Variations on a Theme:
Five Proposed Abbreviated Approval Pathways for Biogenerics

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In the pharmaceutical context, the term "biologics" generally refers to protein-based medicines that are made in living cells, such as insulin and human growth hormone. At the molecular level, biologics are larger and more complex than small-molecule drugs such as Lipitor® and Nexium®. Because biologics are the products of living cells rather than synthetic chemical processes, they can be difficult to manufacture in industrial quantities, and are difficult to produce with the degree of consistency and uniformity seen with small-molecule drugs.

Despite these obstacles, biologics are gaining widespread attention from the pharmaceutical industry and politicians. In addition to small-molecule drugs, the pharmaceutical industry has come to view biologics as a significant driver of future growth.[1]

In recent years, the United States Congress introduced several competing bills that would establish an abbreviated approval process for "follow-on" biologics, or therapeutically similar versions of "reference" biologics that have already been approved for human use. This proposed abbreviated approval process would in some ways resemble the abbreviated new drug application (ANDA) process established under the 1984 Hatch-Waxman Act for the approval of generic small-molecule drugs. Unlike generic small-molecule drugs, however, follow-on biologics are more difficult than generic small-molecule drugs for regulatory agencies to evaluate and approve, because their inherent variability prevents them from being precisely equivalent to their reference counterparts.

Recent bills to propose an abbreviated approval process for follow-on biologics include:[2]

- "The Pathway for Biosimilars Act," H.R. 5629, 110th Cong. (2008), introduced on March 13, 2008 by Representatives Anna Eshoo (D-CA) and Joe Barton (R-TX);
- "The Biologics Price Competition and Innovation Act," S. 1695, 110th Cong. (2007), introduced on June 26, 2007 by Senators Edward Kennedy (D-MA), Orrin Hatch (R-UT), Hillary Clinton (D-NY), Michael Enzi (R-WY), and Charles Schumer (D-NY);
- "The Patient Protection and Innovative Biologic Medicines Act," H.R. 1956, 110th Cong. (2007), introduced on April 19, 2007 by Representatives Jay Inslee (D-WA), Gene Green (D-TX) and Tammy Baldwin (D-WS);
- "The Access to Life Saving Medicine Act," H.R. 1038, 110th Cong. (2007), introduced on February 14, 2007 by Representatives Henry Waxman (D-CA), Jo Ann Emerson (R-MO), Frank Pallone (D-NJ), Rahm Emanuel (D-IL) and Mazie Hirono (D-HI); and
- "The Promoting Innovation and Access to Life-Saving Medicine Act," H.R. 1427, 111th Cong. (2009) introduced on March 12, 2009 by Representatives Waxman, Pallone, Nathan Deal (R-GA) and Emerson.

All five bills propose adding an abbreviated approval pathway for follow-on biologics as an amendment to Section 351 the Public Health Service Act, which presently permits the approval of biologics by the Secretary of the U.S. Department of Heath and Human Services under a non-abbreviated mechanism called a Biologics License Application (BLA).

While none of these bills has yet passed, they nevertheless provide insight into the regulatory approaches that Congress is considering, and may eventually adopt, for the approval of follow-on biologics. Below is a summary of some of the salient features of these bills.

"The Pathway for Biosimilars Act," H.R. 5629

Under H.R. 5629, the approval of an application for a follow-on biologic depends upon a showing of "biosimilarity" to a reference biologic. An applicant must demonstrate biosimilarity using three categories of data: data from analytical studies which demonstrate that the follow-on biologic is "highly similar" to the reference biologic; data from animal studies, including animal toxicity studies; and data from human clinical studies, including assessments of immunogenicity and pharmacokinetics, sufficient to demonstrate the safety, purity and potency of the follow-on biologic as to each therapeutic indication for which the reference biologic is approved.

Note that H.R. 5629 does not require data to prove the efficacy of the follow-on biologic – only data sufficient to establish its safety, purity and potency. Moreover, H.R. 5629 explicitly permits the Secretary, at his or her discretion, to waive the requirements for such data. And H.R. 5629 further requires the Secretary to promulgate formal guidelines establishing biosimilarity criteria for each class of biologics, which potentially could include waivers of certain categories of data for certain product classes.

