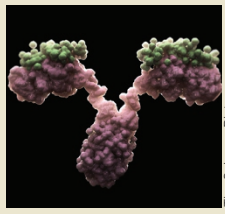
FDA sets hierarchy for biosimilars evidence

On May 13, after years in the making, the US Food and Drug Administration (FDA) issued a draft guidance on biosimilars categorizing the clinical pharmacological data a company will have to submit as evidence of biosimilarity. In the guidance, the agency sets out the type and amount of clinical pharmacological information the agency could see to approve a copy of a biologic medicine. It starts with studies of structure-activity relationships, then moves to nonclinical data, pharmacokinetic and pharmacodynamic data, clinical immunogenicity studies, and if needed, safety and efficacy data. This step-wise thinking is "to be expected," says attorney Paul Radensky of McDermott Will & Emery in Washington, DC—and mirrors the data expected for approval of generics. "It's the natural hierarchy you would think about in terms of the information you would have to help characterize one product versus another," he says.

This provisional guidance evolved from a trio of drafts from February 2012, which marked scientific and quality considerations for biosimilars and addressed the procedures for their implementation under the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which is part of the Patient Protection and Affordable Care Act. The statute requires drug makers to show no meaningful differences between the copies of a biologic medicine and its approved drug.

The latest proposal drills deeper than in earlier guidances. Depending on the differences that show up when comparing a biosimilar candidate to its reference product, the FDA will categorize whether a product candidate is highly similar with fingerprint-like similarity, highly similar, similar (when analyses were inconclusive, and demanding further work) or not similar. The proposed hierarchy of pharmacology evidence and the ensuing categories "show maturation in thinking about the process they are going to use and the criteria and how they will organize the answers people are going to get back," Radensky says.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Fingerprint-like similarity is the gold standard. It is defined through integrated, multiparameter analyses, and allows a very high level of confidence in the analytical similarity of the proposed biosimilar and the reference product. "It's not clear from the guidance document that fingerprint-like will automatically translate into interchangeability (that is, that the biosimilar product can substitute for the branded reference product)," says Radensky. "But it seems to track with that," he says. "It was helpful to see their thinking in terms of the hierarchy of determinations of similarity."

The first cases should reach FDA next year, and candidates such as relatively small and well-characterized recombinant peptide chains (e.g., erythropoietin alfa) could make it through review relatively quickly. Monoclonal antibodies and some naturally sourced biologics with more variability will move more slowly, Radensky says. "I think it will be very much a class-by-class determination," he says. But left unsaid, says James C. Shehan of Hyman, Phelps & McNamara, writing on the law firm's *FDA/Law Blog*, is what [other draft guidance] FDA will issue next relevant to this approval process. The FDA is requesting industry feedback until August 12.

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