provided in the rule to file their substantive responses to the Commission because they will be devoting the first 30 days of that period preparing responses to the Department of Commerce. SMA stated that current requirements for adequacy comments are arduous and that increasing the amount of information that must be provided while reducing the amount of time available to prepare a submission is problematic. Kelley asserted that domestic producers will put more detailed information in a notice of review if they are aware that no respondent interested parties will participate. Notices of appearance need not be filed until 21 days after the notice of institution, and Kelley asserted that nine days would be insufficient time for a domestic producer to compile this more detailed information.

The commenters' objections proceed largely from the premise that a domestic producer will not begin to prepare its responses to either the Commerce notice of initiation or the Commission notice of institution until these notices are published in the **Federal Register**. The Commission does not agree with this premise. Interested parties are in a position to begin compiling information needed for a five-year review well before the publication of notices in the **Federal Register** beginning the reviews. The parties typically know the date that Commerce and the Commission will publish their **Federal Register** notices many months in advance. The Commission requests standardized information in interested parties' responses to notices of institution; the information requests are generally known prior to publication of the **Federal Register** notice. Similarly, the information that Commerce requires to be submitted in a notice of intent to participate in a sunset review is specified by regulation, and thus will be known well before initiation of the review. Kelley's assertion that responses to the notice of institution contain more detailed information in uncontested reviews than in contested reviews is not consistent with the Commission's experience.

List of Subjects in 9 CFR Part 207

Administrative practice and procedure, investigations.

■ For the reasons stated in the preamble, the Commission amends 19 CFR part 207 as follows:

PART 207—INVESTIGATIONS OF WHETHER INJURY TO DOMESTIC INDUSTRIES RESULTS FROM IMPORTS SOLD AT LESS THAN FAIR VALUE OR FROM SUBSIDIZED EXPORTS TO THE UNITED STATES

■ 1. The authority citation for part 207 continues to read as follows:

Authority: 19 U.S.C. 1336, 1671–1677n, 2482, 3513.

■ 2. Amend § 207.61 by revising paragraph (a) as follows:

§ 207.61 Responses to notice of institution.

(a) *When Information Must Be Filed.* Responses to the notice of institution shall be submitted to the Commission no later than 30 days after its publication in the **Federal Register**.

* * * * *

Issued: January 12, 2009.

By order of the Commission.

Marilyn R. Abbott,

Secretary to the Commission.

[FR Doc. E9–860 Filed 1–15–09; 8:45 am]

BILLING CODE 7020–02–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 320

[Docket No. FDA–2003–N–0209] (Formerly Docket No. 2003N–0341)

RIN 0910–AC23

Requirements for Submission of Bioequivalence Data; Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on the submission of bioequivalence data to require an abbreviated new drug application (ANDA) applicant to submit data from all bioequivalence (BE) studies 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 in order 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 amending the regulation 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 product formulation performance.

DATES: The rule is effective July 15, 2009.

FOR FURTHER INFORMATION CONTACT: Aida L. Sanchez, Center for Drug Evaluation and Research (HFD–650), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 240–276–8782.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of October 29, 2003 (68 FR 61640), FDA proposed to amend its regulations in parts 314 and 320 (21 CFR parts 314 and 320) to require an ANDA applicant to submit data from all BE studies that the applicant conducts on a drug product formulation submitted for approval. 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. Under the regulations at § 314.3(b), the approved drug product identified by FDA as the drug product on which an ANDA applicant relies for approval is the RLD. The requirement that an ANDA applicant submit information that shows the proposed product is bioequivalent to the RLD is described in FDA's regulations at § 314.94(a)(7). Section 320.24 sets forth the types of evidence acceptable to establish BE. The most common BE studies are those performed on solid oral dosage forms of drugs that are absorbed into the systemic circulation. BE data provide an estimate of the rate and extent of drug absorption for a test and reference product. These data are examined, using statistical procedures, to determine whether the test product meets BE limits.

A BE study may fail to show that a test product meets BE 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). In some cases, BE will not be demonstrated because there are inadequate numbers of subjects in the study relative to the magnitude of intrasubject variability, and not because

of either significantly high or low relative bioavailability of the product. Where the relative bioavailability of a 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 is not its therapeutic efficacy, but rather its safety relative to the RLD. When the variability of the test product is high, the concern relates to both safety and efficacy. The variability may suggest that the test product does not perform as consistently as the reference product, and the test product may be too variable to be clinically useful.

The act and FDA regulations require that an ANDA applicant submit information demonstrating BE of a proposed drug to the RLD, but do not specify whether all BE studies must be submitted. 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 meet BE limits. Thus, ANDA applicants that have conducted multiple studies on a final formulation, producing both 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 infrequently sees data from such 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.

II. Summary of the 2003 Proposed Rule

FDA determined that the submission of all bioequivalence studies, both passing and nonpassing, is necessary for the purposes of evaluating a drug product submitted for approval under an ANDA. Accordingly, the agency proposed to amend its regulations in parts 314 and 320. Specifically, the agency proposed to amend:

- the ANDA content requirements (§ 314.94(a)(7)(i))
- the ANDA amendment requirements (§ 314.96(a)(1)), and
- the requirements for submission of in vivo bioavailability and bioequivalence data (§ 320.21(b)(1)).

The agency did not propose to amend the text of § 320.21(c). However, because § 320.21(c) references the requirements of § 320.21(b)(1), the proposed changes to § 320.21(b)(1) would also modify the requirements of § 320.21(c). In addition, FDA explained how it intended to interpret two of its current regulations to be consistent with the proposal. Specifically, FDA explained that it intended to interpret the regulation applicable to an ANDA submitted under an approved suitability petition (§ 314.94(a)(7)(ii)) and the postmarketing reporting regulation (§ 314.81(b)(2)(vi)) to require the submission of all BE studies, both passing and nonpassing.

The agency did not propose to amend the section heading of § 320.21 (''Requirements for submission of in vivo bioavailability and bioequivalence data''), but after reviewing the public comments, the agency believes that the section heading of § 320.21 may cause confusion. As explained in the proposed rule, FDA is requiring the submission of all bioequivalence studies conducted on a drug product formulation submitted for approval. This requirement includes both in vivo and in vitro studies that are conducted for the purpose of establishing bioequivalence. Therefore, FDA is changing the section heading of § 320.21 to omit the reference to in vivo studies, to more clearly reflect the fact that both in vivo and in vitro studies must be submitted.

III. Description of the Final Rule

We are revising our regulations to require applicants to submit data on all BE studies, including studies that do not meet passing bioequivalence criteria, which are performed on a drug product formulation submitted for approval under an ANDA, or in an amendment or supplement to an ANDA that contains BE studies. Applicants will 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.

The provisions of the proposed rule stated that BE studies on the ''same drug product formulation'' must be submitted. The proposed rule did not specifically define the term ''same drug product formulation.'' However, in the preamble to the proposed rule, the agency stated that ''FDA intends that the terminology 'same drug product formulation' will 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 will consider the original and modified products to be similar enough to constitute the same drug product formulation for the purposes of the proposed rule'' (68 FR 61640 at 61643). The proposed rule then listed six SUPAC guidances.

FDA received a significant number of comments indicating that using the SUPAC guidances as a way of explaining which BE studies must be submitted to the agency did not provide sufficient clarity. For example, one comment on the proposed rule asked if the rule will require the submission of pilot studies, including pilot pharmacokinetic studies in animals, or in vitro studies. Another comment asked whether it will be necessary to submit prior studies—such as a pharmacokinetic study on the metabolite only, a pharmacokinetic study in urine, a pharmacodynamic study, a clinical endpoint BE study or other clinical study, or a sensitization or irritation study for transdermal patches—that are not directly relevant to the assessment of BE by the current criteria.

