Supporting Statement

Requirements for Submission of In Vivo Bioequivalence Data; Final Rule

A. Justification

1. Circumstances of Information Collection

The final rule amends Food and Drug Administration (FDA) regulations (21 CFR parts 314 and 320) on the submission of bioequivalence data to require an abbreviated new drug application (ANDA) applicant to submit data from all bioequivalence studies (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.

Section 505(j)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(j)(2)(A)(iv)) requires that ANDA applicants submit, among other things, information showing that the applicant's drug is bioequivalent to a drug that has previously been approved by FDA and designated as an RLD. The statutory requirement is reflected in FDA's regulations 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.

Specifically, FDA is revising §§ 314.94(a)(7)(i), 314.96(a)(1), 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 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.

2. Purpose and Use of Information

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 case, BE will not be demonstrated because of 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 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 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.

3. Use of Improved Information Technology

FDA has issued the following guidance documents, among others, to explain the process for submitting information in marketing applications to the agency in electronic format:

--"Providing Regulatory Submissions in Electronic Format – NDAs." This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs. Among other things, the guidance provides recommendations on how to submit "labeling text" in electronic format. "Labeling text" is the term used in the guidance to mean labeling required under 21 CFR 201.100(d)(3), including all text, tables, and figures required by or included under those sections. The guidance recommends that labeling text be submitted as a PDF file.

--"Providing Regulatory Submissions in Electronic Format--General Considerations." This guidance includes a description of the types of electronic file formats that we are able to accept to process, review, and archive electronic regulatory submissions. The guidance also states that documents submitted in electronic format should, among other things, enable you to: (1) Easily view a clear and legible copy of the information; (2) print each document page by page, as it would have been provided in paper, while maintaining fonts, special orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents. To achieve these and other goals, the guidance recommends that all electronic regulatory submissions be submitted as PDF files.

--“Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format.” This guidance provides information to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA).

--"Providing Regulatory Submissions in Electronic Format-—Prescription Drug Advertising and Promotional Labeling." This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.

--"Providing Regulatory Submissions in Electronic Format—ANDAs." This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.

--"Providing Regulatory Submissions in Electronic Format-—Annual reports for NDAs and ANDAs." This draft guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.

--"Providing Regulatory Submissions in Electronic Format-—Postmarketing Periodic Adverse Drug Experience Reports." This guidance discusses general issues related to the electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

--"Providing Regulatory Submissions in Electronic Format-—Human Pharmaceutical Product Applications and Related Submissions." This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional labeling.

--"Providing Regulatory Submissions in Electronic Format-—General Considerations." This draft guidance discusses general issues common to all types of electronic regulatory submissions.

--"Providing Regulatory Submissions in Electronic Format-—Content of Labeling." This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

These documents and other related guidance documents are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

4. Efforts to Identify Duplication

The reporting as a result of this information collection is not currently required by FDA and would not duplicate any other information collection.

5. Involvement of Small Entities

Respondents include applicants wishing to market human drug products. This includes large as well as small businesses and manufacturers. Section VIII of the final rule contains an analysis of the impact of the rule on small entities.

6. Consequences If Information Collected Less Frequently

As discussed in sections 1 and 2 above, it is important that FDA be aware of additional BE studies and have the information necessary to evaluate their significance.

7. Consistencies with Guidelines in 5 CFR 1320.5(d)(2)

There is no inconsistency.

8. Consultations Outside the Agency

FDA received a number of comments on the October 29, 2003, proposed rule. For example, several comments indicated that using the SUPAC guidances as a way of explaining what BE studies must be submitted to the agency did not provide sufficient clarity. One comment 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, 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, in order 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 the 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 eliminates the need to refer to the SUPAC guidances. In addition, FDA is publishing a draft guidance "Submission of Summary Bioequivalence Data for ANDAs" intended to help affected entities better understand which BE studies should be submitted and the format FDA recommends for submission.

9. Remuneration of Respondents

There is no payment to respondents.

10. Assurance of Confidentiality

Confidentiality of the information that would be submitted under the final rule is protected under 21 CFR 312.130 and 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act.

