General Licensing Provisions; Section 351(k) Biosimilar Applications
0910-NEW
SUPPORTING STATEMENT

JUSTIFICATION

1. Circumstances Making the Collection of Information Necessary

On March 23, 2010, the President signed into law the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148). The Affordable Care Act contains a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) which amends the Public Health Service Act (PHS Act) and establishes an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. (See sections 7001 through 7003 of the Affordable Care Act.)

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(k) defines biosimilarity to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product". (See section 351(i)(2) of the PHS Act.) A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and clinical studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application. (See section 351(k)(2).) To demonstrate interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity, and that the biosimilar biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biosimilar biological product is administered more

than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. (See section 351(k)(4) of the PHS Act.) Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider. (See section 351(i)(3) of the PHS Act.)

A summary of the collection of information requirements in the submission of a 351(k) application as described under the BPCI Act follows:

Section 351(k)(2)(A)(i) requires manufactures of 351(k) products to submit an application for FDA review and licensure before marketing a biosimilar product. An application submitted under this section shall include information demonstrating that:

- The biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies (including toxicity) and a clinical study or studies (including immunogenicity and pharmacokinetics or pharmacodynamics). The Secretary of Health and Human Services (the Secretary) may determine that any of these elements is unnecessary.
- The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product.
- The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product.
- The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product.
- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

Section 351(k)(2)(A)(iii) requires the application to include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent. The application may include any additional information in support of the application, including publicly-available information with respect to the reference product or another biological product.

Under section 351(k)(2)(B) and (k)(4), a manufacturer may include information demonstrating that the biological product meets the standards for interchangeability either in the application described above to show biosimilarity, or in a supplement to such an application. The information submitted to meet the standard for interchangeability must show that: (1) The biological product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient and (2) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

A summary of the collection of information requirements under 351(l)(6)(C) follows:

Not later than 30 days after a complaint from the reference product sponsor is served to a 351(k) applicant in an action for patent infringement described under 351(l)(6), section 351(l)(6)(C) requires that the 351(k) applicant provide the Secretary with notice and a copy of such complaint. The Secretary shall publish in the Federal Register notice any complaint received under 351(l)(6)(C)(i).

2. Purpose and Use of the Information Collection

The information collection establishes an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product, and sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. The information submitted in a 351(k) application or supplement is used by FDA to make a determination of biosimilarity or interchangeability of a

proposed 351(k) product.

3. Use of Improved Information Technology and Burden Reduction

One of FDA's continuing objectives is to improve the speed and quality of its review and approval programs. To make the review process more efficient for industry and FDA, the agency utilizes electronic information systems technology and currently accepts the submission of electronic license applications and other similar submissions. FDA believes the increased use of computer-assisted license applications enhances the timeliness, effectiveness, and efficiency of the review process and reduce burdensome, nonessential hard-copy handling and storage. FDA has issued several guidance documents describing the process for submitting applications to FDA in electronic format. These guidance documents are listed on the Internet as follows:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm or

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm218518.htm.

4. Efforts to Identify Duplication and Use of Similar Information

An application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product required by Section 351(k) of the PHS Act would be new submissions and does not duplicate any other submissions to FDA.

5. Impact on Small Businesses or Other Small Entities

This information collection applies to small as well as large manufacturers. Although FDA must apply the statutory and regulatory requirements equally to all enterprises, the agency does provide special help to small businesses. The Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development, Division of Manufacturers Assistance and Training provides assistance to small businesses subject to FDA's regulatory requirements. The Center for Drug

Evaluation and Research (CDER), Office of Communication, Division of Drug Information also provides assistance to small businesses.