The final rule continues to use the term ''same drug product formulation.'' However, to eliminate the confusion caused by reference to the SUPAC guidances, we have added a definition of the term ''same drug product formulation.'' As set forth in § 320.1(g) of this final rule, the term ''same drug product formulation'' means the formulation of the drug product submitted for approval and any 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 (§ 320.1(g)). This definition is consistent with FDA's intended meaning for the term ''same drug product formulation,'' as described in the proposed rule (68 FR 61640 at 61643), and eliminates the need to refer to the SUPAC guidances as discussed further in this document.

In addition, as stated in the preamble to the proposed rule, FDA intends to make available shortly a draft guidance intended to help affected entities better understand which BE studies should be submitted, as well as the format FDA recommends for submission.

FDA is revising §§ 314.94(a)(7)(i), 314.96(a)(1), 320.1(g), 320.21 (section heading), and 320.21(b)(1), as well as modifying § 320.21(c) (which references the requirements of § 320.21(b)(1)) to

require that an applicant submitting BE studies in an ANDA, ANDA amendment, or ANDA supplement submit: (1) Full reports of BE studies upon which the applicant relies for approval and (2) either full or summary reports of all other BE studies conducted on the same drug product formulation. In addition to amending these provisions, FDA is also clarifying its interpretation of two regulations, §§ 314.94(a)(7)(ii) and 314.81(b)(2)(vi) as follows:

As currently written, § 314.94(a)(7)(ii) requires an applicant submitting an ANDA under a petition approved under § 314.93 to 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. Consistent with the regulatory changes described above, FDA intends to interpret § 314.94(a)(7)(ii) to require the submission of results from all bioavailability and BE studies, passing and nonpassing, conducted on the same drug product formulation. An applicant submitting an ANDA under a petition approved under § 314.93 will now be required to submit complete reports of the bioavailability or BE studies upon which the applicant relies for approval, and a complete or summary report for all other bioavailability or BE studies on the same drug product formulation.

As currently written, § 314.81(b)(2)(vi) requires an ANDA applicant 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. FDA intends to interpret this section to require ANDA applicants with approved ANDAs to submit reports of all BE studies, both passing and nonpassing, conducted or obtained by the applicant during the annual reporting period on the approved drug product.

IV. Comments on the Proposed Rule

FDA received 11 comments on the proposed rule from manufacturers, trade associations, and law firms. On June 11, 2004, FDA held a meeting to discuss the proposed rule with the Generic Pharmaceutical Association (GPhA). The meeting minutes have been entered into the docket, and the comments provided by GPhA are included in the comments we respond to in this document. The majority of the comments supported the proposed amendments to FDA's regulations. Several comments requested clarification on various aspects of the rule. The final rule is described in section III of this document.

A. General Comments

(Comment 1) Several comments, including comments from manufacturers, law firms, and trade associations, commended FDA on the proposal. In particular, these comments noted the importance of requiring the submission of all bioequivalence data to assess the safety and effectiveness of ANDA products, and to enhance FDA's knowledge concerning bioequivalence.

(Response) We appreciate the support expressed in these comments and agree that requiring the submission of these data is very important.

(Comment 2) One comment specifically commended FDA for stating in the proposed rule that the agency is not aware of any adverse public health consequences associated with products for which studies were not submitted, nor of any information on any currently marketed generic product suggesting that the product is not bioequivalent to a reference listed drug to which it has been designated as therapeutically equivalent.

(Response) FDA notes that since publication of the proposed rule, we have not become aware of any such information.

(Comment 3) In the preamble to the proposed rule we stated: ''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 promote further development of science-based bioequivalence policies'' (68 FR 61640 at 61641). One comment stated that the goal of increasing FDA's knowledge and understanding of bioequivalence should not be accomplished by imposing regulatory requirements on ANDA applicants. This comment suggested that the appropriate way to achieve this goal will be to hold joint industry-agency meetings and conferences.

(Response) We agree with the comment that if the sole purpose of this rule was to increase the agency's understanding of BE, there would be alternative means for FDA to achieve this goal. As stated in the proposal, however, the primary purpose of the requirement to submit information from all BE studies on the same drug product formulation is that ''[d]ata contained in additional passing and nonpassing BE studies can be important to FDA's assessment of bioequivalence for a specific product'' (68 FR 61640 at 61641). Currently, ANDA applicants are only required to submit one BE study (or two, if a fed study is required). Based on one or two studies, FDA might conclude that the product is bioequivalent to its RLD. If the agency receives other BE studies conducted by the applicant, and these studies failed to show bioequivalence, the agency might make a different decision about whether to approve the ANDA than it would have if the agency had received only the passing study. In such a case, receipt of additional BE studies will be critical to FDA's determination as to whether a generic product is equivalent to its RLD. Unless FDA receives all BE studies on the same drug product formulation, it is not possible for the agency to make an informed, scientifically based decision about bioequivalence. Thus, the rule requires that all BE studies conducted on the same drug product formulation be submitted. In other cases, FDA's receipt of additional BE studies might not change the agency's decision that a product is bioequivalent to its RLD. In both cases, however, review of the additional studies will serve the ancillary purpose of increasing the agency's understanding of bioequivalence, and provide added confidence in the agency's BE determination. In setting out the second purpose (that of increasing the agency's knowledge of bioequivalence), we note in the preamble to the proposed rule that this ancillary purpose is served even when the additional BE studies do not prove to be critical to the agency's bioequivalence determination for the specific product being reviewed (68 FR 61640 at 61641).

(Comment 4) One comment suggested that FDA amend § 314.127(b) of its regulations to reflect that failure to submit all required BE study reports is grounds for receiving an ''unapprovable'' letter.

(Response) FDA generally disagrees with the comment. Failure to submit all BE studies will be grounds for refusing to receive the ANDA under § 314.101(b)(1) of FDA's regulations because the ANDA will not be complete. It should be noted that section 505(j)(4) of the act describes the grounds for refusing to approve an ANDA. Under certain circumstances, one or more unreported BE studies might provide the basis for refusing to approve an ANDA under section 505(j)(4)(F) of the act (''information submitted in the application is insufficient to show that the drug is bioequivalent * * *''). See also § 314.127(a)(6). For example, if,

while an ANDA is pending, FDA discovers that the ANDA omitted one or more studies that failed to demonstrate BE, FDA might conclude that the BE information in the application is insufficient.

(Comment 5) Several comments expressed concern about the burden that will be imposed on the ANDA review process and agency resources (e.g., reviewers and inspectors) when the rule is implemented. One comment expressed concern that the workload created by this rule will slow action on pending ANDAs. Another comment noted that FDA has been trying to reduce the time both for BE review and response to correspondence by the Office of Generic Drug's (OGD's) Division of Bioequivalence. This comment suggested that adequate hiring and retention should be established in the Division of Bioequivalence before implementing the rule.

(Response) FDA crafted the requirements of the rule mindful of balancing its need for additional BE information with the need to ensure that the ANDA review process is not unnecessarily burdened. It was the desire to achieve this balance that, in part, led FDA to require only the submission of BE studies conducted with the ''same drug product formulation'' as that submitted for approval, rather than requiring the submission of all BE studies conducted with all developmental formulations, as some comments suggested. FDA appreciates, however, that the final rule will increase the number of studies reviewed by the Division of Bioequivalence, and the agency is working on hiring additional staff to handle this increase. FDA is also developing databases that will help decrease the amount of correspondence received by OGD. We believe these steps will ensure that the ANDA review process continues to be efficient.

