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Food and Drug Administration
Division of Dockets Management (HFA-305)
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Rockville, MD 20852

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Reference: Docket No. FDA 2017-D-0154

To the Food and Drug Administration:

The Ohio Public Employees Retirement System ("OPERS") appreciates the opportunity to submit comments to the Food and Drug Administration ("FDA") on "*Consideration in Demonstrating Interchangeability With a Reference Product,*" which was published in the Federal Register on January 18, 2017 (Guidance).

OPERS is the largest public retirement system in Ohio, and the twelfth-largest public retirement system in the United States. With more than 218,000 non-Medicare and Medicare Retiree Health Care participants, it is extremely important to us that costs within the health care system remain affordable and sustainable. The availability and accessibility of safe, effective, and affordable biosimilars and interchangeable products is an integral part of OPERS' strategy to manage its future prescription drug costs for our retiree health care plan and plan participants.

OPERS has supported the FDA's efforts to implement the Biologics Price Competition and Innovation Act ("BPCIA"). We commend the FDA for releasing this guidance on Interchangeability. In particular, we appreciate that the FDA Guidance:

- Confirms that FDA anticipates the designation of a biosimilar as interchangeable with its reference product;
- Supports the extrapolation of interchangeability for additional indications for which the reference product is licensed; and
- Will not require numerous additional clinical studies to demonstrate interchangeability.

However, we are concerned with some aspects of the proposed important scientific considerations in demonstrating interchangeability with a reference product specifically aspects that delay and/or reduce patient access to interchangeable products as well as increase manufacturer costs that will ultimately be passed onto patients and healthcare purchasers.

We have provided additional information regarding our comments and concerns below.

Data and information needed to support a demonstration of interchangeability

OPERS appreciates that the FDA is requiring a higher data burden for proof for interchangeability compared to biosimilarity alone, but believe that this could be largely accomplished by increasing reliance on innovation in the use of non-clinical analytical techniques to characterize all structural and functional differences between

the interchangeable product and reference product. As these non-clinical analytical techniques continue to advance, they should begin replacing the need for clinical studies to reduce residual uncertainty regarding interchangeability just as they do today for biosimilarity and comparability in support of manufacturing changes.

We are concerned that if the FDA requires a broad approach to clinical studies necessary to demonstrate interchangeability, this will increase manufacturers' costs and therefore reduce patient access to affordable biological products. After all, an interchangeable product will be a biosimilar product on which additional studies have been done, not a newer or better product. This is all the more evident as the FDA is encouraging sponsors to apply for a biosimilar license first, and only then pursue interchangeability as the second regulatory hurdle. As the products themselves are the same, there is little need for additional clinical studies.

Considerations for the design & analysis of a switching study or studies to support a demonstration of interchangeability

We appreciate that switching studies are likely the most expeditious way to meet the requirements in Public Health Service (PHS) Act 351(k)(4)(B) to demonstrate interchangeability, but we are concerned about the proposed FDA requirements of conducting a switching study or studies on patients only and requiring at least two separate periods for the two products in the switching arm. These study requirements are burdensome in terms of the length of time required for review and substantial patient study size. They will delay patient access to interchangeable products as well as increase manufacturer costs that will ultimately be passed onto patients and healthcare purchasers. In the end, the product demonstrated to be interchangeable will be the same product that was already approved as biosimilar.

It is important that the FDA approval process for interchangeable products strikes an appropriate balance between bringing safe and effective interchangeable products to the market and maximizing patients' access to these more affordable biologics.

Recommendations regarding the use of a U.S. licensed reference product in a switching study or studies

We are concerned about the FDA's recommendation that sponsors use a United States (U.S.) licensed reference product in a switching study or studies. This requirement will likely delay patient access to interchangeable products as well as increase manufacturer costs that will ultimately be passed onto patients and healthcare purchasers.

- Sponsors currently have difficulty accessing some U.S. licensed reference products due to tactics utilized by some manufacturers such as abusing the FDA's REMS Elements to Assure Safe Use (ETASU) requirements to deny product samples. This would be harmful to sponsors needing reference biologic product that is necessary to conduct bioequivalence testing in order to gain an FDA interchangeability designation.
- Sponsors will have significant additional costs if mandated to use U.S. licensed reference products. These reference products are twice as expensive as obtaining the same biological product from the European Union (EU) and account for between 25 and 30% of switching study costs.[i]
- Lastly, the requirement of using a U.S. licensed reference product does not make sense from a scientific perspective, especially for those sponsors who have previously used bridging studies with the same product approved elsewhere to establish the initial biosimilar approval for their

product. For example, Sandoz utilized an EU-approved comparator in their switching study to support FDA approval for their biosimilar Erelzi™ (etanercept).

Considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products

OPERS is concerned about the FDA's proposed requirement that a sponsor developing a product for licensure as an interchangeable biologic should be limited to seeking licensure for the same presentation rather than the focus remaining on the same clinical outcome for the patient. This requirement may delay patient access to interchangeable products as reference product manufacturers can use intellectual property blocks on their devices. Additionally, this requirement limits presentation improvements that could be provided by interchangeable products.

