



May 19, 2017

Submitted electronically via: www.regulations.gov

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Attn: Docket No. FDA-2017-D-0154

**Re: Docket No. FDA-2017-D-0154 - Considerations in Demonstrating
Interchangeability With a Reference Product; Draft Guidance for Industry**

Dear Sir or Madam:

The National Business Group on Health is pleased to respond to the Food and Drug Administration's (FDA's) notice of "Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry," as published in the Federal Register on January 18, 2017.¹ We applaud the Agency for its work and dedication in the biologics and biosimilars space, as well as the work of all of those at the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), the Office of New Drug (OND), and other sister agencies. We recognize the significant challenges associated with this important work and appreciate your continued commitment to a clear regulatory pathway by which manufacturers may bring biosimilars to market while ensuring that patients have access to safe, high quality treatments and therapies.

The National Business Group on Health represents 414 primarily large employers, including 70 of the Fortune 100, who voluntarily provide group health plan coverage and other employee benefit plans to over 55 million American employees, retirees, and their families. While our members see a number of factors driving rising costs, for the first time, specialty pharmacy costs were ranked as the top driver of health care costs in the Business Group's [Large Employers' 2017 Health Plan Design Survey](#)². With that in mind,

¹ Considerations in Demonstrating Interchangeability With a Reference Product. Federal Register Website, available at: <https://www.gpo.gov/fdsys/pkg/FR-2017-01-18/pdf/2017-01042.pdf>. Published January 18, 2017. Accessed April 28, 2017.

² The Large Employers' 2017 Health Plan Design Survey is an annual survey of members of the National Business Group on Health. The survey asked employers to provide information on their 2017 plan offerings, including: medical trend for 2017, the impact of the excise tax, consumer-directed health

the Business Group supports a regulatory environment that favors the robust uptake of biosimilars and interchangeable biosimilars in the biologic marketspace, where they provide safe, high quality, and higher value alternatives for costly biologic reference products.

At a high level, we urge the Agency to continue working toward a regulatory environment in which the 1) requirements for interchangeability status of a biosimilar product are not so financially burdensome that they disincite development of interchangeable products and that 2) interchangeability status does not imply inferiority of biosimilar products lacking interchangeability status.

Specifically, we support:

- FDA’s recognition that residual uncertainty regarding the interchangeability of different proposed products may be different and that, therefore, the data and information necessary to support a demonstration of interchangeability needs to be considered on a case-by-case basis.
- FDA’s flexibility of requirements about the design of switching studies that will be used to demonstrate interchangeability of biosimilar products, to account for switching intervals, clinical concern, duration of therapy, immune responses and structural changes.
- FDA’s willingness to consider “extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed and for which licensure as an interchangeable product is sought.” To this end, we also applaud the FDA for considering that “differences between conditions of use...do not necessarily preclude extrapolation.”
- FDA’s openness to consider circumstances where post-marketing data may provide support for a designation of interchangeability for an approved biosimilar.

We have specific concerns about:

- The potential for an interchangeability designation to create the perception that an interchangeable product is superior or of higher quality than an approved biosimilar that is not interchangeable. We encourage the Agency to consider broader educational outreach to both provider and patient organizations, to ensure that there is no misperception about the safety and/or efficacy of non-interchangeable biosimilars.
- A lack of clarity about certain definitional terms, including a “totality of the data” and “residual uncertainty,” and the potential for those terms to be interpreted arbitrarily. We encourage the Agency to clearly define what it means by these terms, to avoid the potential for arbitrary interpretation these important

care, employee cost-sharing, pharmacy benefits, and health care delivery reform. The survey was fielded between May 15 and June 15, 2016 and reflects the plan design changes of 133 employers. Collectively, these respondents represent a wide variety of industry sectors, employ approximately 7.2 million employees in the U.S., and offer coverage to more than 15 million employees and their dependents

distinctions, which may make it more difficult for biosimilar sponsors to demonstrate interchangeability, or reduce the incentives for sponsors to seek interchangeability status.