11. Questions of a Sensitive Nature

This reporting does not involve any sensitive questions.

12. Estimates of Annualized Hour Burden

The table below 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]).

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 1--Estimated Annual Reporting Burden[1]

21 CFR Section	Number 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.

13. Estimates of Annualized Cost Burden to Respondents

As explained in Section VIII "Analysis of Economic Impacts," the main cost of complying with the final rule is staff time. The weighted average wage rate is $40 per hour. 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 the 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.

14. Estimates of annualized cost burden to the Government

Generally, unless the content of the failed studies raised questions related to approvability, there would be no significant additional amount of time needed by CDER reviewers to review an ANDA because of the additional BE study data that will now be submitted.

15. Changes in Burden

This is a new collection.

16. Time Schedule, Publication, and Analysis Plans

There are no scheduling, publication, and analysis plans.

PAPERWORK REDUCTION ACT SUBMISSION

1. Agency/Subagency originating request FDA	2. OMB control number b. [ ] None a. 0910 -
3. Type of information collection (*check one*) a. [x] New Collection b. [ ] Revision of a currently approved collection c. [ ] Extension of a currently approved collection d. [ ] Reinstatement, without change, of a previously approved collection for which approval has expired e. [ ] Reinstatement, with change, of a previously approved collection for which approval has expired f. [ ] Existing collection in use without an OMB control number For b-f, note Item A2 of Supporting Statement instructions	4. Type of review requested (*check one*) a. [x] Regular submission b. [ ] Emergency - Approval requested by at close of comment period c. [ ] Delegated 5. Small entities Will this information collection have a significant economic impact on a substantial number of small entities? [ ] Yes [x] No 6. Requested expiration date a. [X] Three years from approval date b. [ ] Other Specify:____/____
7. Title Requirements for Submission of In Vivo Bioequivalence Data; Proposed Rule	
8. Agency form number(s) (*if applicable*)	
9. Keywords drugs	
10. Abstract Amend the regulations on submission of bioequivalence data to require an abbreviated new drug application (ANDA) applicant to submit data from all bioequivalence studies (BE studies) that the applicant conducts on a drug product formulation submitted for approval.	
11. Affected public (*Mark primary with "P" and all others that apply with "x")* a. ___ Individuals or households d. ___ Farms b. _x_ Business or other for-profit e. ___ Federal Government c. ___ Not-for-profit institutions f. ___ State, Local or Tribal Government	12. Obligation to respond (*check one*) a. [ ] Voluntary- (guidance document) b. [x] Required to obtain or retain benefits c. [Mandatory
13. Annual recordkeeping and reporting burden a. Number of respondents _____ b. Total annual responses _____	14. Annual reporting and recordkeeping cost burden *(in thousands of dollars)* a. Total annualized capital/startup costs ___0____

1. Percentage of these responses collected electronically up to 100% c. Total annual hours requested 3,672 d. Current OMB inventory none e. Difference _____ f. Explanation of difference 1. Program change _____ 2. Adjustment _____	b. Total annual costs (O&M) 0 c. Total annualized cost requested 0 d. Current OMB inventory 0 e. Difference 0 f. Explanation of difference 1. Program change _____ 2. Adjustment _____
15. Purpose of information collection (*Mark primary with "P" and all others that apply with "X"*) a. _ Application for benefits e._ Program planning or management b. _ Program evaluation f._x_ Research c. _ General purpose statistics g._ Regulatory or compliance d. _ Audit	16. Frequency of recordkeeping or reporting *(check all that apply)* a. [ ] Recordkeeping b. [ ] Third party disclosure c. [x] Reporting 1. [ ] On occasion 2. [ ] Weekly 3. [ ] Monthly 4. [ ] Quarterly 5. [ ] Semi-annually 6. [x] Annually 7. [ ] Biennially 8. [x] Other (describe) one-time
17. Statistical methods Does this information collection employ statistical methods [x] Yes [ ] No	18. Agency Contact (person who can best answer questions regarding the content of this submission) Name: Elizabeth Berbakos Phone: _____

OMB 83-I
10/95

	Date