In addition to a showing of biosimilarity, H.R. 5629 requires that a follow-on biologic applicant provide information sufficient to demonstrate (i) that the follow-on biologic uses the same "mechanism of action" as the reference biologic; (ii) that the proposed therapeutic indications for the follow-on biologic match those that were previously approved for the reference biologic; (iii) that the route of administration and strength of the follow-on biologic are the same as those of the reference biologic; and (iv) that the facility in which the follow-on biologic is made meets standards sufficient to ensure its safety, purity and potency.

Similar to the Hatch-Waxman Act, H.R. 5629 provides periods of market exclusivity both for the reference biologic and the first follow-on biologic. The reference biologic is granted 12 years of exclusivity following the grant of a BLA, extendable by two years if the reference biologic receives approval for a new therapeutic indication, and by a further six months if it is approved for pediatric use. The first follow-on biologic is granted 24 months of exclusivity, beginning on the later of the date of its first commercial marketing, or upon the date that it is determined to be "interchangeable" with the reference biologic. Under H.R. 5629, a follow-on biologic is deemed interchangeable if it is biosimilar to the reference biologic *and* can be expected to produce the same clinical result for each therapeutic indication approved for the reference biologic.

Also similar to the Hatch-Waxman Act, H.R. 5629 provides for the exchange of patent information between a follow-on biologic applicant and a reference biologic maker. Under H.R. 5629, the applicant must notify the reference biologic maker of its application within 30 days after the Secretary accepts the application. The reference biologic maker thereafter has 60 days to notify the applicant of any "relevant" patent, and to explain why it believes such patent would be infringed by a biosimilar product. The applicant then has 45 days to respond with a statement either that it will not market its follow-on biologic before the expiration of the noticed patent, or that the patent is not infringed, or is invalid or unenforceable. If the reference biologic maker sues the applicant within 60 days of receiving a statement of non-infringement, or invalidity or unenforceability, and the court handling the suit determines that the patents are infringed, the Secretary must stay approval of the follow-on biologic application until after patent expiry.

"The Biologics Price Competition and Innovation Act," S. 1695

S. 1695 is similar to H.R. 5629 in several respects. Both bills require follow-on biologic applicants to provide the same types of data to demonstrate the "biosimilarity" of follow-on biologics to a reference biologic, and both bills require the Secretary to issue guidelines establishing criteria for biosimilarity and interchangeability for each class of biologics.

The principal differences between S. 1695 and H.R. 5629 lie in the details of their patent provisions and their market exclusivity periods. S. 1695 provides that a follow-on biologic applicant must notify the reference biologic maker of its application within 20 days of acceptance of the application, and that the reference biologic maker must then notify the applicant within 60 days of any patent for which the reference biologic maker believes a claim of infringement "reasonably" could be asserted. The follow-on biologic applicant thereafter has 60 days to respond with a statement either that it will not market its follow-on biologic before the expiration of the noticed patent, or that the patent is not infringed, or is invalid or unenforceable.

Unlike H.R. 5629, S. 1695 goes on to impose further pre-suit obligations upon the follow-on biologic applicant and the reference biologic maker. Thus, upon receipt of an applicant's statement of non-infringement, or invalidity or unenforceability, the reference biologic maker must reply within 60 days with its own statement setting forth the detailed bases of its infringement claims. The follow-on biologic applicant and the reference biologic maker must then engage in 15 days of negotiation to agree upon which patents are at issue, or, if no agreement is reached, to exchange lists of patents that they believe should be in suit. The reference biologic maker thereafter has 30 days to sue on the agreed-upon or listed patents.

S. 1695 does not provide for an automatic stay of the approval of the follow-on biologic application if suit is brought, but it does require that the applicant provide 180 days notice to the reference biologic maker before the first commercial marketing of the follow-on biologic, and it allows the reference biologic maker to seek a preliminary injunction to prevent such marketing.

As for market exclusivity, S. 1695 makes the exclusivity period for a first follow-on biologic conditional upon the outcome of any patent litigation. Thus, a first follow-on biologic is entitled to an exclusivity period equal to the shorter of one year after the date of its first commercial marketing; 18 months after a final court decision in (or dismissal of) a patent suit brought by the reference biologic maker against the follow-on biologic applicant; 42 months after approval, if the suit is still pending after 36 months; or 18 months after approval, if the follow-on biologic applicant has not been sued. For the reference biologic, S. 1695 simply provides 12 years of market exclusivity, without any extensions for new therapeutic indications or pediatric use.