(Comment 6) In the preamble to the proposed rule, FDA stated that an applicant ''will rarely, if ever, conduct a postmarketing BE study other than one required for an ANDA supplement'' (68 FR 61640 at 61643). One comment suggested that requiring applicants to submit failing BE studies will create an additional disincentive to perform postmarketing BE studies, which may discourage applicants from considering ways to improve their manufacturing processes.

(Response) FDA believes that the concern expressed in the comment is unfounded. The major disincentives to performing postmarketing BE studies are the financial costs and resource expenditures for the applicant. That is why such studies are rarely performed, except when required for an ANDA supplement. In any event, FDA believes that any potential disincentive created by requiring that such studies be submitted to the agency will be negligible. Moreover, FDA believes that industry will agree that because the drug will already be on the market, in the event that a postmarketing study fails to demonstrate bioequivalence, it would be particularly important for the agency and the applicant to examine the reason for the failure.

(Comment 7) One comment stated that if ANDA holders are going to be required to submit failed studies performed in accordance with the SUPAC guidances, new drug application (NDA) holders should also be required to submit such studies.

(Response) NDA applicants and NDA holders are already required to submit failed BE studies. Section 314.50(d)(3) of FDA regulations requires an NDA to contain a description of all bioavailability and pharmacokinetic studies in humans performed by or on behalf of the applicant. The requirement to submit bioavailability studies includes reports of any bioequivalence studies performed by or on behalf of the applicant.

B. Same Drug Product Formulation

(Comment 8) Several comments requested clarification of the term ''same drug product formulation.'' One comment stated that clarification of the language was important to ensure that it was not subject to varying interpretations by ANDA applicants.

(Response) The final rule adds in § 320.1(g) a definition of the term ''same drug product formulation'' to mean the formulation of the drug product submitted for approval and any 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. FDA's draft guidance on the submission of BE data, when available, will expand on this definition by providing specific examples of formulations that FDA considers to be the same drug product formulation. For example, FDA considers two drug products that use different ingredients intended to affect the color or flavor of the drug product, or use a different technical grade and/or specification of an excipient, to be the same drug product formulation. If an applicant has questions that are not answered by the draft guidance on submission of BE data, the applicant should contact OGD for assistance in applying the term ''same drug product formulation.''

(Comment 9) Two comments asked FDA to revise the concept ''same drug product formulation.'' One comment requested that the term be limited to ''studies which are statistically powered correctly and have a batch size of at least 100,000 packaged units.'' Another comment asked that the term be broadly interpreted to require the submission of all BE studies performed on the various formulations of a drug for which an ANDA is ultimately submitted. For example, the comment suggested that ANDA applicants should be required to submit BE studies performed on formulations that differ by SUPAC level 3 changes from the formulation submitted for approval. The comment suggested that failure to broadly interpret ''same drug product formulation'' will result in ANDA applicants making certain SUPAC level 3 changes (such as changing the manufacturing site) in an attempt to avoid submitting failed study results. In addition, the comment noted that the submission of all BE data on all formulations could serve the ancillary purposes of helping FDA to: (1) Refine the SUPAC levels and (2) establish chemistry, manufacturing, and controls specifications.

(Response) FDA disagrees with both of these comments. The term ''same drug product formulation'' is intended to balance competing concerns. To limit the definition to require only the submission of studies that are statistically powered correctly and have a particular batch size could undermine the goals of the rule. Such a limitation will result in FDA failing to receive results from pilot studies. As discussed in greater detail below, FDA appreciates that if a pilot study is underpowered, it cannot be expected to satisfy BE criteria. Nevertheless, such studies provide valuable information that is relevant to FDA's bioequivalence determination. Therefore, FDA declines to limit the scope of the term ''same drug product formulation'' as suggested in the comment.

FDA also declines to broadly interpret the definition to include all formulations tested during the drug's development program. Such an interpretation would: (1) Increase the burden on ANDA applicants, (2) likely result in the submission of data irrelevant to the agency's determination of bioequivalence, and (3) potentially slow the ANDA review process without enhancing FDA's ability to analyze whether the formulation submitted for approval is bioequivalent to the RLD. Moreover, FDA believes that the

comment's concern about ANDA applicants making SUPAC level 3 changes to a formulation to avoid submitting failing results is not relevant to the final rule. As discussed above, the final rule does not use the SUPAC guidances to interpret the term ''same drug product formulation.'' Moreover, if a formulation failed to demonstrate bioequivalence, it is unlikely that manufacturing the same or very similar formulation at a different site would result in a passing BE study for submission in an ANDA. (Note that the issue of a change in manufacturing site is also discussed in the response to comment 15.) In addition, FDA believes that the intended goals of the rule are best served by focusing the agency's review on data relevant to the formulation submitted for approval. Therefore, the agency believes that the disadvantages of employing such a broad interpretation of ''same drug product formulation'' outweigh the theoretical benefits. Overall, FDA believes that its definition of ''same drug product formulation'' strikes an appropriate balance.

(Comment 10) One comment suggested that FDA's definition of ''same drug product formulation'' resulted in an inconsistency between how FDA treats changes pre- and postapproval. Specifically, the comment suggested that because a BE study will not be required for a SUPAC level 1 or 2 change postapproval, FDA should not require that BE data be submitted preapproval for a formulation that differs only by a SUPAC level 1 or 2 change from the formulation submitted for approval.

(Response) This comment reflects the confusion created by our proposal to rely on SUPAC guidance concepts to determine when a drug has the same formulation for purposes of this rule. The SUPAC guidances provide recommendations for when FDA will require the conduct of a BE study to support a formulation or manufacturing change submitted in an amendment or supplement. In short, they provide guidance for when new data will be required to support a change to the drug product.

In contrast, this rule does not address when data are required to support a product application or product change. It does not require that a new study be conducted under any circumstances. The rule merely addresses situations where an applicant has conducted BE studies in addition to those it seeks to rely on in its ANDA or ANDA amendment or supplement. It also indicates when the results from those additional studies must be submitted to FDA, because they were conducted on a drug product formulation that is the same as, or similar to, that covered by the application. While SUPAC is focused on determining what product changes will trigger the need for new data to support the change, this rule focuses on when existing data must be submitted to FDA, because they are relevant to the drug product with the same formulation.

FDA had initially proposed to refer to the SUPAC guidances to determine when drug products with minor changes are considered to be the same formulation. Under SUPAC, level 1 or 2 changes to a drug product formulation do not require a manufacturer to conduct BE testing or submit BE data in order to market the drug product with those changes. Level 3 changes are fairly significant and require a manufacturer to conduct a BE test to demonstrate the equivalence between the new and old formulations before it may market the new formulation. However, under this rule, BE test data on a product that is three SUPAC levels different from the approved or marketed formulation would not need to be submitted if that formulation is not, and will not, be marketed. In the proposed rule, we suggested that BE data on products reflecting modest changes, described as SUPAC level 1 and 2 changes, are relevant to the marketed formulation and would need to be submitted. As a result, reference to the SUPAC concepts created confusion, because the instances where SUPAC recommends that manufacturers conduct and submit BE test data to support product changes were the exact situations where this rule would not require submission of existing BE data, because the data are of limited applicability to the formulation subject to the application. Accordingly, we are no longer referring to the SUPAC guidances in the final rule. Instead, we have included a definition of ''same drug product formulation'' in § 320.1(g) of the final rule, in order to provide assistance in determining when this rule requires submission of BE data on a similar formulation.

