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***Submitted electronically via* www.regulations.gov**

May 18, 2017

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Attn: Docket No. FDA-2017-D-0154-0007

Dear Sir/Madam,

CVS Health, on behalf of its subsidiaries and affiliated entities, appreciates the opportunity to comment on the Department of Health and Human Services (HHS) Food and Drug Administration (FDA) draft guidance for industry on Considerations in Demonstrating Interchangeability with a Reference Product.

CVS Health is a pharmacy innovation company helping people on their path to better health. CVS Health helps people, businesses and communities to manage health care in more affordable, effective ways. Our unique integrated model increases access to quality care, delivers better health outcomes, and lowers overall health care costs.

CVS Health is committed to delivering quality medications to its customers while keeping costs low by encouraging competition in the market and utilizing highly effective, more affordable versions of brand name drug products. This has worked very well within the small molecule prescription drug market, where the use of generic drugs has significantly decreased the cost of medicine and saves the U.S. health care system, especially consumers and patients, billions of dollars every year. In 2010, Congress passed the Biologics Price Competition and Innovation Act (BPCIA) to create a similar abbreviated pathway for biological products, including those that are biosimilar and those that are interchangeable. This pathway is extremely important – biologic products are some of the most expensive drug products available, and their costs have been increasing at a very rapid rate.[1] The Biosimilars Council reports that in 2014, the U.S. spent $115 billion on biologics, and by 2020 that amount is estimated to increase to over $250 billion. Also by 2020, it is estimated that biological products representing over $80 billion in annual global sales will lose their patent exclusivity, opening the door to biosimilars with the potential to significantly lower the cost of biologic medicines.[2]

[1] Biosimilars Council, "The Next Frontier for Improved Access to Medicines: Biosimilars and Interchangeable Biologic Products," accessed March 10, 2017.

[2] *Id.*

A robust, competitive market is crucial to ensure that patients have access to safe, effective, and affordable biologic products. One important piece of this process is demonstrating interchangeability between products. FDA has already established a process for demonstrating biosimilarity, or that a biological product is highly similar to the reference product with no clinically meaningful differences. However, until now there has not been a path to demonstrating interchangeability, or that a biosimilar product may be substituted for the reference product without the intervention of a health care provider. When a new biologic product is designated as interchangeable by FDA, it will be significantly easier for patients to access these more affordable products. The resulting reduction in cost without compromising safety or efficacy was one of the main goals of the BPCIA, and CVS Health is very encouraged that FDA has released its draft guidance, which for the first time lays out a pathway to achieving interchangeability.

CVS Health strongly supports FDA's commitment to reviewing each product seeking the interchangeable designation on a case-by-case basis. This is encouraging and essential, given the complexity and necessary differences between biologic products as compared to small-molecule drugs. We support FDA's intention to utilize postmarketing data as a helpful factor in demonstrating interchangeability, as we believe postmarketing data is extremely valuable and can help inform FDA's decision making process.

Additionally, CVS Health is encouraged by FDA's plan to consider the "totality of factors" when determining interchangeability. In particular, we support FDA's intent to utilize fingerprint-like characterization to inform the process and allow a more selective and targeted approach to demonstrating interchangeability. This is consistent with FDA's current practice in reviewing applications for biosimilarity, and we believe it makes sense to utilize it for demonstrating interchangeability as well.

The draft guidance proposes that to demonstrate interchangeability, a sponsor would need to conduct one or multiple switching studies for products that are intended to be administered to an individual more than once. We appreciate that FDA plans to allow sponsors to submit justification on why a switching study is not needed for products that are not intended to be administered more than once, but we are concerned that the guidelines laid out for the switching studies may be unnecessarily onerous and significantly delay the time taken to demonstrate interchangeability. CVS Health believes that the requirement to evaluate two or more switches between the reference product and the proposed interchangeable product is overly burdensome. While two or more switches may be necessary in certain instances, we believe that in most cases simply one switch would be adequate to establish interchangeability, as well as safety and immunogenicity. From experience in the small-molecule market, we know that it is extremely uncommon to switch a patient back and forth between a brand and generic version of a product. In actuality, the vast majority of patients who switch from a name brand to a generic remain on the generic permanently. In very rare instances, when a switch is not successful, the patient will switch back to the brand, also usually permanently. We anticipate that for interchangeable biological products, the process will be similar, and therefore multiple switching studies are unlikely to be needed. We request that FDA extend its approach of treating each proposal on an

individual basis to the switching studies requirements by not requiring two or more switches except in those rare instances where it is warranted.

