Government Strategies Alert: FDA's Draft Guidance on Scientific Considerations in Demonstrating Biosimilarity

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Yesterday, the U.S. Food and Drug Administration released three draft guidance documents designed to assist industry in developing biosimilars and implementing the new abbreviated biologics approval pathway under section 351(k) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), signed into law in March 2010 as part of the Patient Protection and Affordable Care Act. This Client Alert provides a detailed summary of the draft guidance entitled "Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product." Please refer to our Client Alert entitled "FDA Releases Long-Awaited Draft Guidance on Biosimilar Product Development" for an overview of all three draft guidance documents.

FDA Tells Sponsors: "Step-by-Step" and "Totality of Evidence."

FDA states that the guidance applies to biosimilar applications filed under section 351(k) of the PHS Act, but "may be informative" for sponsors of NDAs filed under section 505(b)(2) of the FDC Act. Encouraging biosimilar sponsors to undertake a "*stepwise approach* to demonstrating biosimilarity" in which FDA will "consider the *totality of the evidence* provided by a sponsor," the draft guidance suggests that developing sufficient analytical, structural, and toxicological data could permit FDA and sponsor to pursue "a *selective and targeted approach*" to subsequent human pharmacokinetics (PK), pharmacodynamics (PD), clinical immunogenicity, and comparative clinical studies. (Guidance at 2, 7.)

To achieve these ends, and citing its discretionary authority to waive analytical, preclinical, and clinical studies, FDA recommends that biosimilar sponsors meet and have "early discussions" with the Agency "to present their product development plans and establish a schedule of milestones that will serve as landmarks for future discussions with the Agency" to "facilitate biosimilar development." (Guidance at 4, 21.)

Focus on Protein Complexity, Significance of Different Manufacturing Processes.

Citing the complexity and structural variance of proteins, including differences in primary amino acid sequence, side chain modifications, glycosylation, and protein folding, FDA rightly acknowledges that "even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency." (Guidance at 4.) Although the draft guidance is not as

explicit regarding the potential impact of small differences in manufacturing processes or materials ("e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria"), it does concede that "different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product."

Describing the necessity of "appropriate analytical testing, functional assays, and/or in some cases animal and/or clinical studies" in demonstrating that manufacturing differences do not adversely affect safety or effectiveness, FDA cites the 2005 International Conference on Harmonisation (ICH) guidance as an authoritative source describing the principles for demonstrating comparability of reference and biosimilar products. Yet FDA also suggests that demonstrating biosimilarity will only "*typically* ... be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer." (Guidance at 2, emphasis added.) Surprisingly, while acknowledging that a reference product manufacturer will have "extensive knowledge and information" that a biosimilar manufacturer will not, and that "more data and information will be needed to establish biosimilarity than would be needed" for establishing the comparability of the same manufacturer's products pre- and post-manufacturing change, the draft guidance is silent about what, if any, circumstances might lead to the demonstration of biosimilarity being *less* "complex" than a reference product manufacturer's demonstration of comparability.

Demonstrating Biosimilarity: "Step By Step."

Because a biosimilar application is intended to be "a demonstration of biosimilarity… but not to independently establish the safety and effectiveness of the proposed product" (Guidance at 7), FDA endorses using a step-wise strategy to allow biosimilar applicants (and potentially sponsors of 505(b)(2) NDAs) to "evaluate the extent to which there is *residual uncertainty*" after each step in comparing their "structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness." (Guidance at 2, 7, emphasis added.)

The first step is "extensive structural and functional characterization" of both reference and biosimilar products. (Guidance at 7.) It is significant that FDA acknowledges the limitations of current analytical characterization methods. The draft guidance describes the "advances in analytical sciences" that enable better protein characterization, but cautions that "[d]espite such significant improvements in analytical techniques, however, current analytical methodology may not be able to detect all relevant structural and functional differences between two proteins." (Guidance at 5.)

