Proposed Legislation Would Authorize FDA To Approve Follow-on Biologics

On September 29, 2006, Representatives Waxman (D-CA) and Brown (D-OH), and Senators Schumer (D-NY), Clinton (D-NY), Leahy (D-VT), and Stabenow (D-MI), introduced the "Access to Life-Saving Medicine Act" (hereafter, "the bill") (H.R. 6257; S. 4016). The bill would empower the Food and Drug Administration ("FDA") to approve abbreviated applications for "follow-on biologics" ("FOBs") that are "comparable" to, or "interchangeable" with, previously approved or so-called "reference" biological products. It also provides incentives for the development of FOBs that are "interchangeable" with innovators, imposes various limits on the level of protection afforded by an innovators' patents, and establishes certain limits on the extent to which FDA's decisions about an FOB may be challenged at both the administrative and judicial levels.

In its current form, the bill would provide manufacturers of FOBs with virtually everything they could wish for. For example, the bill provides FDA with substantial discretion to make a finding that an FOB is "comparable" to an approved biologic product while, at the same time, it removes the agency's discretion to find that two products are not comparable because there are slight differences between them. The bill also establishes strict time limits mandating FDA to make a decision on an application for an FOB. It would also limit the circumstances under which an innovator company may challenge FDA's decision on the application or seek to defend the patents governing the innovator's biologic product. Moreover, in sharp contrast to the current legislative scheme governing drugs, the bill would not afford innovator companies any period of marketing exclusivity whatsoever for their biologic products.

A brief summary of the bill's main provisions follow. For the full text of the bill, please click here.

The Meaning of a "Comparable" Biologic Product

Under the bill, a "comparable biological product" is one for which there are no "clinically meaningful differences" between the FOB and the innovator in terms of the safety, purity, and potency. To determine whether two products are comparable, FDA may consider (A) data derived from chemical, physical, and biological assays and other non-clinical laboratory studies and (B) data from any "necessary" clinical studies "sufficient to confirm safety, purity, and potency in one or more appropriate conditions of use." While the bill does not provide additional guidance on the comparability standard, or provide further details on what constitutes necessary clinical studies, it does require FDA to issue guidelines to be used by reviewers during the review and approval process.

"Thorough Characterization" of an FOB's Principal Molecular Structure

The bill provides that a manufacturer of an FOB should submit an "abbreviated comparable biological product application" that includes evidence that the FOB is comparable to the innovator product. Such evidence would include data demonstrating, by a "thorough characterization," that the two products contain "comparable principal molecular structural features," notwithstanding minor differences in heterogeneity profile, impurities, or degradation patterns. The term "thorough characterization" means an analysis of "structural features based upon appropriate analytical and functional testing sufficient to identify differences" between an FOB and reference product.

Mandated Findings of Comparability for Certain FOBs

While calling for tests to evaluate comparability, the bill also expressly concludes that certain molecular differences between products do not render the two products not comparable. Specifically, the bill directs FDA to find that following types of products contain comparable principal molecular features:

- Two protein biological products with differences in structure solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence;
- Two polysaccharide biological products with similar saccharide repeating units, even if the number of units differ and even if there are differences in post-polymerization modifications;
- Two glycosylated protein 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, and if they had similar saccharide repeating units, even if the number of units differ and even if there were differences in post-polymerization;
- Two polynucleotide biological products with identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars);
- Closely related, complex partly definable biological products with similar therapeutic intent, such as two live viral products for the same indication.

These provisions are largely taken from regulations that FDA has established to determine "sameness" for the purposes of the Orphan Drug Act.

Guidelines and Procedures to Govern Review of an FOB Application

The bill requires FDA to issue guidelines to be followed by those who review the applications. These guidelines are to encompass: promptness in reviewing applications; technical excellence; lack of bias and conflict of interest on the part of the reviewer; and knowledge of regulatory and scientific standards. The bill also establishes a binding mechanism whereby FDA and the applicant may meet and agree to the design and size of any studies necessary for review of an FOB application. Any agreement reached as a result of these meetings must be documented in the administrative record and may not be altered unless (1) the applicant so agrees in writing or (2) "a substantial scientific issue essential to determining the safety, purity, and potency of the biological product has been identified after the testing has begun."