Comments on items not addressed in this Guidance

OPERS continues to believe that interchangeable biological products should have the same nonproprietary name as the reference product. OPERS believes that the FDA should reconsider its final guidance on the Non-Proprietary Naming of Biological Products and not require biological products to have a unique suffix composed of four lowercase letters. If the FDA does not reconsider this final guidance on naming, then we ask that the interchangeable biological product also have the same suffix as the reference biological product because any distinction between a biosimilar and its reference, or between an interchangeable biologic and its reference, is likely to reduce head-to-head competition in the marketplace, and that will reduce access and affordability for patients.

OPERS also believes that interchangeable biological product labels should be identical to reference biological product labels. Specifically, interchangeable product labeling should not be required to state that the drug has been approved as an interchangeable to a specific reference biological product for stated indications and routes of administration as well as provide additional information on immunogenicity or adverse reactions. The listings the FDA is proposing in the Purple Book will suffice for pharmacists (subject to state law) to substitute an interchangeable product for its reference product.

Comments on additional questions posed by the FDA

1. *With respect to interchangeable products, are there considerations in addition to comparability assessments the FDA should consider in regulating post approval manufacturing changes of interchangeable products?*

OPERS believes comparability requirements should be the same for all approved biological products – interchangeable products, biosimilar products and reference products. As biologics approved by the FDA will then be safe, pure, and potent, and all stakeholders will be able to share confidence in a consistent approach as well as a fair regulatory basis for approval of all biologics. If the FDA appears to impose a higher standard for interchangeable products for post approval manufacturing changes this will create confusion and it will be unclear who has to match whom if both the interchangeable product and its reference product are undergoing manufacturing changes concurrently. We are against any disparity in how biosimilars, interchangeable products, and reference products are treated as this will likely become another disincentive for sponsors to pursue interchangeability. Additionally, this will likely reduce patient and provider confidence in the safety and effectiveness of interchangeable products that will likely undergo many post approval manufacturing changes.

We have confidence in the FDA's two decades of experience with using comparability in support of manufacturing changes, and have every confidence that the Agency will apply it equally and appropriately to biosimilars and interchangeable products in the future.

2. *How, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed?*

OPERS supports extrapolation of indications as a key concept behind the abbreviated biologics pathway established under section 351(k) of the Public Health Services Act. OPERS appreciates that this proposed guidance supports sponsors seeking licensure of an interchangeable product for one or more additional conditions of use for which the reference product is licensed as long as the sponsor provides sufficient scientific justification for extrapolating data to support 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.

If new condition(s) of use are licensed for the reference product after an interchangeable product is licensed, then once any exclusivities or other intellectual property for the new condition(s) expire, the interchangeable biologic sponsor should then be able to seek licensure for the new condition(s) of use as long as the sponsor provides sufficient scientific justification for extrapolating data to support determination of interchangeability for the new condition(s). This would require the same scientific reasoning as was applied to any extrapolation already applied to the biosimilar/interchangeable biologic and not necessarily involve the expectation of any further clinical studies.

Conclusion

In 2016, OPERS' total non-Medicare prescription drug cost was $187.5 million, $66.5 million of which was spent on specialty/biological drugs. Although only 3% of current OPERS Retiree Health Care participants utilize specialty drugs, these medications account for 35% of our overall drug spend and represent the fastest growing segment of our annual drug cost. In the absence of biosimilars and interchangeable products, specialty drug costs are projected to grow 14-17% per year through 2021.[ii]

Biosimilar and interchangeable product competition is a necessary part of OPERS' long-term strategy to manage the growth of its health care expenditures and increase patient access to affordable, high quality biological drugs. These innovative biological medicines do and will continue to have the potential to revolutionize medical care in the future, but only if plan sponsors and consumers can afford to cover and purchase them. Marketplace competition is one of the most effective tools we have for managing prescription drug cost inflation moving forward. We believe the Agency is uniquely positioned to protect and promote the public health while also developing policies that facilitate biosimilar and interchangeable products becoming a quick and viable alternative in the marketplace.

We respectfully request that the FDA:

(1) reduce the expectation that clinical studies are the best way to reduce residual uncertainty regarding interchangeability, given that non-clinical analytical techniques offer higher sensitivity and continue to advance;

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(2) modify design requirements for switching studies so they are not too burdensome in either the length of time required to conduct and review or in added costs for the manufacturer seeking the interchangeability designation;

(3) not require manufacturers to use a U.S. licensed reference product in a switching study or studies; and

(4) not require manufacturers developing a product for licensure as an interchangeable to be limited to seeking licensure for the same presentation but to retain the focus on no clinically meaningful differences.

We thank you again for the opportunity to provide comments on this process. If you have questions or would like additional information regarding OPERS' comments, please contact Brian Pack, OPERS Health Care Finance and Policy Officer, at 614-225-1858.

Sincerely,

Tonya Brown,
Interim Director of Member Operations

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[i] King, S. Spotlight On: Will sourcing acceptable reference products make US biosimilar interchangeability studies cost-prohibitive? https://www.firstwordpharma.com/footer/benefits?tsid=17

[ii] QuintilesIMS Institute. Outlook for Global Medicines through 2021, December 2016.