ARNOLD & PORTER LLP

CLIENT ADVISORY

BIOSIMILAR BILL REPORTED FROM SENATE COMMITTEE

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Washington, DC
+1 202.942.5000

New York
+1 212.715.1000

London
+44 (0)20 7786 6100

Brussels
+32 (0)2 517 6600

Los Angeles
+1 213.243.4000

San Francisco
+1 415.356.3000

Northern Virginia
+1 703.720.7000

Denver
+1 303.863.1000

Bipartisan legislation (S. 1695 (the Biologics Price Competition and Innovation Act))* that would create a mechanism for FDA approval of "biosimilar" (also referred to as "follow-on," "comparable," or "biogeneric") biologic products was reported out of the Senate Health, Education, Labor and Pensions (HELP) Committee on June 27, 2007. The bill is co-sponsored by Senators Kennedy (D-MA), Hatch (R-UT), Clinton (D-NY), and Enzi (R-WY). There will likely be an attempt to include the bill's language in omnibus FDA legislation (S. 1082 (the Food and Drug Administration Revitalization Act, as passed by the Senate) / H.R. 2900 (the Food and Drug Administration Amendments Act of 2007, as voted out of the House Energy and Commerce Committee)) in conference. While the Senate legislation has a placeholder for follow-on biologics legislation, the parallel House bill does not, and there has been no Energy and Commerce Committee markup of the such legislation to date. However, the political pressure is building on this issue, and if the biosimilar bill's language is not included in the larger FDA bill, the efforts to seek passage will only grow in intensity in the upcoming election season.

The Senate bill would amend the Public Health Service Act ("PHSA") to create an abbreviated approval pathway for "biosimilar" biological products. The bill defines "biosimilar" as meaning that "(A) that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product."[1]

The statute:

- creates a mechanism for approval of biosimilar biologic products on the basis of reference to an approved innovator product, together with additional data;
- provides a mechanism for an applicant to claim and FDA to find that the biosimilar product is interchangeable with the innovator product;

* This legislation can be viewed through the following link: http://www.arnoldporter.com/docs/resources/s.1695.pdf

- provides data and market exclusivity for the innovator product;
- provides exclusivity vis-à-vis other biosimilars claiming interchangeability for the first approval of an interchangeable biosimilar;
- provides for, but does not require, FDA issuance of guidance documents describing the requirements for approval of particular biosimilar products or classes of products;
- sets up a mechanism for the biosimilar applicant to share its application and potentially additional information with the innovator applicant (or patent licensor) on a confidential basis, and sets up a complex procedure designed to permit identification of and litigation during the FDA approval process concerning patents that are believed to apply to the biosimilar product;
- provides a transition from approval under Section 505 of the Federal Food, Drug, and Cosmetic Act ("FFDCA") to approval under PHSA Section 351 for products that fall within the definition of biologic, which is defined by the statute to include, in addition to the currently described products, a "protein (except any chemically synthesized polypeptide)";
- provides that, over time, FDA shall develop a new type of user fee for biosimilar applications; and
- provides that any savings to the government determined to have been attributable to approval of biosimilar products shall be transferred to a fund to be expended on activities under the PHSA.

A more detailed description of the legislation follows:

Approval Pathway. The biosimilar applicant must submit data derived from:

- analytical studies;
- animal studies;
- a clinical study or studies sufficient to demonstrate safety purity and potency in one or more appropriate conditions of use.[2]

(FDA can, however, waive the requirement to submit any of these studies if appropriate.[3])

- a showing that the biosimilar and reference product utilize the same mechanism(s) of action for the condition or conditions of use recommended in the proposed labeling, but only if the mechanism(s) of action are known for the reference product;[4]
- a showing that the condition or conditions of use for the biosimilar have been previously approved for the reference product;[5]
- a showing that the route of administration, dosage form, and strength are the same as those of the reference product;[6] and
- a showing that the facilities where the biosimilar will be manufactured, processed, packed, and held meet appropriate standards;[7] and
- any additional data the applicant chooses to submit.[8]

The FDA review of the biosimilar application is to be by the review division responsible for the innovator application, rather than by the Office of Generic Drugs.[9] Note that any biosimilar approved under this provision that is not found to be interchangeable will be considered to have a different active ingredient than the innovator, *i.e.,* it will have a different generic name.