C. Bioequivalence Studies That Must Be Submitted

(Comment 11) Several comments requested clarification about the types of studies that will be required to be submitted under the rule. In particular, several comments questioned whether ''pilot studies'' or studies that were designed not to evaluate BE, but to generate BE data, will have to be submitted under the rule. Such studies could be performed to: (1) Obtain information related to the performance of prototype drug formulations, (2) estimate the appropriate number of subjects necessary for the definitive BE study, (3) determine the appropriate plasma concentration time curves, or (4) determine whether a drug entity can be reliably measured in the media chosen. Some comments suggested that such studies should not be required to be submitted because they may not be powered to pass BE statistical criteria and, as a result, are arguably not ''BE studies.''

(Response) The term ''all other bioequivalence studies'' is used in the rule without limitation. It is intended to capture all studies generating BE data, including pilot studies. Therefore, complete or summary reports of pilot studies conducted with formulations that are the ''same drug product formulation'' as that submitted in the ANDA must be submitted under the rule. FDA believes that the submission of pilot studies is important because they may provide valuable BE information. For example, they may provide FDA information about the assay used in the BE study relied on for approval. FDA appreciates the concern raised in the comments about pilot studies potentially being underpowered and not designed to evaluate bioequivalence. The agency will fully consider these issues when reviewing pilot studies. If a pilot study is not properly powered, FDA will not expect it to demonstrate bioequivalence.

(Comment 12) One comment asked if the rule will require submission of pilot pharmacokinetic studies in animals or in vitro studies.

(Response) The final rule does not require the submission of animal studies. In vitro studies must be submitted when in vitro testing is conducted to demonstrate bioequivalence (§ 320.24(b)(5)). Examples include in vitro testing for nasal sprays and resin binding testing for bile acid sequestrants. When an in vivo study is submitted to show bioequivalence of a formulation, all other in vivo and in vitro bioequivalence data, both passing and nonpassing, for that formulation must be submitted as well. Similarly, when an in vitro study is submitted to show bioequivalence of a formulation, all other in vivo and in vitro bioequivalence data, both passing and nonpassing, for that formulation must be submitted. The data from in vitro dissolution studies conducted for purposes other than to show bioequivalence need not be submitted under this rule, but may be required by other regulations (for example, § 314.94(a)(9)). In the proposed rule,

FDA cited § 320.24 as the regulatory requirement which ''sets forth the types of evidence acceptable to establish bioequivalence.'' According to § 320.24(a), bioavailability may be demonstrated by several in vivo and in vitro methods. Section 320.24 makes it clear that bioequivalence studies may consist of either in vivo or in vitro studies.

Since reviewing the comments to the proposed rule, FDA has become aware that the language of the proposed rule may cause confusion regarding the requirement that all in vitro bioequivalence studies must be submitted. In particular, the section heading of § 320.21, ''Requirements for submission of in vivo bioavailability and bioequivalence data,'' may lead to this misinterpretation. Thus, in this final rule, FDA is changing the section heading of § 320.21 so that it removes the specific reference to in vivo data.

(Comment 13) One comment asked if prior studies that are not directly relevant to the assessment of BE by the current criteria must be submitted. For example, if the current BE recommendation for a particular product specifies a pharmacokinetic study on the parent drug in plasma, will the following types of studies have to be submitted: A pharmacokinetic study on the metabolite only, a pharmacokinetic study in urine, a pharmacodynamic study, a clinical endpoint BE study or other clinical study, a sensitization or irritation study for transdermal patches, etc.?

(Response) Yes, all studies on the same drug product formulation as defined in this final rule must be submitted regardless of what FDA's current criteria for BE testing for the product are. Otherwise, the agency might not be aware of a study that is relevant to our determination of whether two products are bioequivalent. For example, if a firm conducted a pharmacodynamic study that failed to show BE, and then conducted a pharmacokinetic study that demonstrated BE, we would want to know about the pharmacodynamic study.

(Comment 14) One comment noted that the SUPAC guidance states that for narrow therapeutic index (NTI) drugs, biostudies are required for all formulation changes except level 1 changes. The comment asked whether this means that biostudies on any formulations differing by more than SUPAC level 1 for NTI drugs will not need to be submitted under the new rule.

(Response) As discussed in section III of this document, the final rule does not use the SUPAC guidances to explain what the regulation means by ''same drug product formulation.'' Instead, the final rule defines ''same drug product formulation'' as the formulation of the drug product submitted for approval and any 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. Under the final rule, all biostudies on the same drug product formulation must be submitted, regardless of the level of change under SUPAC.

(Comment 15) One comment asked if a change in manufacturing site alone (a SUPAC level 3 change) will make the products at the original and new sites not the same drug product formulation even if the formulations and manufacturing processes were otherwise identical.

(Response) No. Manufacturing site changes are not relevant to the definition of ''same drug product formulation.'' Studies conducted for products that are considered the ''same drug product formulation'' must be submitted whether the products are manufactured at the same or different manufacturing sites.

(Comment 16) One comment stated that in some cases, it may be impossible to determine whether a particular older formulation on which a biostudy had been conducted falls within the scope of a SUPAC level 2 change from the approved or submitted formulation. For example, the older formulation has only single point dissolution data, precluding an f2 comparison; or multiple dissolution conditions were used, some of which yield f2 factors greater than 50 and some less than 50. In such cases, how is an applicant to decide whether or not a biostudy on an older formulation needs to be submitted?

(Response) If a biostudy was conducted on a product that is the same drug product formulation as defined in the final rule, it must be submitted. Dissolution testing is not a criterion for submission.

(Comment 17) One comment stated that the language defining the ''final formulation'' may not capture all relevant bioequivalence data. For example, formulations containing an active ingredient with a particle size or morphic form that differs from the drug for which the ANDA is submitted would not be considered the ''final formulation'' of the drug. Thus, ANDA sponsors would not be required to submit bioequivalence data performed on these formulations, although such differences might affect the drug's pharmacokinetic profile, safety, and effectiveness.

(Response) FDA disagrees. The term ''same drug product formulation,'' as defined in § 320.1(g) of this rule, includes formulations that differ in particle size and morphic form; thus, studies on such formulations would need to be submitted to FDA.

Section 505(j)(2) of the act specifies that an ANDA must contain, among other things, information to show that the active ingredient in the generic drug product is the ''same as'' that of the RLD. Section 314.92(a)(1) of FDA regulations provides that the term ''same as'' means, among other things, ''identical in active ingredient(s).'' In the discussion of ''sameness'' of active ingredient(s) in the preamble to the final rule adopting the ANDA regulations, FDA specifically rejected a proposal that would have required an ANDA applicant to show that the active ingredient in its generic drug product and the active ingredient in the RLD ''exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process and that the stereochemistry characteristics and solid state forms of the drug have not been altered'' (57 FR 17950 at 17958, April 28, 1992). Differences in particle size and polymorphic forms of a drug substance are not differences in chemical structure, but only in internal solid-state structure.

(Comment 18) One comment questioned whether FDA's interpretation of § 314.81(b)(2)(vi) will require an applicant to submit studies performed by someone other than the applicant. For example, will the applicant be required to submit a study performed by a competitor (a ''challenge study'')? The comment noted that a complete or summary report may not be available to the applicant. Another comment asked if it will be necessary to conduct literature searches to find BE studies conducted by third parties.

(Response) Section 314.81(b)(2)(vi) requires the submission of data from ''biopharmaceutic, pharmacokinetic, and clinical pharmacology studies * * * conducted by or otherwise obtained by the applicant.'' This language clearly contemplates that if an applicant obtains the results of a study conducted by a third party, the results must be submitted in the annual report. It will not be necessary to conduct literature searches to find BE studies conducted by third parties. However, if an applicant obtains a complete or summary report, that report must be submitted. If the applicant obtains study

results in a form other than a complete or summary report, those results must be submitted in the annual report.