6. Consequences of Collecting the Information Less Frequently

Manufacturers and sponsors are required to submit applications to FDA for approval of biological products prior to marketing such products in interstate commerce. In addition, manufacturers and sponsors are required to submit to FDA a supplement to an approved application prior to implementing a change or in an annual report, depending on the significance of the change. Less frequent collection of this and other information will not provide the information that FDA needs to evaluate the safety, purity, potency, and effectiveness of a biological product.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

An applicant may be required to submit to FDA proprietary trade secret or other confidential information when submitting a license application, change to an approved application, or other related information. FDA protects confidential information received from manufacturers to the extent permitted by law. In addition, certain changes to an approved application are required to be submitted each time a change is made. This information is necessary for FDA to ensure that the proposed changes do not have an adverse effect on the strength, quality, purity, or potency as they may relate to the safety and effectiveness of a product.

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

In the Federal Register of February 15, 2012 (77 FR 8880), FDA published a 60-day notice requesting comment on the proposed information collection. In the Federal Register of February 23, 2012 (77 FR 10752), FDA published a correction to the 60-day notice providing the correct docket

number to submit comments. We received no comments that pertained to the information collection analysis.

On November 2 and 3, 2010, FDA held a public hearing and established a public docket to obtain input on specific issues and challenges associated with the implementation of the BPCI Act. (See Docket No. FDA-2010-N-0477.) Based in part on this input, FDA announced, in the Federal Register of February 15, 2012 (77 FR 8883; 77 FR 8884; 77 FR 8885) the availability of three draft guidances describing FDA's current interpretation of certain statutory requirements added by the BPCI Act as well as quality and analytical issues, demonstrating biosimilarity, and implementation policy issues. These draft guidances are: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," and "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product."

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

The confidentiality of information received by FDA would be handled consistent with the Freedom of Information Act (FOIA) and FDA's published regulations under 21 CFR Part 20, 21 CFR 601.51, and 601.70(e).

11. Justification for Sensitive Questions

Questions of a sensitive nature are not applicable to this collection of information.

12. Estimates of Annualized Hour Burden and Costs

12a. Annualized Hour Burden

In estimating the information collection burden for 351(k) applications, FDA has reviewed the collection of information regarding the general licensing provisions for biologics license applications (BLAs) under section 351(a) of the PHS Act to OMB (approved under OMB control number 0910-0338). For the information collection burden for 351(a) applications, FDA described § 601.2(a) (21 CFR 601.2(a)) as requiring a manufacturer of a biological product to submit an application on forms prescribed for such purpose with accompanying data and information including certain labeling information to FDA for approval to market a product in interstate commerce. FDA also added in the burden estimate the container and package labeling requirements provided under §§ 610.60 through 610.65 (21 CFR 610.60 through 610.65). The estimated hours per response for § 601.2, and §§ 610.60 through 610.65, were 860 hours.

In addition, in submitting a 351(a) application, an applicant completes the Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use." The application form serves primarily as a checklist for firms to gather and submit certain information to FDA. The checklist helps to ensure that the application is complete and contains all the necessary information, so that delays due to lack of information may be eliminated. The form provides key information to FDA for efficient handling and distribution to the appropriate staff for review. The estimated burden hours for biological product submissions using FDA Form 356h are included under the applicable requirements approved under OMB control number 0910-0338.

FDA intends for an applicant to submit a 351(k) application following Form FDA 356h, modifying the information submitted to support the information required under section 351(k) of the BPCI Act. To submit an application seeking licensure of a proposed biosimilar product under section 351(k)(2)(A)(i) and (k)(2)(A)(iii), FDA believes that the estimated burden hours would be approximately the same as noted under OMB control number 0910-0338 for a 351(a) application--860 hours. The burden estimates for seeking licensure of a proposed biosimilar product that meets the

standards for interchangeability under section 351(k)(2)(B) and (k)(4) would also be 860 hours. Until we gain more experience with biosimilar applications, FDA believes this estimate is appropriate for 351(k) applications because to determine biosimilarity or interchangeability of a proposed 351(k) product, the application and the information submitted is expected to be comparably complex and technically demanding as a proposed 351(a) application. FDA may determine, in its discretion, that an element required under a 351(k) application to be unnecessary to support licensure of a biosimilar or interchangeable product. In those cases, the number of hours per response may be less than the hours estimated.

