AIPLA
AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION

May 24, 2012

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2011-D-0605: Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
Docket No. FDA–2011-D-0602: Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
Docket No. FDA–2011-D-0611: Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009[1]

Dear Sir or Madam:

The American Intellectual Property Law Association ("AIPLA") is pleased to have the opportunity to present its views with respect to the Draft Guidances referenced above. AIPLA is a U.S.-based national bar association with approximately 15,000 members who are primarily lawyers in private and corporate practice, government service, and the academic community. AIPLA represents a diverse spectrum of individuals, companies, and institutions involved directly and indirectly in the practice of patent, trademark, copyright, unfair competition, and trade secret law, as well as other fields of law affecting intellectual property. Our members practice or are otherwise involved in patent law and other intellectual property law in the United States and in jurisdictions throughout the world.

The primary interest of AIPLA is legal matters pertaining to intellectual property. While the Food and Drug Administration's role in the scientific regulation of biologic drugs is generally outside this primary interest, implementation of the new abbreviated regulatory pathway for biosimilar products authorized under the Biologics Price Competition and Innovation Act of 2009 (BPCIA) contains some aspects that impact intellectual property rights, including patents, trademarks, trade secrets, regulatory exclusivity, and IP litigation. In view of this impact, AIPLA provides comments on those aspects of the Draft Guidances that more or less directly impact intellectual property rights, and therefore impact our membership. Specifically, AIPLA provides comments on three issues: (1) definition of "protein (except any chemically synthesized polypeptide)"; (2) molecules having a changed amino acid sequence compared with the reference product; and (3) publication of exclusivity expiration dates.

[1] Referred to herein as the "Scientific Guidance," the "Quality Guidance," and the "Q&A Guidance," respectively.

Definition of "protein (except any chemically synthesized polypeptide)"

Whether a product will qualify for licensing as a biological product under § 351(a) of the Public Health Services Act (PHSA), and thus be eligible for 12 years or for 12 years and 6 months of exclusivity, will depend upon how FDA interprets the expression "protein (except any chemically synthesized polypeptide)" in the definition of "biological product."[2] The proposed interpretations given in Section II of the Q&A Guidance seem to set arbitrary and unnecessarily rigid boundaries.[3] AIPLA recommends that FDA adopt a more inclusive and/or a more flexible interpretation than that proposed in the Q&A Guidance.

Specifically, under the proposed interpretation, a molecule that is an "alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size," produced in any way except by chemical synthesis, and a molecule that is an "alpha amino acid polymer with a specific defined sequence that is greater than 100 amino acids in size," produced by any method, will be considered biological products. These will qualify for 12 years of exclusivity as biological products, whereas other "alpha amino acid polymers" will qualify for only 5 years of exclusivity under the Hatch-Waxman amendments to the Food, Drug, and Cosmetics Act (FDCA).[4] A summary of the exclusivities under FDA's proposed interpretation is provided below.

Exclusivity per the Q&A Guidance

	Size		
Method of Synthesis	<40 amino acids	40-100 amino acids	>100 amino acids
Chemical	5 years	5 years	12 years
Biological	5 years	12 years	12 years

Because placement of a molecule outside of the definition of a "biological product" will greatly impact its development and commercialization potential, AIPLA recommends that FDA adopt a more inclusive interpretation or that FDA be flexible in its application of the proposed categories. Specifically, AIPLA urges FDA to presumptively categorize all molecules synthesized in biological systems to be biological products. The need for comparability exercises for proteins that are less than 40 amino acids and that are produced in biological systems indicates that FDA recognizes greater risks in biological production systems, regardless of the length of the protein. Furthermore, the exclusion of molecules having less than 40 amino acids from being considered biological products seems inconsistent with FDA's longstanding practice, which would permit licensing a "therapeutic DNA-derived product" as a biological product regardless of its amino acid length.[5] Under current rules, any recombinant DNA-derived product could qualify under the PHSA as a biological product.

[2] 42 U.S.C. § 262(i)(1).
[3] Q&A Guidance at 12-14.
[4] 21 U.S.C. §§ 355(c)(3)(E)(ii) and (j)(5)(F)(ii).
[5] See 21 C.F.R. § 601.2(c) (c)(1) ("To obtain marketing approval for a biological product subject to licensure which is a therapeutic DNA plasmid product, therapeutic synthetic peptide product of 40 or fewer amino acids, monoclonal

AIPLA believes FDA should include within the definition of "biological product" any therapeutic DNA-derived alpha amino acid polymer with a specific defined sequence. However, if FDA decides not to adopt such an approach, AIPLA urges FDA to apply the definition of "biological product" liberally and flexibly considering the risks inherent in biological production. Doing so would provide the greatest incentive for the development of innovative new biological products. This especially applies to molecules having little or no effective patent protection. Such molecules typically will not be commercialized unless regulatory exclusivity substantially exceeds that provided under the Hatch-Waxman amendments.

