FDA Discusses Initial Considerations for Biosimilar Guidance Documents

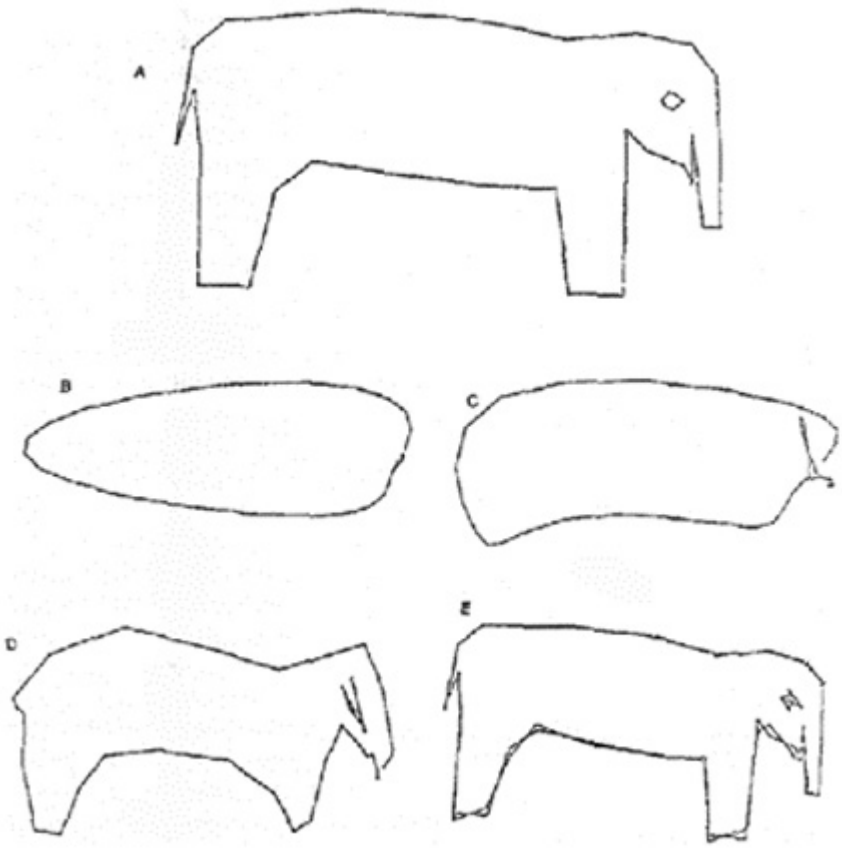
By James DeGiulio -- February 27, 2012

Earlier this month, the U.S. Food and Drug Administration recently published its long-awaited guidance documents on Biosimilars/Biosimilarity (*see* "FDA Publishes Draft Guidelines for Biosimilar Product Development" and "More on FDA Draft Guidelines for "Follow-on" Biologic Drug Approval Pathway"). Some of the first public statements made by the FDA regarding these newly-published biosimilar guidance documents were made in a February 15 presentation by Dr. Rachel E. Sherman, Associate Director for Medical Policy at the Center for Drug Evaluation and Research. Dr. Sherman moved through the guidance documents quickly, without exploring any particular issues in detail, but there were several notable messages in her presentation that expand beyond the text of the statute and the guidance documents.

Dr. Sherman (at left) opened by noting that the presentation represented the first opportunity for the FDA to interact with the audience targeted by the guidance documents. The FDA has continually emphasized the guidances' wide target audience, comprising consumers (patients), patient advocacy groups, health care providers, as well as those in the pharmaceutical industry. The FDA's effort to draft the guidelines so as to be understandable to the average consumer may partially explain the minimal specific requirements throughout the guidance documents. The presentation continued with an overview of the Biologics Price Competition and Innovation Act (BPCIA) and its effects on the approval of biologics under the current statutory framework (PHSA and FFDCA). The BPCIA will consolidate the approval of all biologics, as the FDA strongly disapproves the current two-option framework, allowing certain biologics to be approved under either the PHSA or the FFDCA. The transition to a single approval pathway under the BPCIA is expected to be completed by 2020.