(Comment 19) One comment asked whether the rule requires applicants to contact previous owners of the ANDA to obtain BE studies.

(Response) Section 314.72 of FDA regulations concerns change in ownership of an application. Section 314.72(a)(2)(iii) requires the new owner of an application either to submit to FDA a statement that the new owner has a complete copy of the approved application, or to request a copy of the application from FDA. In addition, FDA believes it is incumbent upon the purchaser of an ANDA to request from the owner all biostudies conducted on the drug product, even if they were not submitted to the ANDA.

D. Summary and Complete Reports

(Comment 20) One comment stated that FDA should clarify the appropriate content of complete and summary reports to ensure that FDA receives the information necessary to fully evaluate bioequivalence.

(Response) FDA believes that applicants are aware of the appropriate content of a complete BE study report, as they are currently required to submit such a report for the study relied on for ANDA approval. The draft guidance on the submission of BE data, when available, will discuss the content of summary reports in greater detail.

(Comment 21) One comment suggested that the submission of complete or summary reports of all other BE studies is unnecessary. Instead, the comment suggested, the product development report submitted as part of the ANDA may be the most appropriate place to put a small summary of the results of all bioequivalence studies performed on the product prior to ANDA submission.

(Response) FDA disagrees with this comment. While FDA agrees that the product development report provides helpful information for the ANDA review process, a small summary of all bioequivalence studies in the product development report will be insufficient to satisfy the objectives of the rule. The agency is requesting complete or summary reports of the studies in order to be able to evaluate the study design and the resulting data. A small summary in the product development report will likely provide insufficient information for the agency to adequately evaluate why certain studies failed and others passed.

(Comment 22) One comment stated that in many cases, an applicant may request only a summary report from a contract research organization (CRO) when a test product has failed to meet standard BE criteria. Therefore, if after the applicant submits the summary report, FDA requests a complete report, the applicant will need additional time and will incur additional costs for the CRO to generate a complete report.

(Response) FDA appreciates that industry's current practice may be to request only summary reports from CROs for failing studies. As noted in the preamble to the proposed rule, FDA foresees that in the majority of cases, a summary report will be sufficient to satisfy the rule. For example, in the case of a pilot study that was not powered to demonstrate bioequivalence, the agency does not foresee the need for a complete report. However, in light of the new submission requirements, the agency encourages applicants to consider whether there is a clear reason, such as failure to properly power the study, for a study's failure to demonstrate bioequivalence. In cases where the reason the study failed is unclear, the applicant may want to consider requesting a complete report rather than a summary report from the CRO to assist the applicant in evaluating the study.

E. FDA Criteria for Evaluating Studies

In the preamble to the proposed rule, FDA listed the following four factors as examples of criteria it will use to evaluate BE studies when at least one study failed to demonstrate bioequivalence: (1) The statistical power of the studies, (2) minor differences in the formulation used in each study, (3) whether the product was administered consistently with the RLD's labeling in every study, and/or (4) various other study design issues (68 FR 61640 at 61641).

(Comment 23) While recognizing that it is impossible for FDA to prospectively identify all potential issues, two comments requested clarification about the criteria FDA plans to use to: (1) Determine when to require the submission of a complete report of a study when a summary report has been previously submitted and (2) evaluate bioequivalence when at least one of the studies submitted by the applicant failed to demonstrate bioequivalence. In particular, the comments requested clarification about: (1) What additional data will be required to demonstrate to FDA that a drug is bioequivalent to the RLD, (2) whether FDA will be primarily concerned with the conditions under which the drug was administered or the rationale for the selection of certain types of study design characteristics, and (3) whether decisions about bioequivalence will be at the sole discretion of the reviewer. Another comment asked how conflicting results from two or more BE studies will be assessed. In particular, the comment asked if FDA will perform a meta-analysis on pooled studies. One comment expressed concern that if criteria were not provided, it could increase the costs associated with compliance with the rule.

(Response) Generally, the criteria FDA reviewers will use to evaluate BE studies submitted in response to the rule are the same as the criteria they currently use to evaluate BE studies relied on for ANDA approval. Those criteria have been discussed in detail in various FDA guidances (available on the Internet at *http://www.fda.gov/cder/guidance/index.htm* under Biopharmaceutics). When an applicant is submitting both passing and nonpassing studies, it should include its own analyses of the data and any potential explanations for nonpassing results. The decision tree used by the applicant will likely be similar to that used by FDA. While it is impossible to prospectively state which issues will be most relevant in any particular case, examples of likely questions that should be included in that decision tree are:

- Was the study correctly powered?
- Was the assay appropriate?
- Was the formulation inappropriate, and if so, how has the formulation been changed?
- Was the drug properly administered in the failing study?
- Were there technical flaws in the way the study was conducted?

The applicant's explanations for failing results will likely be a reviewer's first step in evaluating whether to request the submission of a complete report of any particular study. FDA anticipates that, in most cases, a summary report will be sufficient. The applicant's explanations will also likely be a reviewer's first step in evaluating how to weigh conflicting BE data. However, the reviewer will also undertake an independent scientific analysis of the study reports submitted. FDA will not rely on a meta-analysis of pooled studies.

As the comments recognize, it is difficult to predict what type of information FDA may request to assure the agency that the drug is bioequivalent to the RLD. For example, FDA may choose to inspect the site where a submitted study was conducted, or FDA may request additional data. As discussed in the proposed rule, the responsibility to demonstrate that the ANDA product is bioequivalent to the RLD rests with the applicant. Therefore, it will ultimately be the applicant's

responsibility to demonstrate why the nonpassing study or studies should not affect a determination that the ANDA product is bioequivalent to the RLD.

(Comment 24) One comment stated that the four examples provided by FDA in the preamble to the proposed rule regarding the criteria for evaluating BE studies submitted (i.e., statistical power, minor differences in formulations, product administration, and other study design issues) are so critical that FDA should require the submission of all BE studies conducted on all formulations of the drug, rather than only requiring the submission of studies conducted on the ''same drug product formulation.'' As an example, the comment stated that requiring the submission of all studies conducted on all formulations will allow FDA to identify situations where an applicant used increasingly larger sample sizes in their bioequivalence studies. Similarly, the comment notes that, by listing ''minor differences in formulation'' as an evaluation factor, FDA has acknowledged that formulation changes are relevant to analyzing bioequivalence. The comment states that this underscores the need to require the submission of passing and nonpassing studies on all formulations.

(Response) As discussed in greater detail in response to comment 5, the decision to require the submission of BE studies conducted on the ''same drug product formulation'' as that submitted for approval was based on a need to balance competing concerns. Requiring the submission of all studies conducted on all formulations, regardless of their relationship to the formulation submitted for approval, will unnecessarily burden applicants and the review process without a resulting benefit. Therefore, FDA declines to adopt this suggestion.

(Comment 25) Several comments requested information about the dispute resolution procedure that will be used if both passing and nonpassing studies are submitted. In particular, the comments highlighted the need for prompt resolution when the applicant and the agency disagree about how study results should be interpreted. The comments suggested that the dispute resolution procedure should be efficient to ensure a timely review process. One comment questioned whether a new administrative procedure is going to be developed for the resolution of potential disputes.

(Response) FDA does not believe that a new procedure will be necessary to resolve any potential disputes arising from the submission of additional BE studies. If FDA has questions about an applicant's explanation as to why a particular study failed or needs additional information to continue its review of the application, FDA will communicate with the applicant in the same manner as it does to resolve any other ANDA issue. FDA also notes there are dispute resolution procedures available to resolve differences between applicants and FDA. See 21 CFR 10.75 and 21 CFR 314.103, as well as Center for Drug Evaluation and Research/Center for Biologic Evaluation and Research guidance for industry entitled ''Formal Dispute Resolution: Appeals Above the Division Level.''

