales after marketing approval.

In recognition of the potential economic impact on small entities, the agency has structured the rule to minimize the reporting burden. For example, the agency believes that summary reports of additional BE studies would suffice 80 percent of the time provided that complete results are available to FDA upon request. The agency believes that a summary report would require only 60 hours of staff time per BE study, or half the time and expense required to prepare and submit a complete report. This provision should prove particularly beneficial for small entities.

Furthermore, no specific educational or technical skills are required to complete and submit the additional BE study reports. Trained and qualified employees of an establishment who are involved in normal operations generally complete similar activities. Also, FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the proposed rule.

FDA has evaluated only two regulatory options: (1) Continuing the current practice of requiring the submission of only pivotal BE study results, or (2) requiring the submission of results from all BE studies conducted by an applicant on a final drug product formulation. Under the first option, firms would incur no additional reporting costs, although some firms might experience significant costs if their product were initially approved and subsequently recalled or had approval withdrawn because the product is found not to be bioequivalent to the RLD. The agency believes that the second option, requiring that results from all BE studies conducted on the final drug product formulation be submitted for approval, is important for assessing bioequivalence. The proposed rule would require reporting of all BE studies, but would permit summary reports for nonpivotal BE studies except where full reports are specifically requested by the agency. The agency believes that the proposed rule therefore addresses the perceived regulatory need in the least intrusive and most cost effective way. FDA specifically requests public comment regarding any other viable alternatives to this proposed rule.

E. Benefits of the Proposed Rule

The proposed rule would generate economic benefits both for individuals and for society as a whole to the extent that the reporting of data from all BE studies would prevent product discontinuation and adverse health effects. Also, the data from additional BE studies could provide valuable scientific information, thereby increasing the agency's understanding of bioequivalence and generic drug development issues, and improving the drug approval process. Therefore, this proposed rule would permit FDA to make more informed BE determinations in the future.

X. Paperwork Requirements

This proposed rule contains information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these requirements is given below with an estimate of the annual reporting burden. Included in this estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Requirements for Submission of In Vivo Bioequivalence Data; Proposed Rule.

Description: FDA is proposing to alter the requirements for certain ANDAs, ANDA amendments, and ANDA supplements submitted under §§ 314.94, 314.96, and 314.97. Specifically, FDA is proposing to amend §§ 314.94(a)(7)(i), 314.96(a)(1), and 320.21(b)(1), as well as modify the requirements of § 320.21(c) (which refers to § 320.21(b)(1)), to require an ANDA applicant to submit information from all BE studies, both passing and nonpassing, conducted by the applicant on the same formulation of the drug product submitted for approval under an ANDA, amendment, or supplement.

In addition, FDA is proposing through this rulemaking to interpret § 314.94(a)(7)(ii) as requiring that ANDA applicants who submit ANDAs under a petition approved under § 314.93 submit information on all bioavailability or BE studies conducted on the same drug product formulation submitted for approval.

FDA is also proposing to clarify through this rulemaking that it intends to interpret § 314.81(b)(2)(vi) as requiring the submission of postmarketing reports of all BE studies conducted or otherwise obtained by ANDA applicants in the applicant's annual report. However, as discussed in section IV.C of this document, FDA believes it would be highly unusual that an applicant would 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.

Description of Respondents: Persons and businesses, including small businesses and manufacturers.

Burden Estimate: Table 1 of this document provides an estimate of the annual reporting burden under the proposed rule.

The proposed rule would affect establishments that submit ANDAs. FDA does not know the precise number of entities, either large or small, that will submit ANDAs in the future. In the year 2000, 57 applicants submitted 346 BE studies 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 the assumptions that approximately 20 percent of all BE studies conducted produce results that do not meet bioequivalence limits and that about half of these studies are conducted on formulations that are not submitted for approval.

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 each additional BE summary report. The agency believes that a complete report would be required approximately 20 percent of the time, while a summary would suffice approximately 80 percent of the time. Based on a weighted-average calculation using the information presented above, the submission of each additional BE study is expected to take 72 hours of staff time ([120 x 0.2] + [60 x 0.8]).

