May 18, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Considerations in Demonstrating Interchangeability With a Reference Product: Draft Guidance for Industry; Availability

Dear Commissioner Gottlieb,

All of the undersigned groups share the FDA's deep commitment to the development of a robust biosimilars market for patients, and greatly appreciate all the work the agency has done in creating certainty around the approval pathway created by the Biologics Price Competition and Innovation Act (BPCIA), including the long anticipated proposed guidance detailing the requirements of obtaining an interchangeability designation for a biosimilar. This latest guidance is a critical piece unique to the American market that will help foster access to these medicines, maximizing savings for patients and the U.S. healthcare system. We believe that providing biosimilar manufacturers as much clarity and flexibility as possible, while maintaining the FDA's high standards for patient safety, is the appropriate guiding principle for agency decisions around specific provisions of the proposal. We are generally supportive of the draft guidance, but wish to point out a few areas for consideration. Most importantly, FDA should permit a designation of biosimilarity parallel to granting an interchangeability designation if the applicant seeks both at the time of initial approval. Any applications which demonstrate that the product can be expected to produce "the same clinical results as the reference product in any given patient," as required by statute should be deemed interchangeable.

Totality of the Evidence Standard

We appreciate the agency maintaining the "totality of the evidence" standard and "stepwise approach" it has used in making biosimilarity decisions to date. We believe it is important that the agency, when appropriate, be able to accept various forms of clinical and analytical evidence presented by the sponsor of a biosimilar application. By looking at applications on a case-by-case basis, the agency ensures that it will be able to consider new methods of clinical and analytical characterization as they are developed and presented. The BPCIA does not create proscriptive guidelines on what evidence the agency must consider, and this approach allows the agency to work with applicants to ensure that sufficient information is provided to reviewers. It also ensures the BPCIA pathway does not become so burdensome that it effectively undermines the purpose of the BPCIA, to create an abbreviated pathway that is less costly to navigate so that manufacturers can bring lower-cost competitors to brand name biologics.

- POSITION: Support. The totality of evidence approach will provide the Agency the flexibility necessary to evaluate biologic products as appropriate including structural complexity, toxicity, and immunogenicity risk. The FDA should be able to adjust its review standards to account for the high level of complexity and variability in these products.

Extrapolation of Data in Support of Interchangeability

We also believe that it is scientifically and legally appropriate for the agency to continue to allow biosimilar manufacturers to extrapolate data from one indication to other indications, when appropriate. Interchangeable biosimilars should be treated by the agency in the same manner as it has done for multiple applications seeking

biosimilar approvals. While some brand manufacturers have claimed that increased variability and increased immunogenicity of biologics should preclude this practice, much of this variability can be due to product-specific and patient-specific factors. As the agency has demonstrated in the past, depending on numerous factors, it is entirely reasonable for the agency to rely on analytical characterization when appropriate. An interchangeable designation should not preclude the agency from extrapolating when there is sufficient analytical data to assure reviewers that the biosimilar product will meet the legal standard for approval.

- POSITION: Support. The extrapolation of data will be adequate to demonstrate interchangeability for some or all of the conditions of use of the reference product, subject to sufficient scientific justification. We do not support an interchangeability pathway that requires switching studies for each condition of use of the reference product, as this places an undue burden on sponsors and delays demonstration of interchangeability.

Postmarketing Surveillance and Studies

We agree with the agency that postmarketing surveillance and studies can provide valuable evidence for a subsequent review for interchangeability. This type of real-world evidence may already exist for many products currently available in other markets; and therefore, can provide important insight into the effects of patient switching, comparative effectiveness, and other factors.

We would note however, that we would not support the agency requiring postmarket studies for a subsequent interchangeability designation. While certainly valuable for products that choose to pursue an interchangeability designation, once they have already been introduced to the market, a biosimilar manufacturer should not be precluded from building a submission that properly demonstrates interchangeability prior to distributing a product. It is not unreasonable to expect that some sponsors may wish to enter their products into the market as interchangeables, similar to the small-molecule market.

- POSITION: Support, however, while maintaining the Agency's standards for biological products, we urge the FDA not to *require* biosimilar approval and postmarket surveillance data prior to designating a product as interchangeable. Sponsors should have the opportunity to seek FDA approval of an interchangeable biosimilar product without such data when it is supported by the totality of evidence.

Use of Foreign Reference Product

Finally, we do not agree with the agency's decision to require an applicant seeking an interchangeable designation to rely on switching studies exclusively using U.S.-licensed reference product. There is no scientifically justifiable distinction between reference products acquired in the U. S. and those licensed in other comparable markets. This requirement will create significant burden on biosimilar manufacturers pursuing switching studies, who can often acquire equivalent samples of reference products from other highly regulated markets at much lower costs. Requiring switching studies to rely on more expense, U.S.-licensed reference product samples over less costly samples from other markets, without any real clinical difference between the two will simply create additional, unnecessary barriers to entry for biosimilar developers.

- POSITION: Oppose. This requirement places unnecessary burdens and costs on biosimilar sponsors. We urge the FDA to align its policy in this guidance with its policy for the 351(k) pathway, where it is acceptable to use a non US-licensed reference product when there is a bridging study to the US-licensed product.

Conclusion

We support the biosimilar pathway created by the BPCIA as a critical tool for lowering spending on and

improving patient access to medicines, and believe that clarity around the interchangeability designation will help achieve these outcomes. We believe these principles outlined above will foster competition, from interchangeable biosimilars for the benefit of America's patients.

Thank you for your time and consideration.

Academy of Managed Care Pharmacy
Blue Cross Blue Shield Association (BCBSA)
CVS Health
Express Scripts
Healthcare Supply Chain Association
National Association of Chain Drug Stores (NACDS)
Pharmaceutical Care Management Association (PCMA)
Premier, Inc. healthcare alliance
Prime Therapeutics
Public Sector HealthCare Roundtable

Yours truly,

cc: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research