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FDA Sheds New Light On Biosimilars Approval Pathway

By **Jeff Overley**

Law360, New York (May 13, 2014, 9:37 PM ET) -- The U.S. Food and Drug Administration on Tuesday released its most detailed guidance yet on evidence needed to prove that biosimilars are close matches of their brand-name counterparts, providing more clarity on the scientific expectations that will determine the cost of bringing generic biologics to market.

In the new guidance, regulators focused on how drugmakers can demonstrate biosimilarity through so-called clinical pharmacology — relatively early research in small groups of human subjects. The FDA had broached the subject two years ago in guidance on scientific considerations related to biosimilars, but Tuesday's document drilled down much more deeply.

"It's an increasingly sophisticated presentation and understanding by FDA of the requirement for showing similarity," said Stephen Paul Mahinka of Morgan Lewis & Bockius LLP.

The FDA's scientific standards will decide how much drugmakers have to spend to get biosimilars approved, and in turn, how much drugmakers charge for the products. That's especially relevant because brand-name biologics routinely carry five-figure or six-figure annual price tags.

Experts say the guidance's granularity is a reflection of the FDA's ongoing interactions with manufacturers that are eager to take advantage of a biosimilars approval pathway created by the Affordable Care Act in 2010. An agency spokeswoman on Tuesday said there had been 55 meetings with drugmakers regarding 13 products as of late March.

A new theme in Tuesday's guidance was the FDA's description of four categories of similarity — not similar, similar, highly similar and highly similar with fingerprint-like similarity. How a product is categorized will be decided based on data about a biosimilar's attributes, and the degree of similarity will determine the extent to which further study is required, regulators said.

"Which bucket they end up putting you in is, I think, going to have a very significant effect on what data they're going to want to see next," said Paul A. Calvo of Sterne Kessler Goldstein & Fox PLLC.

The fourth category of fingerprint-like similarity is a reference to similarity that's gauged by comprehensive and ultra-precise analyses of a biosimilar's molecules. That's important because organism-derived biologics are more complex than traditional drugs made from synthetic chemicals, and small differences could potentially render products ineffective or unsafe.

Moreover, the fingerprint category seemingly relates to the concept of interchangeability, which is the highest level of biosimilarity and is viewed as essential to convincing doctors and patients to substitute biosimilars for brand-name versions. Although the FDA hasn't yet explained what will be required to achieve interchangeability, experts called the discussion of fingerprint-like similarity a window into the agency's thought process.

"You would think that if you could show that, you're well on your way to interchangeability," Mahinka said.

The guidance's description of how levels of similarity affect the amount of additional data that the FDA will require also underscored the "stepwise" approach that biosimilars makers are expected to take. Under that approach, a drugmaker performs research, identifies outstanding areas of uncertainty, then tailors future research to tie up loose ends.

With that in mind, the FDA seemed to be reinforcing prior statements about the need to consult early and often with regulators about how a product is progressing and how study designs should be tweaked, Calvo said.

"The FDA has been really trying to hammer home that, 'We want this to be a process where you're going to keep coming back in, and we're going to tell you what to do next,'" he said.

Multiple portions of the guidance described the FDA's preferred study methods while also carving out possible exceptions. It's not unusual for the agency to afford that sort of leeway because it doesn't want to invite disputes by imposing ironclad rules, but the latitude could be especially important in some areas.

As one example, several lawyers pointed to a provision allowing similarity to be demonstrated in part through comparisons to drugs not licensed for sale in the U.S. That could be helpful because Europe and Japan have moved more rapidly to approve biosimilars, which means data from earlier studies could be given to the FDA instead of doing everything over again.

"It's so cumbersome to redo everything," said William J. Simmons, a biosimilars expert at Simmons IP Law PLLC. "I think they're trying to be a little bit generous in terms of what kinds of data can be brought to their attention."

Another potentially helpful area of the new guidance has to do with pharmacokinetics, which looks at how a drug is dispersed and broken down in the human body, and pharmacodynamics, which looks at how the body responds to a drug. Traditionally, a generic is expected to fall within a range of 80 percent to 125 percent with respect to those attributes, meaning that its measurements are no more than a little lower or a little higher than those recorded for a brand-name drug.

But the FDA on Tuesday said that missing those targets wouldn't necessarily disqualify a product so long as a manufacturer could prove that the differences aren't clinically meaningful.

"It's a little broader range to be able to show biosimilarity," said Peter S. Reichertz of Sheppard Mullin Richter & Hampton LLP.

Despite the level of detail in Tuesday's guidance, key issues are still unresolved with respect to interchangeability, labeling and naming of biosimilars, as well as earlier guidances that haven't been

finalized. And with that in mind, experts said that Tuesday's guidance does only so much to fulfill the vision of lower-cost biologics that was enshrined in the ACA back in 2010.

"A little over four years later, and nothing is even close to approval," said Timothy J. Shea Jr. of Sterne Kessler. "So again, this reflects a very careful, cautious approach by the FDA."

--Editing by Jeremy Barker and Philip Shea.