F. Enforcement

(Comment 26) One comment questioned how FDA intends to enforce and monitor compliance with the rule. In particular, the comment suggested that FDA should not rely on its preapproval inspection authority to monitor compliance with the rule. The comment expressed concern that investigators may not have the opportunity to look for failed studies during preapproval inspections or, at a minimum, may not be focused on looking for them. The comment also points out that Compliance Program Guidance Manual 7346.832 states that preapproval inspections are not mandated for narrow therapeutic range index drugs or the top 200 prescribed drugs. The comment suggested that rather than relying on investigators to examine studies, OGD scientists are the most appropriate personnel for determining whether study results affect FDA's bioequivalence determination.

(Response) As discussed in the response to comment 7, § 314.50(d)(3) of FDA regulations already requires NDA applicants to submit a description of all bioavailability and pharmacokinetic studies in humans performed by or on behalf of the applicant. That regulation does not contain a specific enforcement provision, and FDA believes it is not necessary to provide a specific enforcement mechanism for this final rule, which imposes similar duties on ANDA applicants. Moreover, in certain circumstances, noncompliance with this final rule could be considered a violation of 18 U.S.C. 1001, which prohibits knowingly and willfully falsifying or concealing a material fact from a branch of the Federal government.

FDA agrees that it is not appropriate to rely solely on preapproval inspections of manufacturing facilities to look for BE studies. However, the agency has a variety of different enforcement and oversight mechanisms that we use to ensure compliance with data submission requirements.

FDA agrees with the comment's suggestion that OGD's scientists are the most appropriate personnel to determine how BE study results should affect a bioequivalence determination. Any studies identified by FDA will be forwarded to OGD scientists for consideration.

FDA's initiative ''Pharmaceutical cGMPs for the 21st Century'' promotes a science and risk-based approach to product quality regulation. Compliance Program Guidance Manual 7346.832 was revised to reflect the approach described in the 21st Century initiative.

(Comment 27) In the preamble to the proposed rule, FDA stated that it may inspect sites where BE studies were conducted to determine whether there were technical flaws in the way they were performed (68 FR 61640 at 61641). Two comments questioned whether such inspections, particularly of sites in foreign countries, will slow down the ANDA review process. One comment focused on pilot studies performed by CROs in foreign countries and questioned whether the inspection of such sites could lead to approval delays.

(Response) FDA appreciates the concern expressed in the comments. FDA's inspection resources are limited, and the agency does not anticipate routinely inspecting every site for every BE study submitted. The agency may, however, inspect any study sites it determines appropriate in order to assess whether a generic drug is bioequivalent to its RLD.

(Comment 28) One comment stated that FDA should not rely on field investigators to discover the existence of BE studies.

(Response) FDA expects that most, if not all, applicants will comply with this final rule and submit the appropriate BE studies of which they are aware. The agency will not comment on its methods of investigation with respect to enforcement of the final rule. However, the agency agrees that field investigators should not be the only source for discovering the existence of BE studies.

G. Miscellaneous

(Comment 29) One comment asked what event determines the date the study was conducted for purposes of deciding whether a biostudy needs to be submitted.

(Response) The event that should be considered to determine whether a BE study must be submitted under this regulation is the date the first dose in the study was administered. This date should be readily identifiable by the applicant and FDA.

(Comment 30) Two comments questioned whether it was necessary for

applicants to retain samples for studies other than the BE study relied on for approval.

(Response) It is not necessary to retain such samples. Applicants are only required to retain samples for the BE study relied on for approval.

(Comment 31) Two comments asked whether FDA will apply the Freedom of Information Act (FOIA) to failed BE studies submitted to FDA under the rule. The comments expressed concern that if such studies are made available to the public, confidence in generic drugs could be undermined, and companies may use this information to disparage other companies and their products.

(Response) Information submitted on passing and nonpassing bioequivalence studies will be available for public release after approval of the application or supplemental application, consistent with FDA's disclosure regulations in 21 CFR part 20 and § 314.430, and with the FOIA. While FDA appreciates the concern expressed in the comment, the agency notes that in addition to the study results, the applicant's explanations concerning failed studies and the agency's determination and the basis for its determination of bioequivalence will also be publicly available. We believe the availability of this information should assuage the comments' concerns.

H. Economics

(Comment 32) Two comments suggested that FDA's estimate that the rule will result in a 10 percent increase in the number of BE studies submitted to the agency was too conservative. One comment stated that, based on its informal survey of generic drug companies, the number will be larger. The other comment noted that, because the number of ANDA applications and correspondence documents has risen in recent years, the 10-percent estimate is not reflective of recent trends.

(Response) FDA recognizes that the number of ANDAs and related submissions has increased in recent years. However we are not able to accurately predict the number or pattern of future submissions. Due to this uncertainty, the agency assumed, for the reasons discussed in the preamble to the proposed rule, that the number of BE studies submitted annually will increase by approximately 10 percent. 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. The comments appear to acknowledge the uncertainty of trying to predict the exact increase in the number of studies submitted, because neither comment suggests an alternative number to FDA's estimate of 10 percent. Therefore, FDA continues to estimate that the increase in the number of studies submitted will be approximately 10 percent. The economic analysis in the proposed rule, however, relied on year 2000 data for the number of submissions received by the agency. To ensure that the economic analysis reflects current trends, FDA has revised the economic analysis (section VIII of this document) to reflect the most current data available on the number of submissions received by the agency.

(Comment 33) One comment suggested that the compliance requirements and cost analysis in the preamble to the proposed rule were flawed because they failed to consider costs in addition to staff time. The comment noted that companies often employ CROs to conduct activities related to the design, initiation, conduct, and report generation of BE studies. The comment suggested that companies may routinely request complete reports from CROs, as opposed to summary reports, in the event FDA requests a complete report. The comment also questioned FDA's estimate that summary reports will be required approximately 80 percent of the time and complete reports will be required approximately 20 percent of the time.

(Response) FDA acknowledges that it is impossible to predict precisely how often a complete report will be requested in the future. However, the agency's estimate that a complete report will be required only 20 percent of the time was based on its belief that, in most cases, the reason a study failed will be evident from the information provided in the summary report and the applicant's explanations. FDA does not believe that the use of a CRO to conduct a study affects its economic analysis. When a company contracts with a CRO, it may stipulate the reporting format for the study. FDA does not believe that stipulating a report format for BE studies in accordance with this rule will create a significant burden for any affected entity.

(Comment 34) One comment noted that FDA cited its desire to increase the agency's knowledge and understanding of bioequivalence as an objective of the rule. The comment questioned whether the costs associated with the submission of ''all other bioequivalence studies,'' and the resolution of why various studies failed, were justified by this objective.

(Response) As discussed in greater detail in section VIII of this document, FDA believes the costs of the rule are justified by the multiple objectives we hope to achieve through this final rule. The objective cited by the comment is a secondary objective of the rule. In addition to increasing FDA's knowledge, the submission of all BE studies is necessary because the data contained in passing and nonpassing BE studies provide information that can be important to FDA's assessment of the bioequivalence for a specific product.