In addition to the collection of information regarding the submission of a 351(k) application for a proposed biosimilar or interchangeable biological product, section 351(l) of the BPCI Act establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act. The burden estimates for the patent provisions under section 351(l)(6)(C) of the BPCI Act are included in the table below and are based on the estimated number of 351(k) biosimilar respondents. Based on similar reporting requirements, FDA estimates this notification will take 2 hours.

FDA has not yet received any 351(k) applications. In the table below, the estimated number of respondents submitting 351(k) applications is based on the estimated annual number of manufacturers that would submit the required information to FDA and the estimated annual number of 351(k) submissions FDA would receive. In making this estimate, FDA has taken into account, among other things, the expiration dates of patents that relate to potential reference products, and general market interest in biological products that could be candidates for 351(k) applications.

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

Estimated Annual Reporting Burden

351(k) Application for Biosimilars (42 U.S.C. 262(k))	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
351(k)(2)(A)(i) and (k)(2)(A)(iii)	2	1	2	860	1720
351(k)(2)(B) and (k)	1	1	1	860	860

Estimated Annual Reporting Burden

351(k) Application for Biosimilars (42 U.S.C. 262(k))	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
(4)					
351(l)(6)(C)	2	1	2	2	4

FDA announced, in the Federal Register of February 15, 2012 (77 FR 8883; 77 FR 8884; 77 FR 8885), the availability of three draft guidances describing FDA's current interpretation of certain statutory requirements added by the BPCI Act as well as quality and analytical issues, demonstrating biosimilarity, and implementation policy issues. These draft guidances are: "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," and "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product." The Federal Register documents for these guidances reference this information collection document regarding the burden on the submission of a 351(k) application not otherwise covered by existing OMB approvals. In addition, we note that the draft guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" recommends that labeling for a product subject to approval under section 351(k) include statements that indicate that: (1) The product is approved as biosimilar to a reference product for stated indication(s) and (2) the product (has or has not) been determined to be interchangeable with the reference product. FDA has determined, under 5 CFR 1320.3(c)(2)), that these labeling recommendations are not "collections of information" for the purposes of the PRA because the statements will comprise solely information that FDA will supply to the applicant for the purpose of disclosing it to the public, i.e. FDA's determination upon review of the application submitted under section 351(k), that the product is biosimilar and/or interchangeable to its reference product.

12b. Annualized Costs

The estimated annual cost to respondents is $118,864.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	2,584	$46	$ 118,864

The cost estimate is based on a regulatory affairs specialist, at a pay rate of $46/hour, who would be responsible for filling out the form, and preparing an application, supplement, or other similar submission. The estimated average hourly pay rate includes benefits but no overhead costs.

13. Estimates of Other Total Annual Cost Burden to Respondents and Recordkeepers

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

14. Annualized Cost to the Federal Government

FDA's review of these applications and supplements would be consistent with the annualized Federal cost approved by OMB for the information collection entitled "General Licensing Provisions: Biologics License Application, Changes to an Approved Application, Labeling, Revocation and Suspension, Postmarketing Studies Status Reports, and Forms FDA 356h and 2567 (OMB Control # 0910-0338)." This estimated cost is as follows:

The estimated annualized cost to FDA is $12,482,982. This estimate is based on full-time equivalents (FTEs) associated with the review of license applications including supplemental applications. The amount of time and expense incurred by the Federal government includes the time to the review of all material submitted with an application or supplement. This information is essential to determine the safety and effectiveness of products in support of FDA's mission to protect the public health. This information may include clinical data, safety updates, samples submitted for evaluation by

the agency, case report tabulations, case report forms, and patient information. The estimated average annual salary for FDA reviewers includes benefits but no overhead costs.

Activity	Number of FTEs	Average Annual Reviewer Salary	Total Cost
Application/Supplement Review	103	$121,194	$12,482,982

15. Explanation for Program Changes or Adjustments

This is a new collection of information.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

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

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.