Interchangeability. The biosimilar application, or a supplement to that application, can include information demonstrating that the biosimilar product is interchangeable with the reference product.[10] The term "interchangeable" is defined as meaning that the biosimilar product "may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product."[11] To determine that a biosimilar is interchangeable with a reference product, FDA must find that the biosimilar can be "expected to produce the same clinical result as

the reference product in any given patient" and, if it is expected to be administered more than once to an individual, that there is no more risk in terms of safety or efficacy of alternating or switching between the use of the biosimilar and the reference product than there would be of using the reference product without alternation or switch.[12]

Exclusivity for the Innovator. The statute provides that:

- no biosimilar application may be submitted until 4 years after the date in which the reference product is first licensed;[13] and that
- approval of the biosimilar application may not be made effective until 12 years after the date of first licensure of the reference product.[14] A supplement or new BLA for a new indication, route of administration, dosage form, or strength of a previously licensed product will not count as first licensure for this purpose.[15]

Exclusivity for First Interchangeable Biosimilar. Once one biosimilar product has been approved as interchangeable, no second or subsequent biological product can be found to be interchangeable for any condition of use until the earlier of:

- one year after first commercial marketing of the first biosimilar to be approved as interchangeable; or
- 18 months after either a final court decision (of the Federal Circuit if there is an appeal) on all patents in any action brought under the new provision (see discussion below) or the dismissal with or without prejudice of actions brought under that provision; or
- 42 months after approval of the first interchangeable biosimilar if the applicant has been sued for patent infringement under the new statutory provision and the litigation is still ongoing; or
- 18 months after approval of the first interchangeable if the applicant has not been sued under the statutory provision. [16]

Guidance Documents. FDA may issue guidance documents but must provide the public an opportunity to comment on any proposed guidance before issuing it in final. No guidance is, however, necessary for consideration of a biosimilar application.[17]

Patents. The bill creates a process by which the biosimilar applicant would provide, to outside counsel for the innovator and to one in-house counsel for the innovator (and the licensor of a patent when the licensor has retained the right to sue), on a confidential basis, a copy of the biosimilar application and other information that describes the process or processes used to manufacture the biosimilar product and, at its option, other information requested by the innovator. The application is to be provided not later than 20 days after FDA notifies the biosimilar applicant that its application has been accepted for review.[18]

The statute then provides the following mechanism for attempted resolution of patent disputes:

- Not later than 60 days after receipt of the application, the innovator provides the biosimilar applicant a list of patents that it says claim the product and identification of any patents on that list that the innovator would be prepared to license to the biosimilar applicant.[19]
- Not later than 60 days after receipt of that list, the biosimilar applicant provides the innovator a detailed statement that describes, on a claim-by-claim basis, the factual and legal reasons why it believes each patent is invalid, unenforceable, or will not be infringed, or a statement that the biosimilar applicant does not intend to begin commercial marketing before the date that such patent expires.[20]
- Not later than 60 days after the innovator receives the biosimilar applicant's list and statements, the innovator applicant must provide a detailed statement that describes, for each patent on a claim-by-claim basis, the

reasons why it believes that the patents will be infringed and the response to any arguments made concerning validity and enforceability.[21]