V. Legal Authority

Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act. 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 (a)(6)(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. 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 drug product formulation as that 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. It may not include nonpassing results and/or the 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. Effective Date

Revised §§ 314.94(a)(7)(i), 314.96(a)(1), 320.1(g), 320.21 (section heading), 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 III of this document), apply to ANDAs, amendments, or supplements submitted on or after the effective date. Thus, with respect to ANDAs, amendments, or supplements submitted prior to the effective date, applicants are not required to report additional BE studies that were conducted in conjunction with their applications. However, when 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, the applicant is required under §§ 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, all applicants with approved ANDAs, including ANDAs that were approved or submitted for approval prior to the effective date, are required to comply with § 314.81(b)(2)(vi), as interpreted by FDA in section III of this document. As stated in response to comment 6, in the event that a postmarketing study of an approved and marketed drug fails to demonstrate bioequivalence, it would be particularly important for the agency and the applicant to examine the reason for the failure. Therefore, any annual report submitted on or after the effective date by an applicant with an approved ANDA must include reports of all BE studies on the approved drug product, both passing and nonpassing, conducted or obtained by the applicant during the annual reporting period, including those studies conducted before the effective date but within the applicant's annual reporting period.

VII. 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.

VIII. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (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 agency believes that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Based on our economic analysis and review of comments submitted in response to the proposed rule, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $130 million, using the most current (2007) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

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. 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, this final rule requires ANDA applicants to submit the results of all BE studies, passing and nonpassing, on the same drug product formulation submitted for approval under an ANDA, amendment or supplement.

As discussed in response to comment 6, the agency also believes that it is important to clarify that the responsibility to submit the results of all BE studies, passing and nonpassing, continues after approval under the annual report submission requirements. However, the agency believes that it will be highly unusual for an ANDA applicant to conduct a postmarketing BE study. In particular, the agency believes that an applicant will rarely, if ever, conduct a postmarketing BE study other than one required for an ANDA supplement.

B. Affected Entities

This final rule will 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 2006, there were 511 BE studies submitted by 177 applicants in 622 original ANDAs, amendments, and supplements. FDA estimates that this final rule will result in a 10-percent increase in the total number of BE studies submitted annually, or 51 (511 x 0.10) additional studies. As stated in the proposed rule, 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. Because we did not receive any comments suggesting specific alternative figures that would be more appropriate, we continue to rely on these assumptions for the economic analysis of this final rule.

C. Compliance Requirements and Costs

The main cost of complying with this final rule will be staff time. The analysis in the proposed rule assumed a weighted average wage rate of $40 per hour. The current, comparable figure for 2006 assumed in this analysis is $47 per hour (Ref. 1). FDA estimates it will 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 will be required

approximately 20 percent of the time, while a summary will 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 $3,384 ([120 x $47 x 0.2] + [60 x $47 x 0.8]). Thus, the overall impact on the industry of reporting an additional 51 BE studies per year will be about $173,000 ($3,384 x 51 = $172,584). Assuming it equally likely that each of the 51 additional BE studies will be conducted by any of the 177 applicants, a binomial distribution can be used to predict how many firms will submit additional studies. Based on this distribution, 38 firms will incur costs of $3,384 for 1 additional BE study, 6 firms will incur costs of $6,768 (2 x $3,384) for 2 additional studies, and 1 firm will incur costs of $10,152 (3 x $3,384) for 3 additional studies (the total number of studies in the calculation does not equal 51 because of rounding). Thus, the maximum expected annual cost burden associated with this final rule for any one firm is $10,152. Approximately 75 percent (132 of 177, or 74.6 percent) of all firms are expected to incur no additional annual costs under the final rule.

D. Impact on Small Entities

FDA recognizes that some of the establishments required to submit additional BE study reports under this final rule will be small entities with limited resources. In the proposed rule, the agency acknowledged the uncertainty of its estimates with respect to the number of additional BE studies that will be submitted, their distribution among large and small entities, and the number of small entities affected. We also requested detailed comments on these important issues. After revising our Initial Regulatory Flexibility Analysis in response to the public comments received, FDA has determined that this final rule will not have a significant economic impact on a substantial number of small entities.

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 will 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, a small pharmaceutical preparation manufacturer (North American Industry Classification System (NAICS) Code 325412) employs fewer than 750 employees (Ref. 2). An FDA review of ANDA records 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 applicants (64 of 164) were small entities. (Resource limitations prevented the agency from being able to perform a similar, labor intensive manual search of similar records for a more recent time period.) Thus, the majority of ANDAs are not submitted by small entities. Assuming these proportions continue to hold, there will be about 69 small entities (0.39 x 177) submitting ANDAs annually. FDA also assumes that this group of small entities will submit 16 of the additional 51 BE studies (0.10 x 0.32 x 511) per year.

Assuming it is equally likely that each of the 16 additional BE studies will be reported by any of the 69 small entities, a binomial distribution can be used to predict how many of these firms will submit additional studies. Based on this distribution, 13 small entities will incur costs of $3,384 for one additional BE study, and two firms will incur costs of $6,768 (2 x $3,384) for two additional BE studies. Thus, the maximum expected burden of this final rule for any one small entity is $6,768. Nearly 80 percent (55 of 69, or 79.5 percent) of all small entities are expected to incur no additional annual costs under the final rule.

In the proposed rule, FDA relied on information indicating that the cost of preparing and submitting an ANDA was between $300,000 and $1 million (68 FR 61640 at 61645). Because we were unable to identify any similar, more recent cost estimates, we have adjusted these earlier figures for inflation to estimate the economic impact of this final rule. Our inflation adjustment was made based on percent changes in the Biomedical Research and Development Price Index (BRDPI) (Ref. 3). Based on these inflation adjustments, FDA estimates that the cost to prepare and submit an ANDA is now between $361,500 and $1.24 million. The details of our inflation adjustment calculations are summarized in table 1 of this document.

TABLE 1.—DETAILS OF INFLATION ADJUSTMENT

ANDA Cost Estimate	Base Year	Percent Change in the BRDPI from Base Year	Inflation Adjusted ANDA Cost Estimate
$300,000	2001	20.5%	$361,500
$1 million	2000	24.4%	$1.24 million

Based on this information, the maximum expected cost burden of this final rule on any one firm will be between 0.8 percent ($10,152 for three additional BE studies / $1.24 million) and 2.8 percent ($10,152 / $361,500) of the total cost of preparing and submitting an ANDA. The maximum expected cost burden for any one small entity will be between 0.6 percent ($6,768 for two additional BE studies / $1.24 million) and 1.9 percent ($6,768 / $361,500) 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 (as described in the proposed rule, 68 FR 61640 at 61645). Because FDA was unable to identify a similar, more recent survey available in the public domain, we have relied on this information to estimate the impact of the final rule on small entities. The 15 small entities identified in the survey had an average of 331 employees and average annual revenues of $115 million. The maximum expected burden of this final rule for any one of these small entities is therefore expected to be only 0.006 percent ($6,768 / $115 million) of average annual 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 will suffice 80 percent of the

time, provided that complete results are available to FDA upon request. The agency believes that a summary report will 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 final 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 will incur no additional reporting costs, although some firms might experience significant costs if their product was 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 final rule requires reporting of all BE studies, but also permits summary reports for BE studies other than those the applicant relies on for approval, except where full reports are specifically requested by the agency. The agency believes that the final rule therefore addresses the perceived regulatory need in the least intrusive and most cost effective way.

E. Benefits of the Final Rule

The final rule will generate economic benefits both for individuals and for society as a whole, to the extent that the reporting of data from all BE studies on the same drug product formulation as that submitted for approval prevents product discontinuation and adverse health effects. Also, the data from additional BE studies may 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 final rule will permit FDA to make more informed BE determinations in the future.

IX. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are shown 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.

