Requirements for Submission of In Vivo
Bioequivalence Data

0910-0630

Supporting Statement

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

Section 505(j)(2)(A)(iv) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)(2)(A)(iv)) requires that Abbreviated New Drug Application (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 reference listed drug (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.

In the Federal Register of January 16, 2009 (74 FR 2849), FDA published a final rule revising FDA 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 to an ANDA that contains BE studies. In the final rule, FDA amended §§ 314.94(a)(7)(i), 314.96(a)(1), 320.21(b)(1), and 314.97, 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 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 amended that requirement because data from additional BE studies may be important in determining whether the proposed formulation is bioequivalent to the RLD and are relevant to an evaluation of ANDAs in general. In addition, such data will increase the understanding of how changes in components, composition, and methods of manufacture may affect product formulation performance.

FDA revised §§ 314.94(a)(7)(i), 314.96(a)(1), and 320.21(b)(1), as well as modified § 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 the above provisions, FDA also clarified 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 now interprets § 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 now interprets 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 the Information Collection

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 intra-subject 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 FD&C 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 and Burden Reduction

FDA has issued guidance documents encouraging the electronic submission of information related to ANDAs and other applications. These guidance documents are available at FDA's Web site: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

4. Efforts to Identify Duplication and Use of Similar Information

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

5. Impact on Small Businesses or Other Small Entities

Respondents include applicants wishing to market human drug products. This includes large as well as small businesses and manufacturers. The Analysis of Economic Impacts of the final rule concluded that, based on its economic analysis and a review of the comments submitted in response to the proposed rule, the final rule will not have a significant economic impact on a substantial number of small entities.

6. Consequences of Collecting Information 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. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5(d)(2)

There is no inconsistency with these guidelines.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice for public comment in the FEDERAL REGISTER of June 26, 2014 (79 FR 36320). No comments were received on the information collection.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and has no intention of providing any payment or gift to respondents.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information that would be submitted under these requirements 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 FD&C Act.

11. Justification for Sensitive Questions

This reporting does not involve any sensitive questions.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

In table 1 of this document, FDA has estimated the reporting burden associated with each section of this requirement. FDA believes that the majority of additional BE studies will be reported in ANDAs (submitted under § 314.94), rather than supplements (reported in § 314.97), because it is unlikely than an ANDA holder will conduct BE studies with a drug after the drug has been approved. 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.

FDA estimates applicants 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 previously in this document, the submission of each additional BE study is expected to take 72 hours of staff time ([120 × 0.2] + [60 × 0.8]).

FDA estimates the burden of this collection of information as follows:

Table 1-- Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
314.94(a)(7)	84	1	84	72	6,048
314.96(a)(1)	1	1	1	72	72
314.97	1	1	1	72	72
Total					6,192

12b. Annualized Cost Burden Estimate

As explained in the Analysis of Economic Impacts section of the final rule, the main cost of complying with these requirements is staff time. The weighted average wage rate is $40 per hour. FDA estimated 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. FDA 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 these requirements.

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal 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. Explanation for Program Changes or Adjustments

The burden hours have changed from 3,672 to 6,192 because of CDER data showing an overall increase in ANDA-related submissions.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no scheduling, publication, or analysis plans.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

This request does not seek approval to exempt display of the OMB approval date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.