- The complexity of the analytical approach as laid out by the FDA, which will require that biosimilar sponsors “detect and characterize all relevant structural and functional differences between the reference product and the proposed interchangeable product.” We encourage the Agency to review all relevant comments to identify ways that this analytical approach could be simplified, particularly when these differences do not impact the safety and/or efficacy of the proposed interchangeable biosimilar.
- The failure to acknowledge that variability among different batches of biologic products is inherent and occurs even within branded reference products when comparing batches overtime, and that failure to acknowledge this part of “residual uncertainty” may make it extremely difficult for biosimilars to be considered interchangeable. We encourage the Agency to recognize that variability occurs, even among batches of the same reference product, and to maintain some level of flexibility with regard to “residual uncertainty” to accommodate for this variability.
- Mandating the use of US-licensed reference products in switching studies, where a clinical justification is absent and would urge the Agency to consider allowing non US-licensed reference products to be permitted for use to establish interchangeability where safety and efficacy can be established, to minimize exorbitant and unnecessary costs. Non US-licensed products are already used to demonstrate biosimilarity, thus small structural differences in products should not preclude the same non US-licensed products to be used to demonstrate interchangeability, particularly since the safety and efficacy of the underlying biosimilar has already been established. Further, at a minimum, if the Agency is going to stand by this particular provision of the guidance, it should consider whether originator manufacturers should be required to provide product to biosimilar applicants and/or if originator manufacturers would be required to provide enough samples to biosimilar applicants for comparability purposes. How the FDA will monitor the reformulation and/or manufacturing changes of reference products, and how those reformulations will be evaluated against its interchangeable biosimilar products to ensure the proper balance is struck. At the heart of the matter, we do not believe a minor change, or “evergreening,” should nullify a biosimilar’s designation as interchangeable, even if the biosimilar does not make the same reformulation. Unless the product reformulation is dictated by a concern with regard to the safety and/or efficacy of the product, we do not believe that failure of a previously deemed interchangeable product to reformulate in accordance with arbitrary modifications should require a new application for interchangeability.

Safety and Efficacy of Biosimilar Products is Established

All approved biosimilar products in the US already meet FDA’s rigorous standards in demonstrating that they have the same effectiveness and safety profile as the reference

biologic. All biologics, including biosimilars, approved by FDA are safe, pure and potent for their intended use. Further, biosimilar medicines are approved by the same regulatory authorities, with the same scientific rigor, using the same regulatory systems as original brand biologics.³

Thus, after initial biosimilar approval by the FDA, minor reformulations or manufacturing changes should be regulated consistently across all classes of biologics: originator, biosimilar and interchangeable. If a biosimilar manufacturer has provided a comprehensive data package to establish the safety and efficacy required for interchangeability designation and the FDA has reviewed and approved any post-approval manufacturing changes, it should not be necessary to re-establish interchangeability.

Additionally, in the event the manufacturer of a reference product obtains a new indication that is not covered by pediatric or orphan exclusivity, manufacturers of interchangeable biologics should be permitted to submit a request to the agency to obtain the new indication by applying the concept of extrapolation, as the product has already been demonstrated to be interchangeable to the reference biologic.

Finally, because all approved biosimilar products in the US meet FDA's rigorous standards demonstrating they have the same effectiveness and safety profile as the reference biologic, we believe the U.S. regulatory designation of interchangeability does not represent a higher standard for product quality but is instead a request for additional information.

Therefore, we recommend that the FDA continue to work with stakeholders to disseminate provider and patient education to firmly establish the safety and efficacy of biosimilar drugs to their reference products, recognizing that key successes to the uptake of biosimilar medicines in other countries has been predicated on the creation of trust and confidence among all the stakeholders involved, including prescribers, pharmacists and patients.⁴

Nonproprietary Naming of Biological Products

We would also like to take this opportunity to comment on the FDA's proposal final guidance for renaming all biological drugs described in the Agency's January 2017 Guidance "Nonproprietary Naming of Biological Products."⁵ We have concerns that the FDA's mandate to rename every biological drug, including drugs that have been

³ European Commission. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products.

<http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native>.

⁴ Vogler S, Zimmermann N, Ferrario A, et al. Pharmaceutical policies in a crisis? Challenges and solutions identified at the PPRI Conference. *Journal of Pharmaceutical Policy and Practice*. 2016; 9:9

⁵ Nonproprietary Naming of Biological Products Guidance for Industry. Federal Register Website, available at: <https://www.regulations.gov/document?D=FDA-2013-D-1543-0187>

marketed for years under a different nonproprietary name, will require every segment of healthcare including, but not limited to, hospitals, payers, and providers to engage in thousands of hours of information technology redesign and reprogramming.

In addition to the considerable impact on the private sector, the impacted government entities would include Veterans Health Administration, Ryan White Centers, Indian Health Service, Centers for Medicare and Medicaid Services, Department of Defense, National Institutes of Health, and all other Federal, state, and local government health agencies.

Initial direct implementation costs have been cited in the billions of dollars, with extensive on-going indirect costs associated with drug price increases, adverse patient safety issues, drug shortages, and supply chain disruption.⁶

Again, thank you for considering our comments and recommendations to FDA's notice of "Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry. Please contact me or Steven Wojcik, the National Business Group on Health's Vice President of Public Policy, at (202) 558-3012 if you would like to discuss our comments in more detail.

Sincerely,

A handwritten signature in black ink that reads "Brian J. Marcotte". The signature is written in a cursive, flowing style with a long horizontal tail stroke.

Brian J. Marcotte
President and CEO

⁶ FDA biologics naming guidance could cost providers billions. Accessed at: <http://gabionline.net/Biosimilars/General/FDA-biologics-naming-guidance-could-cost-providers-billions>