Title: Requirements for Submission of Bioequivalence Data; Final Rule

Description: FDA is amending the requirements for certain ANDAs, ANDA amendments, and ANDA supplements submitted under §§ 314.94, 314.96, and 314.97. Specifically, FDA is amending §§ 314.94(a)(7)(i), 314.96(a)(1), and 320.21(b)(1), as well as modifying 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 drug product formulation as that submitted for approval under an ANDA, amendment, or supplement.

In addition, FDA is announcing its intention 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 clarifying 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, FDA believes an applicant will 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 2 of this document provides an estimate of the annual reporting burden under the rule.

The rule will 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 2006, 177 applicants submitted 511 BE studies in 622 original ANDAs, amendments, and supplements. FDA estimates that this rule will result in a 10-percent increase in the number of BE studies submitted annually, or 51 (511 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 will 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 will be required approximately 20 percent of the time, while a summary will 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 2 of this document, FDA has estimated the reporting burden associated with each section of the rule. FDA believes that the vast majority of additional BE studies will be reported in ANDAs (submitted under § 314.94) rather than supplements (submitted under § 314.97), because it is unlikely that an ANDA holder 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 will 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 will be conducted on a drug prior to the submission of the ANDA and will be reported in the ANDA itself.

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.94(a)(7)	49	1	49	72	3,528
314.96(a)(1)	1	1	1	72	72
314.97	1	1	1	72	72
Total					3,672

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

The information provisions of this final rule have been submitted to the Office of Management and Budget (OMB) for review, as required by section 3507(d) of the Paperwork Reduction Act of 1995. The requirements were approved and assigned OMB control number 0910–0630. This approval expires November 30, 2011. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

X. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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 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.

XI. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. U.S. Department of Labor, Bureau of Labor Statistics, Table 11. Employer costs per hour worked for employee compensation and costs as a percent of total compensation: Private industry workers, by occupational group and full-time and part-time status, December 2006, Management, professional, and related series.

2. U.S. Small Business Administration, Office of Size Standards, Table of Size Standards, available online at *http://www.sba.gov/idc/groups/public/documents/sba_homepage/serv_sstd_tablepdf.pdf*.

3. National Institutes of Health, Office of Science Policy Analysis, Biomedical Research and Development Price Index (BRDPI), available online at *http://officeofbudget.od.nih.gov/PDF/BRDPI_2_5_07.pdf* (viewed April 20, 2007).

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, 21 CFR parts 314 and 320 are 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, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 2. Amend § 314.94 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 as defined in § 320.1(g) of this chapter, 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. Amend § 314.96 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 as defined in § 320.1(g) of this chapter, 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. Amend § 320.1 by adding paragraph (g) to read as follows:

§ 320.1 Definitions.

* * * * *

(g) *Same drug product formulation* means the formulation of the drug product submitted for approval and any 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.

■ 6. Amend § 320.21 by revising the section heading and paragraph (b)(1) to read as follows:

§ 320.21 Requirements for submission of 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) of this chapter). 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: January 13, 2009.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E9–884 Filed 1–15–09; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF LABOR

Wage and Hour Division

29 CFR Parts 3 and 5

Protecting the Privacy of Workers: Labor Standards Provisions Applicable to Contracts Covering Federally Financed and Assisted Construction, Effectiveness of Information Collection Requirements

AGENCY: Department of Labor, Employment Standards Administration, Wage and Hour Division.

ACTION: OMB approval of information collection requirements.

SUMMARY: The Office of Management and Budget (OMB) has approved under the Paperwork Reduction Act (PRA) information collection requirements contained in recently revised final regulations published by the Department of Labor in the **Federal Register** on December 19, 2008. The PRA requires this notice to set forth the effectiveness of information collection requirements contained in a final rule.

DATES: The amendments to §§ 3.3(b) and 5.5(a)(3)(ii)(A) and (B)(1) published in the **Federal Register** on December 19, 2008 (73 FR 77504) have been approved by OMB and are effective January 18, 2009.

ADDRESSES: Written comments regarding the burden-hour estimates or other aspects of the information collection requirements contained in 29 CFR parts 3 and 5 may be submitted to: Administrator, Wage and Hour Division, Room S3502, 200 Constitution Avenue, NW., Washington DC 20210.

FOR FURTHER INFORMATION CONTACT: Richard M. Brennan, Director, Division of Interpretations and Regulatory Analysis, Wage and Hour Division, Employment Standards Administration, U.S. Department of Labor, Room S–3506, 200 Constitution Avenue, NW., Washington, DC 20210; telephone: (202) 693–0051.

Questions of interpretation and/or enforcement of regulations referenced in this notice may be directed to the nearest Wage and Hour Division (WHD) District Office. Locate the nearest office by calling the WHD toll-free help line at (866) 4US–WAGE ((866) 487–9243) between 8 a.m. and 5 p.m. in your local time zone, or log onto the WHD's Web site for a nationwide listing of WHD District and Area Offices at: *http://www.dol.gov/esa/whd/america2.htm*.

This notice is available through the printed **Federal Register** and electronically via the *http://www.gpoaccess.gov/fr/index.html* Web site.

Copies of this notice may be obtained in alternative formats (Large Print, Braille, Audio Tape or Disc), upon request, by calling (202) 693–0023. TTY/TDD callers may dial toll-free (877) 889–5627 to obtain information or request materials in alternative formats.

SUPPLEMENTARY INFORMATION: On December 30, 2008, the Office of Management and Budget (OMB) approved under the PRA the Department of Labor's information collection request for requirements in 29 CFR 5.5(a)(3)(ii)(A), and 5.5(a)(3)(ii)(B)(1), as published in the **Federal Register** on December 19, 2008. See 73 FR 77504. The current expiration date for OMB authorization for this information collection is December 31, 2011. The regulations implement Davis-Bacon and Related Acts and the Copeland Anti-Kickback Act requirements, and the regulatory changes reduce respondent burden and improve privacy protections for laborers and mechanics employed on federally financed or assisted construction contracts by lessening the transmission of personal information regarding individuals who work on contracts subject to Davis-Bacon Act labor standards. The preamble to the new regulations stated a general effective date of January 18, 2009; however, the OMB had not yet provided a PRA-required approval for the revised information collection requirements contained in 29 CFR 3.3, 5.5(a)(3)(ii)(A), and 5.5(a)(3)(ii)(B)(1) at the time of their publication. 44 U.S.C. 3507(a)(2). An agency may not conduct an information collection unless it has a currently valid OMB approval; therefore, in accordance with the PRA, the effective date of the information collection requirements in the revised regulations was delayed until the OMB approved them under the PRA. 44 U.S.C. 3506(c)(1)(B)(iii)(V). On December 30, 2008, the OMB approved the Department's information collection request under Control Number 1215–0149; thus, giving effect to the requirements, as announced and published in the **Federal Register** on December 18, 2008, under the PRA. The current expiration date for OMB authorization for this information collection is December 31, 2011.

Dated: January 9, 2009.

Victoria A. Lipnic,

Assistant Secretary, Employment Standards Administration.

Alexander J. Passantino,

Acting Administrator, Wage and Hour Division.

[FR Doc. E9–675 Filed 1–15–09; 8:45 am]

BILLING CODE 4510–27–P

DEPARTMENT OF LABOR

Wage and Hour Division

29 CFR Part 825

The Family and Medical Leave Act of 1993, Effectiveness of Information Collection Requirements

AGENCY: Department of Labor, Employment Standards Administration, Wage and Hour Division.

ACTION: OMB approval of information collection requirements.

SUMMARY: On December 14, 2008, the Office of Management and Budget (OMB) approved under the Paperwork Reduction Act (PRA) the Department of Labor's information collection request for requirements regarding Family and Medical Leave Act regulations, as published in the **Federal Register** on November 17, 2008. The PRA requires this notice to set forth the effectiveness