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Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Comment on "Considerations in Demonstrating Interchangeability With a Reference Product: Guidance for Industry"; **FDA-2017-D-0154**

Submitted electronically via www.regulations.gov

March 17, 2017

Acting Commissioner Ostroff:

As the Coalition of State Rheumatology Organizations (CSRO), part of our mission is to advocate for access to the highest quality medical care for rheumatic disease patients with autoimmune inflammatory and degenerative diseases. As patient and physician advocates, we have been deeply involved in the debate surrounding implementation of the Biologics Price Competition and Innovation Act (BPCIA) and wish to provide you with our input on the Food and Drug Administration's (FDA) "Considerations in Demonstrating Interchangeability with a Reference Product: Guidance for Industry" ("guidance").

The guidance repeats the BPCIA's general principles that any interchangeable biosimilar must first prove biosimilarity and can be expected "to produce the same clinical result as the reference product in any given patient." Additionally, there can be no increased risk in safety or diminished efficacy as a result of switching between the interchangeable biosimilar and the reference product.

We applaud FDA's release of this long-awaited guidance and offer the following thoughts.

First, we thank FDA for stating unequivocally that interchangeability cannot be established via analytical data alone. Rather, the analytical data should guide the necessary clinical studies. We agree that these products are too complex and the unknown risk from switching is too great to rely only on analytics. However, the draft guidance is open-ended as to what data would be required, noting instead that "the data and information necessary to support a demonstration of interchangeability needs to be considered on a case-by-case basis." This does not provide patients and providers with much comfort. We urge the FDA to outline a minimum data package that would apply across all products. This would provide a "floor" for clinical studies on which FDA could build on a case-by-case basis, should the agency feel that additional data is required for a particular product or population.

Second, with regard to post-marketing surveillance, the guidance notes that "post-marketing data collected from products first licensed and marketed as a biosimilar, without corresponding data derived from an appropriately designed, prospective, controlled switching study or studies, generally would not be sufficient to support a demonstration of interchangeability." We agree with this position. The alternative approach of allowing manufacturers to rely on post-market data alone to establish interchangeability would create little incentive for a manufacturer to ever invest resources in controlled trials to establish interchangeability. After all, the aggressive behavior of payers in the marketplace would likely provide a manufacturer with a free switching trial for its biosimilar, based on which the manufacturer could then return to FDA and request the interchangeability designation. Additionally, post-marketing data would not necessarily be totally objective or free of confounding background. These data for purposes of analytics would be difficult to interpret, given the wide variability of patients' presentations, variable serologies, and comorbid conditions. By their very nature, double blind clinical trials would control for these variables and produce more valid data. For these reasons, we strongly support FDA's approach of leveraging post-market data to inform what clinical data is required to show interchangeability.

Third, FDA states that sponsors will be expected to conduct a switching study or studies evaluating changes in treatment that result in two or more alternating exposures to the proposed interchangeable product and the reference product. We strongly support this, but again urge FDA to provide more clarity on exactly what such a study or studies would entail. While FDA provides some guidance on endpoints and design, the guidance is relatively vague and, indeed, notes its "flexible approach." At a minimum, we urge FDA to standardize immunogenicity testing of biosimilar agents across all disease conditions as well as control subjects.

Fourth, we are concerned about FDA's proposal to allow a sponsor who has established interchangeability for one indication to seek licensure as an interchangeable product for additional indications. One of the hallmarks of biologic medicines is that they are often approved for a variety of conditions that have very different patient populations: for example, inflammatory bowel disease and rheumatoid arthritis. The differences in the pathophysiologic mechanisms of disease and patient populations in these two diseases alone warrant a cautionary approach. This is why Health Canada, when it first approved a biosimilar for infliximab, excluded inflammatory bowel disease from its list of approved indications. The reason was "the absence of clinical studies in IBD."[1] We urge FDA to take a similarly cautious approach and require some clinical data for all indications especially when the pathophysiologic mechanisms involved in the diseases are clearly different. We acknowledge this may create challenges when a biosimilar is interchangeable for, say, 5 out of 7 indications, but not the remaining two. However, the label could clearly delineate which indications are interchangeable, and which are not.

[1] Available: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php#a5.

Fifth, the guidance notes FDA's preference for the use of actual patients in switching studies, as opposed to healthy subjects. We appreciate and agree with FDA's rationale behind this preference, which is that any switching study should mimic the "real world" as much as possible. However, we are concerned that, for rare diseases, the need to find real patients may create a hurdle that is unreachable for manufacturers. We suggest that FDA establish use of real patients as a presumptive requirement, but allow manufacturers to enroll healthy subjects where appropriate, such as in the case of a product seeking licensure for a rare disease.

Finally, FDA states that "using a non-U.S.-licensed comparator product generally would not be appropriate in a switching study[.]" We strongly agree. As FDA explains, there may be differences between U.S. and international products, and even among international products. While these differences may be subtle, they could be sufficient to render them useless for a switching study designed to prove interchangeability for U.S. patients. We urge FDA to maintain this position.

In closing, we thank the agency for proposing this critical guidance and, while there are some areas of concern as outlined above, we believe the guidance reflects a thoughtful approach. Please do not hesitate to contact me or our D.C. staff, should you have any questions or require additional information: Judith Gorsuch, jgorsuch@hhs.com.

Sincerely,

Michael Schweitz, M.D.
Federal Advocacy Chair
Coalition of State Rheumatology Organizations