FDA Approval of Comparability Applications and an Appeals Process

The bill establishes a general presumption that FDA will approve the application for the FOB license for all conditions of use of the innovator that share the same mechanism of action or, if the mechanism of action is unknown, for the conditions of use for which the applicant demonstrates comparability. This presumption *may* be overcome if FDA determines, among other things, that there is insufficient information to conclude that the FOB and the innovator contain comparable principal molecular structural features. Before FDA may disapprove an FOB application, however, it must give the applicant notice and an opportunity for a hearing. If the applicant avails itself of that hearing, the FDA must hold a hearing on an expedited basis and reach a final decision on the application shortly thereafter.

The bill would create strict time limits for FDA action on FOB application. Indeed, the bill expressly provides that such applications are subject to user fees and, accordingly, the deadlines for action on an application established under the Prescription Drug User Fee Act ("PDUFA"). The bill also directs that FDA must take action on an application either within eight months of submission of the application or within 180 days of the agency's filing of the application,

whichever is earlier. This "final action date" may, however, be extended if the sponsor and FDA agree to do so through a written instrument.

Limits on Challenges to FDA's Decisions on Comparability Applications

The bill establishes controls to prevent innovators from challenging the approval of an FOB application. For example, the bill prescribes certain time limits governing FDA's consideration of citizen petitions, and it requires the Commissioner of the agency to meet with the sponsor of an FOB if it decides that granting a petition is necessary to protect the public health. Curiously, elsewhere the bill declares that FDA may not fail to take action on an FOB application in response to a citizen petition.

The bill also sets forth a stringent standard under which a court may issue an injunction against FDA's issuance of a license, requiring an express finding based on clear and convincing evidence that the innovator (1) has prevailed on the merits of the complaint against the Secretary, (2) will suffer imminent and irreparable injury (constituting more than irrecoverable economic loss) that will threaten imminent destruction of the business, and (3) has an interest that outweighs the "overwhelming" general public interest in access to FOBs.

FDA Findings of "Interchangeable" Biologic Products

In addition to authorizing FDA to approve abbreviated applications governing comparability of biologic products, the bill also allows a manufacturer of an FOB to request a determination as to whether its product is "interchangeable" with the innovator product. The bill sets forth two requirements for interchangeability. The FOB must: (1) contain an active ingredient with principal molecular structure features comparable to the innovator; and (2) be expected to produce the same result as the innovator in any given patient in the condition of use for which both products are labeled. In the event that an FOB is found to be interchangeable, and in a fashion mirroring the AB rating process for drug products, FDA must publish a "therapeutic comparability evaluation code" essentially indicating whether the FOB can be substituted for the reference biological product.

Incentives for the Development of "Interchangeable" Products

The bill provides several incentives for the development of interchangeable products. Foremost among these is a provision that would extend at least six months of marketing exclusivity to a manufacturer that secures an "interchangeability" finding from FDA. Thus, upon a finding by FDA that an FOB is interchangeable with a reference product, the agency would be barred from approving a second or subsequent comparable biological product application. Moreover, the bill would prohibit any holder of a biologic product license from manufacturing, marketing, or distributing a "rebranded interchangeable biologic" product until this exclusivity expired. Additional incentives in the bill for the development of interchangeable products include tax credits for clinical testing expenses incurred in an attempt to establish that an FOB is interchangeable with an innovator. The bill would also allow a manufacturer of an FOB to include a denotation of interchangeability directly on the FOB's product label.

Provisions Relating to an Innovator's Patents

Finally, the bill outlines certain procedures to govern an innovator's patents on its biologic product. Specifically, the bill would allow manufacturers of FOBs to request from the innovator a list of all patents and licenses related to a particular product. Within 60 days, the innovator must provide that list, and for the two years following the request, the innovator must continually update the list to reflect any new patents or licenses relevant to the initial request. If the innovator fails to disclose the relevant patents and licenses upon the FOB's request, the innovator is foreclosed from enforcing the

patent or license. Moreover, the bill would prohibit an innovator from bringing actions for declarations of patent infringement, validity, or enforceability unless the patent was disclosed in response to the request.

On the basis of the patent notifications received from the innovator, a manufacturer of an FOB may, at any time, notify the innovator that it intends to challenge one or more of the patents. Such notice must contain (1) a description of the factual and legal bases for the FOB manufacturer's claim of invalidity or non-infringement and (2) an identification of the judicial district in which the FOB consents to be sued. The innovator then has 45 days to bring a patent enforcement action in the judicial district previously designated by the FOB manufacturer. In contrast to the current legislative scheme governing generic drugs, however, a lawsuit by the innovator would not bar FDA from approving the FOB manufacturer's application for up to 30 months.

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