In table 1, FDA has estimated the reporting burden associated with each section of the proposed rule. FDA believes that the vast majority of additional BE studies would be reported in ANDAs (submitted under § 314.94) rather than supplements (submitted under § 314.97) because it is unlikely that a sponsor will conduct BE studies with a drug after the drug has been approved. Moreover, drugs approved under an ANDA prior to the effective date of the final rule would only be required to report additional BE studies conducted after the effective date, which should not result in the submission of many BE study reports in supplements. With respect to the reporting of additional BE studies in amendments (submitted under § 314.96), this should also account for a small number of reports because most BE studies would be conducted on a drug prior to the submission of the ANDA and would be reported in the ANDA itself.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency of Response	Total Annual Responses	Hours per Response	Total Hours
314.94(a)(7)	33	1	33	72	2,376
314.96(a)(1)	1	1	1	72	72
314.97	1	1	1	72	72
Total					2,520

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding this information collection to the Office of Information and Regulatory Affairs, OMB (see **ADDRESSES**).

XI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Minutes, Pharmaceutical Sciences Advisory Committee, November 16, 2000.

2. U. S. Department of Labor, Bureau of Labor Statistics, Table 20: Private Industry, Health Services, Employer Costs per Hour Worked for Employee Compensation, Professional Specialty and Technical Occupations, available online at *www.bls.gov/ncs/ect/sp/ecechist.pdf*.

3. U. S. Small Business Administration, Office of Size Standards, Table of Size Standards, available online at *www.sba.gov/size/indextableofsize.html*.

4. Balaji, K., ''Generics, The Opportunity Beckons,'' as reported by Frost and Sullivan (*www.frost.com*), 4 July 2001.

5. Humphreys, A., ''Generics: Gaining Momentum, Special Report,'' *Med Ad News*, vol. 19, p. 42, October 2000.

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 314 and 320 be amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 355a, 356, 356a, 356b, 356c, 371, 374, 379e.

2. Section 314.94 is amended by revising paragraph (a)(7)(i) to read as follows:

§ 314.94 Content and format of an abbreviated application.

(a) * * *

(7) *Bioequivalence*. (i) Information that shows that the drug product is bioequivalent to the reference listed drug upon which the applicant relies. A complete study report must be submitted for the bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation, the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA; or

* * * * *

3. Section 314.96 is amended by adding four sentences at the end of paragraph (a)(1) to read as follows:

§ 314.96 Amendments to an unapproved abbreviated application.

(a) * * *

(1) * * * Amendments containing bioequivalence studies must contain reports of all bioequivalence studies conducted by the applicant on the same drug product formulation, unless the information has previously been submitted to FDA in the abbreviated new drug application. A complete study report must be submitted for any bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation, the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA.

* * * * *

PART 320—BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4. The authority citation for 21 CFR part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 371.

5. Section 320.21 is amended by revising paragraph (b)(1) to read as follows:

§ 320.21 Requirements for submission of in vivo bioavailability and bioequivalence data.

* * * * *

(b) * * *

(1) Evidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the reference listed drug (defined in § 314.3(b)). A complete study report must be submitted for the bioequivalence study upon which the applicant relies for approval. For all other bioequivalence studies conducted on the same drug product formulation, the applicant must submit either a complete or summary report. If a summary report of a bioequivalence study is submitted and FDA determines that there may be bioequivalence issues or concerns with the product, FDA may require that the applicant submit a complete report of the bioequivalence study to FDA; or

* * * * *

Dated: October 7, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03–27187 Filed 10–28–03; 8:45 am]

BILLING CODE 4160–01–S

POSTAL SERVICE

39 CFR Part 111

Refund Procedures for Metered Postage

AGENCY: Postal Service.

ACTION: Proposed rule.

SUMMARY: The Postal Service proposes to revise the *Domestic Mail Manual* (DMM) to allow refunds for unused, undated metered postage. The proposed mailing standard would benefit any mailer who generates significant quantities of unused, undated metered postage and is able to meet the refund criteria. The Postal Service also proposes minor clarifications to the procedures for requesting refunds for unused, dated metered postage.

DATES: Submit comments on or before November 28, 2003.

ADDRESSES: Mail or deliver written comments to Charles Tricamo, New