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REGULATORY ROUNDUP

FDA Moves Forward with Biosimilars Guidance

On February 9 FDA released the first 3 in an anticipated series of long-awaited guidance documents for the development of biosimilars in the United States. These guidances are intended to help define the pathway for approval of biosimilars under an abbreviated licensure pathway allowed under section 351(k) of the Public Health Service Act (PHS Act) as established under the Biologics Competition and Innovation Act of 2009 (BPCI ACT).

BACKGROUND

FDA's intention with BPCI is roughly analogous to the regulatory pathways allowed for small molecules under the 1984 Waxman-Hatch provisions of the Federal Food, Drug and Cosmetic Act (FD&C) which allows for follow on products as generics under section 505 (j) or New Drug Applications (NDAs) under section 505 (b)(2). The approval pathway for follow on biologics is referred to as a section 351 (k) application and shares some characteristics of both the 505 (j) and 505 (b)(2) pathways. The biosimilar product to be approved under the 351 (k) route must reference a single biological product licensed under section 351 (a) of the PHS against which it is to be compared.

The BPCI provides a definition of biosimilar products, provides 12 years of marketing exclusivity and 4 years of data exclusivity to the innovator, and provides a complex

process patent dispute resolution and exclusivity related to this process. Interestingly, the BPCI also allows for pediatric exclusivity with the provision that a biosimilar contains a new active ingredient for the purposes of PREA.

BPCI has left FDA with some administrative hurdles to overcome in that the agency has not always been consistent with respect to approvals of protein products meeting the definition of biologics under the PHS Act. Several of these older proteins were approved under the FD&C Act with 5 years of exclusivity and an allowance for generic entry after patent protection and exclusivity exhaustion. BPCI provides for a transition period for Biologics approved under section 505 of the FD & C Act through March 23, 2020. In a similar effort to overcome issues related to which products will have 5 years exclusivity under FD & C and which products will have 12 years exclusivity under PHS, the regulatory jurisdiction of small peptides has been revised and refined. The new definition of protein and peptide defines "proteins" as alpha amino acid polymers of greater than 40 amino acids and "chemically synthesized polypeptides" as alpha amino acids made by chemical synthesis and containing fewer than 100 amino acids.

FDA GUIDANCES ON BIOSIMILARS

The 3 guidance documents now released for comment include:

- 1) *Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009;*
- 2) *Scientific Considerations in Demonstrating Biosimilarity for a Reference Product;* and
- 3) *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product.*

A 4th guidance, *Submission of Clinical Pharmacology Data as Evidence of Biosimilarity for Biologics and Protein Products* is scheduled for release by FDA later in 2012. In their current versions the 3 released guidances are identified as "draft" and stakeholder comments on the guidances were invited in the Federal Register Notices.

For a product to be a biosimilar it must be shown to be "highly similar" to an approved reference product and interchangeable in clinical practice. Minor differences in clinically inactive components are allowed but there can be no clinically meaningful differences in safety, purity and potency. In addition, some limited differences between the biosimilar and its reference product are allowed with respect to formulation, delivery system, route of administration and conditions of use. These allowable "differences" as

discussed in the biologics guidance should not be confused with the wide array of product differences available under the 505 (b)(2) type application process; the differences allowed per the 351 (k) path are limited to those that do not significantly affect interchangeability.

Applicant pursuing the biosimilar route under 351 (k) are required to show this similarity through analytical comparison, animal studies and clinical studies as required. The guidance stresses that some of the scientific considerations for demonstrating biosimilarity to the reference protein product will include an evaluation of the expression systems, manufacturing processes, physiochemical properties, functional activity, receptor binding and immunochemical properties, impurities and stability.

With respect to interchangeability, biosimilars are expected to have the same clinical effect as the reference product and with no greater change in safety and efficacy with repeated administration compared to the reference product, and must be substitutable without the intervention of healthcare professional. Interchangeability may not be possible to demonstrate at the time of BLA submission and may require some clinical comparison with the marketed product and evaluation of adverse events. Until such time as complete interchangeability is shown, new patients may be placed on the biosimilar but existing patients may not be switched to the biosimilar without healthcare provider intervention.

In the same vein, with respect to Pediatric exclusivity, the approved biosimilar is considered a new active ingredient until interchangeability with the reference is demonstrated and sponsors are encouraged to discuss plans for pediatric studies at the IND stage.

Key approaches emphasized in the guidances include a “risk-based totality of the evidence approach” and a “step-wise approach” in developing evidence to support biosimilarity. Sponsors and applicants are encouraged to formally seek FDA advice after initial work to demonstrate biosimilarity has been conducted and when FDA guidance with respect to additional studies needed to support the 351 (k) application will provide the greatest value. User Fees are required and be paid throughout the development stage.

USER FEES FOR BIOSIMILARS

In the United States user fees have traditionally been backloaded with no fees until submission of a NDA or BLA. FDA has proposed a very different scheme for biosimilar applicants in the Biosimilar User Fee Act of 2012. Biosimilar fees will begin with an upfront fee of 10% of the full BLA fee for that year at the time of initial request for FDA guidance with a 10% per year fee during each year of development. To discourage sponsors from moving in and out of development and avoiding yearly fees, reactivation fees will be levied for a product moving back into development after exit. FDA has explained the biosimilar fee structure as being required because, unlike traditionally approved products, there is no existing fund base to support biosimilar development agency efforts. After development is complete, biosimilars will pay the same application, product and establishment fees as other drugs and biologics.

HARMONIZATION ON THE GLOBAL HORIZON

FDA has been behind the EMA in the area of biosimilars or similar biological medicinal products with the first EMA guidance on the topic released as CHMP/437/04 followed by guidance on Non-clinical and Clinical issues, CHMP/BMWP/42832/2005 and

guidance on Quality issues, CHMP/BMWP/42832/2005. EMA currently has a number of product type specific biosimilar guidances. Now with 14 biosimilar approvals based on 3 reference products (Filgrastim, Epoetin, and Somatropin), EMA is updating and revisiting these guidances. In the spirit of harmonization, it is likely that there will be more similarities than differences between the US and EMA when the final guidances are finalized in the two regions. ●

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Regulatory Affairs for Biologics
October 22-25 (#12432)
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OTHER COURSES OF INTEREST IN DIA'S REGULATORY CURRICULUM:

Adverse Event Reporting Requirements: IND: Post-Marketing
3 part online series
July 9, 10, 11 (#12475)

Supplements and Other Changes to an Approved Application
1 part online series
July 30 (#12477)

Regulatory Affairs Part I: The IND Phase and Part II: The NDA Phase
August 13-16, Boston, MA (#12427)
November 12-15, Philadelphia, PA (#12428)

Navigating Chemistry, Manufacturing and Controls in Drug Development
September 10-11, Horsham, PA (#12436)

Regulatory Affairs Part I: The IND Phase
September 12-14, Horsham, PA (#12431)

Regulatory Affairs Part II: The NDA Phase
October 15-17, Horsham, PA (#12430)

European Regulatory Affairs
October 22-23, San Diego, CA (#12410)

Global Considerations for Regulatory Strategy Development
November 8-9, Horsham, PA (#12439)