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3 Takeaways As FDA Dishes On Interchangeable Biosimilars

By **Jeff Overley**

Law360, New York (January 17, 2017, 9:32 PM EST) -- The U.S. Food and Drug Administration's long-awaited guidance on biosimilar interchangeability contains lots of flexible language that means the coveted designation could be more attainable for some products than others, experts say.

The guidance has been anticipated since 2010, when the Affordable Care Act created a special pathway for biosimilar approval. It's hugely important because the first interchangeable biosimilar of a given biologic gets temporary market exclusivity. In addition, interchangeability allows pharmacies to automatically substitute lower-cost biosimilars, just as they have long substituted traditional generics that help Americans save billions of dollars annually.

Tuesday's guidance contained approval standards that are likely to vary significantly from product to product, clearing the road to interchangeability for some and creating high hurdles for others, according to experts.

"There's a lot of flexibility in this guidance," Hogan Lovells partner David M. Fox said. "There's a lot of room to calibrate the interchangeability program to each particular product."

Leah Christl, head of biosimilars at the FDA, said as much in a blog post on Tuesday, writing that "the data needed to demonstrate interchangeability are ... determined on a case-by-case basis."

Here are three takeaways from Tuesday's draft guidance.

Evidence Needed for All Indications

One of the most important sections of the guidance said that interchangeability should be demonstrated in every indication held by an innovator product that a biosimilar is copying. That's significant because innovator products often accrue numerous indications.

"If you're not willing to say you're interchangeable for all of these approved indications, then you're probably not going to be meeting that high interchangeability standard," Duane Morris LLP partner Kevin M. Nelson said.

However, the FDA said that clinical research might only be required for one of those indications, and that the research findings can potentially be extrapolated to the remaining indications. That's a less demanding approach than AbbVie Inc. requested in a prominent citizen petition — which was denied

Tuesday — arguing that every indication should be subject to clinical trials before any interchangeability designation is granted.

“Everyone was worried you'd have to show full-blown clinical trials for all indications, and that would just be so cost-prohibitive that smaller biosimilar manufacturers would be unable to meet that hurdle,” Morgan Lewis & Bockius LLP partner Christopher J. Betti said.

At the same time, extrapolation isn’t easy. Tuesday’s guidance spelled out precise requirements for showing that extrapolation is scientifically justified, including details on immune system reactions and a product’s mechanism of action in different types of patients.

“It’s not as onerous as what AbbVie is [requesting], but it does add an extra layer,” Goodwin Procter LLP partner Scott Lassman said.

As with many aspects of biosimilar development, experts said that the requirement may seem more challenging in the short term, and that it may become more manageable for biosimilar makers as the FDA gets increasingly comfortable approving the copycat products.

“It’s a little bit more daunting, but not so much from a scientific standpoint [as] from an FDA comfort level,” Nelson said. “When FDA gets more comfortable with interchangeability, I think that extrapolation showing might be easier.”

Product-Specific Factors Cited

Tuesday’s guidance described product-specific factors that will determine what sort of evidence is needed to demonstrate interchangeability. The guidance stressed that analytical laboratory data could play a key role in showing that a biosimilar is virtually identical to an innovator product, thus reducing the scope of clinical studies.

“A clinically relevant and thus meaningful fingerprint-like characterization may reduce residual uncertainty regarding interchangeability and may lead to a more selective and targeted approach to the clinical studies necessary to demonstrate interchangeability,” the guidance said.

Lassman called that a big win for biosimilars. “The way the FDA laid it out, the interchangeability requirements could be a lot less onerous than I think a lot of people expected,” he said.

Notably, for biosimilars with fingerprint-like similarity and satisfactory clinical data, the FDA said it may be willing to recognize interchangeability without first awarding biosimilarity and then waiting for post-market data. That would be a departure from the status quo, where biosimilars are expected to take a two-step approach of getting baseline approval and then coming back later for the interchangeability designation.

Experts say the agency probably won’t make that departure right away, but that it could do so fairly soon.

“Practically speaking, for at least the first couple of years, they’re going to require you to get approved as a biosimilar first,” Lassman said. “But I think they’re giving themselves flexibility ... and looking for the right product where it would be appropriate that they could be comfortable approving something as an interchangeable without having the post-market experience.”

Switching Studies Fleshed Out

Much of the guidance focused on clinical studies in which patients are switched between a biosimilar and its innovator counterpart to determine whether they are in fact interchangeable.

In one notable section, the FDA said it doesn't want biosimilars compared with non-U.S. versions of innovator biologics. That's a break with how baseline biosimilarity is established: the FDA has allowed for comparisons to non-U.S. products, so long as "bridging" can prove that the comparison would be relevant for a U.S. product.

Attorneys said that the refusal is reasonable, given that bridging introduces one more factor into the analysis and complicates matters a bit.

"It seemed like an appropriately conservative position," Fox said. "I think they're minimizing the number of variables."

The guidance also said that clinical studies should include at least three switches. That means a patient will have to start using one product, switch to another, then switch back, and then switch back yet again. The provision means that studies will take longer and cost more money.

"I read that and thought that it was a bit much," Betti said. "I'm not sure if they have any empirical data to support the number."

However, in a victory for biosimilars, the FDA said that clinical studies should mainly focus on how products function in the body — so-called pharmacokinetics and pharmacodynamics, or PK and PD. That's quicker and easier to study than clinical endpoints that concretely measure a product's effectiveness.

"For the switching studies, they talked about PK and PD endpoints and really relying more on those rather than clinical endpoints, so I think that's going to really helpful as well," Lassman said.

--Editing by Philip Shea and Brian Baresch.