Citing the required elements for biosimilar applications under the statute, FDA confirms that analytical, preclinical, and clinical studies are presumptively necessary "to demonstrate biosimilarity *unless FDA determines an element unnecessary*." (Guidance at 5, emphasis added.) Such waivers are presumably

possible, according to FDA, to the extent that a biosimilar sponsor undertakes "rigorous structural and functional comparisons [that] show minimal or no difference[s] between the proposed product and the reference product," justifying what FDA terms "a *selective and targeted approach*" to subsequent "animal and/or clinical testing" – meaning the full range of animal toxicity studies, human PK and PD studies, clinical immunogenicity assessments, and, ultimately, human comparative clinical studies. (Guidance at 7, emphasis added, see also at 9.)

Clinical Evidence and a "Totality-of-the-Evidence" Approach.

FDA reiterates repeatedly in the draft guidance that it intends to use "a risk-based, *totality-of-the-evidence* approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product." (Guidance at 8.) The draft guidance cites the 1998 guidance on clinical evidence of effectiveness as providing "insight to the concept of the totality-of-the-evidence approach in a different content" which may "also be relevant in the design of a [biosimilar] development program." (Guidance at 2 n.4.)

Just as the 1998 draft guidance cites approvingly to FDA's 1972 review of previously licensed biologics, in which the waiver of "adequate and well-controlled studies" to demonstrate safety and effectiveness was warranted when such studies were "not … essential … when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2))" (1998 Guidance at 4), FDA indicates clearly it will employ the "totality of evidence" approach to supplant the conduct of extensive or comparative clinical studies whenever scientifically justified by the sponsor's preceding analytical and preclinical work.

However, because the statute requires a demonstration that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (section 351(i)(2)(B) of the PHS Act), the draft guidance acknowledges that "[i]n general, the clinical program for a 351(k) application *must* include a clinical study or studies (including an assessment of immunogenicity and PK or PD)"- the "scope and magnitude of such studies depend[ing] on the extent of residual uncertainty about the biosimilarity of the two products after conducting structural and functional characterization and possible animal studies," as well as "the frequency and severity of safety risks and other safety and effectiveness concerns for the reference product." (Guidance at 12, emphasis added.)

Following stepped completion of product characterization, animal studies, and human PK/PD studies, the draft guidance recommends head-to-head studies for the assessment of clinical immunogenicity to establish that "there are no clinically meaningful differences in immune response between a proposed product and the reference product," which FDA describes as "a key element in the demonstration of biosimilarity." (Guidance at 14.) Finally, if "residual uncertainties" about biosimilarity remain, comparative

safety and effectiveness studies will be required; FDA provides a series of points to consider in designing such studies, including:

1. The nature and complexity of the reference product, the extensiveness of structural and functional characterization, and the findings and limitations of comparative structural, functional, and nonclinical testing, including the extent of observed differences;

2. The extent to which differences in structure, function and nonclinical pharmacology and toxicology predict differences in clinical outcomes, as well as the degree of understanding of the MOA of the reference product and disease pathology;

3. The extent to which human PK or PD predicts clinical outcomes (e.g., PD measures known to be clinically relevant to effectiveness);

4. The extent of clinical experience with the reference product and its therapeutic class, including the safety and risk/benefit profile (e.g., whether there is a low potential for off-target adverse events), and appropriate endpoints and biomarkers for safety and effectiveness (e.g., availability of established, sensitive clinical endpoints); and

5. The extent of any clinical experience with the proposed product. (Guidance at 16.)

Clinical Extrapolation, Non-U.S. Reference Products, Labeling and Post-Market Study.

The draft guidance also touches on the possibility of allowing biosimilar sponsors to use non-U.S.-licensed reference products if this can be scientifically justified on the basis of bridging studies, other "adequate data or information," and discussions with FDA. (Guidance at 6.) The draft guidance cites again to the ICH guidance, as issued by FDA in 1998, in relation to bridging studies. The draft guidance also suggests that extrapolation from one approved indication of use to another for which the reference product is licensed would require "sufficient scientific justification." (Guidance at 19.) Finally, the draft guidance briefly discusses the need for "adequate" post-market mechanisms to differentiate between all - but particularly novel - adverse events associated with the biosimilar and reference products. FDA also notes in passing that biosimilar labeling must include sufficient information for providers to understand that the new product is biosimilar to, and, as appropriate, is interchangeable or not interchangeable with, the reference product. (Guidance at 21.)