The FDA next responded to the criticism that the abbreviated approval pathway does not promote innovation. The FDA considers the biosimilarity approval pathway to be innovative because each analytical study required of biosimilar applicants will advance the field of knowledge regarding the molecule of interest. For example, a biosimilar applicant may have to characterize the function of particular amino acids in binding domains of its biosimilar product, thus providing date to others in the field as to the homology requirements of its biologic. The FDA would then make a determination of biosimilarity, and consider whether the FDA would require additional testing/studies to support a finding of biosimilarity. This determination is presented using an entertaining analogy. Dr. Sherman's presentation contains a line drawing of an elephant (below), where each line represents an analytical or clinical study performed by the biosimilar applicant (Wel J. "Least squares fitting of an elephant." *Chemtech* Feb. 128-29 (1975)). The FDA will have to compare the reference product (figure A) with the biosimilar products (figures B-E) to determine what level of detail is required for a determination of

biosimilarity (whether the drawing is an elephant or not). The biosimilar applicant will attempt to draw the minimum amount of lines such that the FDA can make a finding that the biological product is biosimilar to the reference product (elephant). The FDA will not permit any "tracing" of the lines in the drawing, as these attributes of the biosimilar are already known. The FDA considers repetition of any animal or human studies to be unethical, therefore they must be avoided. Each test or study must add something to the whole body of evidence. This elephant analogy is also used to define "fingerprint" studies, which may tell the biosimilar applicant at an early stage that its product will not qualify for approval under 351(k) (*e.g.*, if early lines in the drawing show a beak or fins).



Animal analogies aside, Dr. Sherman reiterated the importance of meeting with the FDA "early and often" during biosimilar development. By issuing the guidance documents, the FDA only intended to address the highest priority uncertainty in the biosimilarity standards. Only the minimum amount of information was included to provide biosimilar applicants with some level of expectation regarding the minimum studies required prior to contacting the FDA. The FDA expects the minimum characterization outlined in the guidance documents to be performed up front, and then the expectation is that the biosimilar applicant will contact the FDA armed with this subset of data. The FDA has every intention of, essentially, making up the standards as it goes, and is strongly encouraging anyone who is considering entering the biosimilar space to set up an FDA meeting as soon as possible to discuss.

Perhaps most interesting was the FDA's status report on the current status of received biosimilar proposals. According to Dr. Sherman, the FDA has currently received 35 pre-IND meeting requests for proposed biosimilar products, corresponding to eleven reference products. Of course, the applicants and the corresponding reference products were not disclosed. However, for comparison, the EU has approved fourteen biosimilar products, which correspond to three reference products: Filgrastim (Amgen's Neupogen), Epoetin (Amgen's Epogen), and Somatropin (Genentech's Nutropin). From this status report, it appears that many of the biosimilar applicants and sponsors are already aggressively meeting with the FDA regarding the future of their particular biological products. Other proposals have gone even farther, for there have been 21 pre-IND sponsor meetings held as of February 15, and the FDA has received nine IND applications thus far.

Dr. Sherman commented briefly on interchangeability, confirming that the FDA had not come to any type of conclusions on the standards for interchangeability. In contrast to the "biosimilarity" standard, the FDA will not be able to rely on the EU guidelines as a model for determining interchangeability, for the EU does not have a comparable provision in its biosimilar regulatory pathway. The FDA will have to start from scratch in generating this standard, which is unlikely to be clarified anytime soon. The presentation did note that, under the FDA's step-by-step analysis, the agency would have to first make a finding of biosimilarity before any requests for interchangeability would be accepted. So the clock on a FDA interchangeability guidance won't start ticking until after the first biologic is approved as a biosimilar. Unsurprisingly, Dr. Sherman stated that the FDA will "invariably" require at least one human clinical study to show interchangeability once biosimilarity is established.

Finally, Dr. Sherman indicated that the FDA intends to publish future guidance documents on several issues directed to biosimilars (beyond interchangeability): Package inserts; Product Naming and Pharmacovigilance; and an Orange Book-like publication listing which products are biosimilar and/or interchangeable for a particular reference product.

For those that are interested in viewing the full webinar, a link to the webinar can be found on the FDA's Biosimilars webpage.