"The Patient Protection and Innovative Biologic Medicines Act," H.R. 1956

H.R. 1956 provides that a follow-on biologic that is "similar" to a reference biologic shall be approved (i) if the applicant shows that the follow-on biologic conforms to applicable product class guidelines, including providing data sufficient to demonstrate that it is safe, pure and potent; (ii) if the facility in which the follow-on biologic is made meets standards sufficient to ensure its safety, purity and potency; and (iii) if the applicant consents to inspection of the facility.

Unlike H.R. 5629 and S. 1695, which do not explicitly prescribe what should or should not be included in product class-specific guidelines for biosimilarity or interchangeability, H.R. 1956 demands that such guidelines include the following six categories of information, regardless of product class: (i) data demonstrating "consistency and robustness" in the manufacture of the active ingredient; (ii) data demonstrating "stability, compatibility and biological and physicochemical integrity" of the active ingredient; (iii) data "fully characterizing" the follow-on biologic at the level of both the active ingredient and finished product; (iv) data showing similar pharmacokinetic and immunogenic profiles for the follow-on and reference biologic; (v) data from clinical trials demonstrating similar safety, purity and potency profiles for the follow-on and reference biologic; (vi) and a plan for post-marketing safety monitoring. H.R. 1956 also requires the establishment of a separate "Similar Biological Products Advisory Committee," to advise the Secretary on the development and approval of follow-on biologics.

While H.R. 1956 emphasizes public health and safety concerns by specifying requirements for product class-specific guidance, it is simpler than the other bills in many respects. Under H.R. 1956, reference products are entitled to a market exclusivity period of 14 years, with a one year

extension available for new indications. There is no pediatric market exclusivity for the reference biologic, and no market exclusivity for the first follow-on biologic. Nor are there any provisions governing patent disclosures or patent litigation.

"The Access to Life Saving Medicine Act," H.R. 1038

H.R. 1038 incorporates many of the same concepts of H.R. 5629 and S. 1695, albeit using somewhat different nomenclature. Under H.R. 1038, an "abbreviated biological product application" (ABPA) for a follow-on biologic must include data showing that the follow-on biologic is "comparable" or "interchangeable" with the reference biologic. Under H.R. 1038, follow-on biologic is "comparable" if there is an absence of any clinical meaningful differences between the follow-on and reference biologic in terms of safety, purity and potency; it is "interchangeable" if it is comparable to, and can be expected to produce the same clinical result as, the reference biologic.

An ABPA under H.R. 1038 must include eight categories of information: (i) data showing that the follow-on biologic is comparable or interchangeable with the reference biologic; (ii) data showing that the follow-on biologic and reference biologic contain "highly similar principal molecular structural features"; (iii) data demonstrating that the follow-on and reference biologic use the same "mechanism of action"; (iv) information showing that the proposed therapeutic indications were previously approved for the reference biologic; (v) information showing that the route of administration, dosage form and strength of the follow-on product are the same as those of the reference biologic; (vi) data demonstrating that the manufacturing facility for the follow-on biologic meets sufficient standards to assure its safety, purity and potency; (vii) publicly-available information regarding the Secretary's previous determination that the reference biologic is safe, pure and potent; and (viii) any additional data or information in support of the ABPA.

H.R. 1038 provides a number of benefits to follow-on biologic applicants not seen in the other bills. It requires that the Secretary automatically consider certain "molecular structural features" to be "highly similar" – for example, two protein biological products "with differences in structure between them solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence." It requires the Secretary to meet with the applicant, upon the applicant's request, to discuss and agree upon the size and parameters of the studies necessary to obtain approval. Unlike most of the other bills, which set no express deadline for promulgating product class-specific guidance for biosimilarity or interchangeability, H.R. 1038 requires the Secretary to issue such guidance within a year after the enactment of the bill. And H.R. 1038 requires the Secretary to take final action on an application within a short timeframe: the earlier of eight months following the submission of the application, or 180 days after its receipt by the Secretary.