- The innovator and biosimilar applicant are then required to engage "in good faith negotiations" to agree on which patents shall be the subject of a patent infringement suit. If those negotiations fail to result in agreement within 15 days, the parties then exchange lists of the patents they believe should be the subject of patent litigation. The innovator's list cannot exceed the number of patents listed by the biosimilar applicant, unless the biosimilar applicant does not list any patents, in which case the innovator may list one patent.[22]
- If the parties agree on the patents to be subject to litigation, then the innovator must bring an action for patent infringement within 30 days with respect to each patent. If there is no agreement and the parties exchange lists of patents, the innovator (or licensor) must bring an action within 30 days with respect to each patent included on each list.[23]
- Not later than 30 days after the complaint is served, the biosimilar applicant must provide the complaint to the FDA, which then must publish notice of the complaint in the Federal Register.[24]
- For newly issued or licensed patents, the innovator must provide a supplement to the list it provided to the biosimilar applicant within 30 days after issuance or licensure.[25]
- The biosimilar applicant must provide notice to the innovator not later than 180 days before the date of first commercial marketing of the biosimilar product. The innovator may then seek a preliminary injunction with respect to any patent that was included in the list provided to the biosimilar applicant originally but not included on the lists of patents that were either agreed by the parties or otherwise exchanged between the parties as being patents to be subject to litigation.[26]
- No declaratory judgment action may be brought by either the biosimilar or innovator applicant prior to the notice that the biosimilar will begin to market within 180 days. Innovator applicants can, however, bring declaratory judgment actions if a biosimilar applicant does not satisfy its obligations under the new statute with respect to patent resolution (e.g., it fails to provide the required lists) or fails to provide a copy of its application to the innovator.[27]
- If the innovator fails to sue on a patent covered by one of the lists discussed above within the required 30-day period, or if its suit is dismissed without prejudice or not prosecuted to judgment in good faith, then any subsequent lawsuit on that patent can only result in a reasonable royalty. If the patent owner did not include the patent on the required list under the statutory provision, it is blocked from bringing any action for infringement of the patent.[28]

Pediatric Study Requirements. A biosimilar product will be considered to have a new active ingredient for purposes of being required to do pediatric studies, unless it is found to be interchangable.[29]

Transition of Biologics Approved Under FFDCA. There is a ten-year period after enactment of the new provisions during which any applicant can submit its application under the FFDCA so long as another biological product in its product class has been the subject of an FFDCA approval prior to enactment.[30] Ten years after enactment, any biological product approved under an NDA will be deemed to have been approved under PHSA § 351.[31]

User Fees. The statute provides that, beginning in October 2010, the FDA should develop recommendations for

user fees for biosimilar applications which would be submitted to Congress to coincide with the next user fee negotiation cycle in 2012.[32]

Special Reserve Fund. The statute states that the amount of savings to the federal government as a result of this enactment is to be transferred to a "special reserve fund" that will be available to the Secretary of Health and Human Services for activities under the PHSA.[33]

For further information, please contact:

Donald O. Beers
+1 202.942.5012
Donald.Beers@aporter.com

Daniel A. Kracov
+1 202.942.5120
Daniel.Kracov@aporter.com

Gregory H. Levine
+1 202.942.5378
Gregory.Levine@aporter.com

Arthur N. Levine
+1 202.942.5740
Arthur.Levine@aporter.com

William W. Vodra
+1 202.942.5088
William.Vodra@aporter.com

Endnotes

1 Section 2(b)(3), amending Public Health Service Act (PHSA) Section 351(i), 42 U.S.C. 262(i).

2 Section 2(a), adding PHSA Section 351(k)(2)(A)(i)(I), 42 U.S.C. 262(k).

3 Id., (k)(2)(A)(ii).

4 Id., (k)(2)(A)(i)(II).

5 Id., (k)(2)(A)(i)(III).

6 Id., (k)(2)(A)(i)(IV).

7 Id., (k)(2)(A)(i)(V).

8 Id., (k)(2)(A)(iii).

9 Id., (k)(5)(B).

10 Id., (k)(2)(B).

11 Section 2(b), amending PHSA Section 351(i), 42 U.S.C. 262(i) by adding subsection (3).

12 Section 2(a), creating new PHSA Section 351(k)(4).

13 Id., (k)(7)(B).

14 Id., (k)(7)(A).

15 Id., (k)(7)(C).

16 Id., (k)(6).

17 Id., (k)(8).

18 Section 2(a), creating new PHSA Section 351(l), 42 U.S.C. 262(l).

19 Id., (l)(3)(A).

20 Id., (l)(3)(B).

21 Id., (l)(3)(C).

22 Id., (l)(3)(D).

23 Id., (l)(6).

24 Id.

25 Id., (l)(7).

26 Id., (l)(8).

27 Id., (l)(2)-(9).

28 Section 2(c), creating new Section 271(e)(6), 35 U.S.C. 271(e).

29 Section 2(d), amending FFDCA Section 505(B), 21 U.S.C. 355(c), by adding a new subsection (i).

30 Section 2(e)(2).

31 Id., (e)(4).

32 Section 2(f)(1)(a).

33 Section 2(g).