Molecules having a changed amino acid sequence

The Draft Guidance documents state the general expectation that a proposed expression construct for a biosimilar product will encode the same primary amino acid sequence as the reference product, but that "minor modifications such as N- or C- terminal truncations that will not affect safety and effectiveness may be justified and should be explained by the sponsor."[6] The proposed flexibility should be balanced against potential for harm. AIPLA suggests that the impact of any amino acid changes, deliberate or not, must be well understood in terms of safety, purity, and potency.[7] FDA should provide greater specificity as to the types of "minor modifications" permissible.

Additionally, AIPLA recommends that FDA include clearer guidance for subsection (k) applicants who intend to deliberately modify the primary amino acid sequence in order to avoid patent rights. Such clearer guidance will also benefit companies seeking to obtain patent rights to protect their investments in developing and commercializing innovative biological products. Clearer guidance would emphasize the difficulties expected in demonstrating biosimilarity or interchangeability for a molecule deliberately altered for reasons not related to a scientifically or medically valid concern involving safety, purity, or potency. Ideally, FDA would more clearly dissuade applicants from the 351(k) pathway when the motivation for deliberate changes is avoidance of patent rights. AIPLA believes that providing such clarification would improve certainty for both reference product sponsors and for subsection (k) applicants.

Publication of exclusivity expiration dates

Section III of the Q&A Guidance poses just two questions relating to exclusivity.[8] Neither question, however, deals with a question that reference product sponsors and subsection (k) applicants would pose: On what date may FDA license a product that is biosimilar to or interchangeable with a biological product that may serve as a reference product? Thus, AIPLA recommends that FDA publish the date on which a biological product is or was "first licensed under subsection 351(a)" of the PHSA, and/or the dates that are 4 years or 4 years and 6 months

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antibody product for in vivo use, or <u>therapeutic recombinant DNA-derived product</u>, an applicant shall submit a biologics license application in accordance with paragraph (a) of this section except that the following sections in parts 600 through 680 of this chapter shall not be applicable to such products: 600.10(b) and (c), 600.11, 600.12, 600.13, 610.11, 610.53, and 610.62 of this chapter.")

[6] Scientific Guidance at 9; Quality Guidance at 9.

[7] 42 U.S.C. §§ 262(i)(2) and (k)(2).

[8] Q&A Guidance at 15.

after such date, and the dates that are 12 years or 12 years and 6 months after such date.[9] AIPLA further recommends that FDA publish the dates of supplementary approvals of products licensed under PHSA § 351(a) that may implicate the anti-evergreening provisions[10] or that may affect whether a biological product licensed prior to the enactment of the BPCIA may serve as a reference product.[11]

While the BPCIA does not mandate such publication, there is precedent in FDA's publication of expiry dates of exclusivities in the Orange Book.[12] FDA provides this listing of exclusivity expiry dates, even though the Hatch-Waxman Amendments to the FDCA did not mandate such publication.[13] Likewise, FDA maintains a public, searchable database for approved and licensed products that have Orphan designations, which database includes the "Exclusivity Start Date" for each such product,[14] even though the Orphan Drug Act did not mandate FDA to make such information about exclusivity available.[15]

Publishing such information would improve certainty for both reference product sponsors and subsection (k) applicants alike, and thereby foster investment and innovation. In addition, where there is disagreement or uncertainty over the exclusivity expiry dates, publication of the date of first licensure or the date exclusivities expire would provide all concerned parties the ability to resolve such disagreement or uncertainty before significant changes in position are made.

AIPLA appreciates the opportunity to present comments on these important issues.

Sincerely,

William G. Barber
AIPLA President

[9] See 42 U.S.C. §§ 262 (k)(7) and (m)(3).
[10] 42 U.S.C. § 262(k)(7)(C).
[11] Citizen Petition filed by Covington & Burling LLP on behalf of Abbott Laboratories, FDA Docket No. FDA-2012-P-0317, April 2, 2012.
[12] Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, which is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
[13] See, e.g., 21 U.S.C. § 355(b)(1)(A).
[14] Available at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm.
[15] See, e.g., 21 U.S.C. § 360aa.