We are also concerned that FDA's draft guidance would require a sponsor to use a U.S.-licensed reference product for the switching studies. As noted in the draft, FDA allows non-U.S.-licensed products to be used for demonstrating biosimilarity. While we recognize FDA's note that it is possible for proposed interchangeable products and non-U.S.-licensed products to have subtle differences that could in certain cases cause differences in immunologic responses, such differences could also potentially result from different batches of the reference product. We believe that the safety and efficacy guidelines to determine biosimilarity should also be used for determining interchangeability unless there is specific evidence or reason to believe there are meaningful differences between U.S.-licensed and non-U.S.-licensed products. Also, as noted above, we believe that it would be highly unusual that a patient would switch back and forth between a reference and interchangeable biological product, and therefore any differences in immunologic response would be extremely unlikely to occur in practice. We believe that this requirement is unnecessarily limiting and could cause unintended consequences. For example, this could discourage sponsors from seeking the interchangeability designation using data conducted outside the U.S. Additionally, sponsors who have previously completed or begun switching studies to demonstrate biosimilarity would not be able to use those studies in support of interchangeability and might have to conduct new studies using a U.S.-licensed reference product. We would also note that this would have a significant impact on cost, as U.S.-licensed reference products are often far more expensive than biological products available in the European Union (EU)[3]. Therefore, we ask that FDA change this requirement and allow non-U.S.-licensed products to be used to demonstrate interchangeability except in cases where FDA has reason to believe that differences in the U.S.-licensed and non-U.S.-licensed product could lead to meaningful differences in immunologic responses.

Throughout the draft guidance, FDA emphasizes the importance of working with the product sponsors both in advance of seeking interchangeability and throughout the process. CVS Health supports this approach because it may avoid unnecessary delays or disapprovals and will help ensure an efficient process. We also believe that this communication is vitally important given the lack of historical precedent and case knowledge regarding interchangeability. However, we encourage FDA to revisit its process periodically and provide additional or revised guidance that gives greater clarity and, where appropriate, streamlines the process further as the agency gains experience in interchangeability approvals. This would not only aid product sponsors, but would hopefully reduce the amount of time and resources needed by both the sponsors and the FDA.

We are pleased that FDA plans to support extrapolation so that the same data and information used to support interchangeability may be used to demonstrate extrapolation for multiple indications for which the reference product is approved. Requiring separate clinical trials for

[3] Simon King, "Spotlight On: Will sourcing acceptable reference products make US biosimilar interchangeability studies cost-prohibitive?," Jan. 24, 2017.

each indication would not only be unnecessary in many cases, but would create significant burden and cost. CVS Health is supportive of FDA's draft guidance to use extrapolation, and request that FDA allow and encourage extrapolation whenever appropriate.

In conclusion, we believe that FDA's draft guidance is an important step in realizing the potential of the biosimilar market and reducing the cost of biologic products. Given the life-changing benefits these products have, it is extremely important to foster a robust market with strong competition to increase the accessibility and affordability of these critical medications.

CVS Health supports FDA's work in drafting this guidance, and hopes that FDA will take these comments into account in the final guidance. We are very hopeful that this guidance will advance the goals of the BPCIA and provide increased access to affordable medications.

CVS Health appreciates the opportunity to provide our comments, and welcomes the opportunity to work with FDA in this important area. If you have any questions, please do not hesitate to contact Donald Dempsey, Vice President, Policy and Regulatory Affairs at donald.dempsey@cvshealth.com or (202) 772-3534.

Sincerely,

Donald Dempsey
Vice President
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