Like S. 1695, H.R. 1038 provides market exclusivity periods for the first follow-on biologic: the shorter of 180 days after the date of its first commercial marketing; one year after a final court decision in (or dismissal of) a patent suit brought by the reference biologic maker against the applicant; 36 months after approval, if such suit is still pending after 36 months; or one year after approval, if the applicant has not been sued. H.R. 1038 also expressly prohibits the reference biologic maker from selling any "rebranded" product during the market exclusivity period for the first follow-on biologic. Moreover, H.R. 1038 provides no market exclusivity period for reference biologics.

With regard to patents, H.R. 1038 gives the follow-on biologic applicant the right to request patent information from the reference biologic maker, who must respond within 60 days with a list of patents that concern the reference biologic. The applicant, by contrast, is not obligated to notify the reference biologic maker of its application, or of its non-infringement or invalidity or unenforceability contentions, and if it does, it may specify the judicial district in which it will consent to suit. The reference biologic maker thereafter has 45 days to bring suit, and must do so in the judicial district specified by the follow-on biologic applicant. As in S. 1695, H.R. 1038 does

not provide for an automatic stay of the approval of the follow-on biologic application if suit is brought.

"The Promoting Innovation and Access to Life-Saving Medicine Act," H.R. 1427

H.R. 1427 incorporates many of the features of H.R. 1038. The primary difference between H.R. 1427 and H.R. 1038 is that the former provides a five-year market exclusivity period for certain types of reference biologics, and a three-year market exclusivity period for new therapeutic indications. As noted above, H.R. 1038 provides no such market exclusivity periods.

H.R. 1427 also promulgates a new definition of "interchangeability." Under H.R. 1427, a follow-on biologic is deemed interchangeable if it is biosimilar to the reference biologic and, if it is intended to be administered more than once to a patient, the patient can be switched one or more times between the reference and follow-on biologic "without an expected increase in the risk of adverse effects," compared to the expected risks from continuing to use the reference biologic without such switching.

In other respects, H.R. 1427 is similar to H.R. 1038. H.R. 1427 requires the Secretary to issue product class-specific guidance within two years after enactment, and requires the Secretary to take final action on an application within the earlier of ten months following the submission of the application or 180 days after receipt by the Secretary. The market exclusivity periods for the first follow-on biologic, and the sequence and timing of patent disclosures under H.R. 1427 and H.R. 1038 are largely the same. However, unlike H.R. 1038, H.R. 1427 does not give the follow-on biologic applicant the right to specify the district in which the reference biologic maker can bring a patent infringement suit.

Common Themes

In broad strokes, the abbreviated approval processes proposed by these bills resemble the ANDA process provided under the Hatch-Waxman Act: each – except perhaps H.R. 1038 – attempts to strike a similar balance between the interests of reference drug makers and follow-on drug makers by providing the former with market exclusivity periods to allow them to recoup the considerable expense of developing and testing their reference biologics for clinical efficacy, while allowing the latter to forego such costly testing and simply requiring a demonstration of the "safety, purity and potency" of their follow-on biologics.

In addition to attempting to balance the interests of reference and follow-on biologic makers, the bills also attempt to grapple with challenging public health and safety issues. Unlike small-molecule drugs, the variability inherent to the structure and manufacture of biologics renders it difficult to determine whether any follow-on biologic truly is equivalent to its reference counterpart. In recognition of this variability, the bills do not demand a showing that follow-on biologics be equivalent to reference products, as required under the Hatch-Waxman Act. Instead, the bills require that follow-on biologics be "biosimilar" to, or "interchangeable" with, their reference counterparts, with an attempt to provide specific guidelines for determining biosimilarity or interchangeability on a product class-by-product class basis.

Given the growing public and political interest in follow-on biologics, the United States legislature may eventually establish an abbreviated approval process for this group of drugs. If it does, it will be interesting to see which features of the current bills make their way into the final legislation, and whether such measures will adequately address the economic, safety and patent issues to follow.

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[1] *Biologics Driving Growth To 2010*, Datamonitor Expert View, Jun. 22, 2006.

[2] During the time that this article was being finalized, Representative Eshoo on March 18, 2009 introduced another bill, "The Pathway for Biosimilars Act," H.R. 1548, 111th Cong. (2009). This bill includes biosimilarity requirements, market exclusivity periods and patent provisions that are largely the same as those of H.R. 5629.