PORTAL
Program On Regulation, Therapeutics, And Law

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Division of Dockets Management
Food and Drug Administration
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COMMENTS ON PUBLIC DOCKET:
The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Biosimilar and Interchangeable Insulin Products
Docket Number: FDA-2019-N-1132

To Whom It May Concern:

We would like to submit this comment on affordable insulin and issues related to the development and approval of biosimilar insulins for the FDA's public docket FDA-2019-N-1132, published on April 3, 2019.[1] The authors—Jing Luo, M.D., M.P.H., Ameet Sarpatwari, Ph.D., J.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.—are members of the Program On Regulation Therapeutics And Law (PORTAL), an interdisciplinary research program within the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital and Harvard Medical School, which focuses on how laws and regulations influence the development, utilization, and affordability of therapeutics, as well as the ethical questions these issues raise for patients, physicians, policymakers, and payors. PORTAL is the largest and most productive non-industry-funded research program in the US studying the interactions among the regulatory, legal, clinical, economic, and clinical components of the pharmaceutical marketplace.

On May 29, PORTAL and the Harvard-MIT Center for Regulatory Science hosted an expert roundtable on "Biosimilar Insulin for the Benefit of Patients with Diabetes." The discussion that transpired forms the substance of this comment. The meeting was organized because although insulin was originally isolated and used in clinical care about 100 years ago, with the key scientists famously donating the intellectual property for $1 each so that "anyone would be free to prepare the extract," high and rising costs of insulin products have led to decreased access, poor patient health outcomes, and strained health care resources. These developments have led many patients and policymakers to ask why insulin remains without low-priced "generic" alternatives, which are common in nearly every other class of drugs with such a long history. In the meeting, we heard from experts from academia, industry, the patient advocacy community, and

[1] Proposed criteria for "first generic" submissions for Purposes of Abbreviated New Drug Application Review Prioritization Under the Generic Drug User Fee Amendments. Available at: http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-1741-0001.

government about key scientific, regulatory, and clinical issues facing the production, dissemination, and use of affordable insulin products.

I. Clinical Considerations

The experts generally agreed that the high-cost of insulin is a major clinical barrier to medication adherence and availability for diabetic patients. For uninsured diabetics in particular, high insulin costs often force patients to ration their insulin-products and withhold insulin administration. For insured diabetics with employer-based plans, fear of unemployment encourages stockpiling of insulin-products and use of expired insulins rationed beyond their best-use date.

The group also discussed the inconsistency as to which insulin-products were available, either because patients could no longer afford their original insulin-products or because hospital and insurance formularies changed. Often, providers may be unaware of changes to these formularies when they write prescriptions. Such unpredictable insulin switching affects the quality of patient care, since some diabetics have different therapeutic responses to different insulin types.

To lower insulin prices and improve clinical outcomes, some policymakers have suggested adoption of biosimilar and interchangeable insulins for use in diabetes. The group agreed that such intervention could improve patient outcomes through cost reduction; however, widespread adoption would likely only occur after addressing clinical concerns. The group discussed the possibility that the FDA work with provider systems to demonstrate the clinical equivalency of these "follow-on" products and allay the possible perception that they are "inferior" to their original insulin products. Along these lines, the group agreed that follow-on products should have packaging as similar as possible to their original products, especially since previous research has shown changes to the color and shape of generic pills can confuse patients and reduce adherence.

The group discussed how the FDA could consider the ways that regulatory decisions on insulins could differentially affect patients with Type I and II diabetes. The two populations, though similar, have sub-disease-specific insulin responses and needs.

II. Market Considerations

In highly regulated pharmaceutical markets like Norway and European Union nations, biosimilar adoption has led to dramatic price reduction with minimal therapeutic complications (e.g., a 75% price reduction for Norwegian infliximab). To see the similarly widespread adoption of biosimilar insulin-products and associated cost savings in the US, manufacturers must be able circumvent existing restrictions to market entry and attain more robust coverage on formularies.

In the US commercial market, biologic formulary inclusion is largely driven by the rebate savings that pharmacy benefits managers (PBMs) can negotiate down from the manufacturer's list price. Such savings may be 12-25% below list price for insulin products. While these savings are important for payors, net insulin prices are likely still much higher than equivalent follow-on biologics would cost in a competitive market.

The group discussed several market conditions that disincentivize the widespread use of follow-on biologics in the US, including: 1) Biosimilars are non-interchangeable with biologics and must be specifically prescribed by physicians – meaning without contracted biosimilar dispensing from a hospital system or greater physician education (e.g. detailing) about the value of biosimilars, biosimilar uptake will likely be substantially limited; 2) Rebate bundling, in which

manufacturers simultaneously negotiate net price for multiple products, often encourages continued use of brand-name biologics despite biosimilar availability. Additionally, legal restrictions limit the adoption of biosimilars: several FDA-approved biosimilars cannot enter the US market because of patent litigation.

For biosimilars that are marketed, authorized biosimilars and outcomes-based contracting have been proposed has potential ways to encourage greater use. However, the group discussed how overreliance on these methods might fail to adequately correct existing market problems. As with authorized generics, authorized biosimilars will likely not generate as robust cost savings as biosimilars produced by an independent company. Likewise, outcomes-based contracting may lead hospital systems to pay for unnecessarily high-cost products.

To reduce insulin costs, the group discussed how regulatory and antitrust officials could work to prevent schemes that limit biosimilar entry at a contractual level (e.g., rebate bundling). Second, the group discussed ways to encourage greater biosimilar entry into the market. Such reform could involve addressing patent thickets preventing FDA-approved biosimilars from earning "marketed" status and promoting interchangeable insulin development, following recent FDA guidance on the topic.

III. Regulatory Considerations

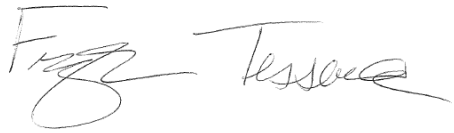
To ensure that biosimilar and interchangeable insulin-products enter the market, the group noted that there are several regulatory challenges that must be addressed. Chief among these are the high cost of patent litigation and the legal expertise necessary for manufacturers to enter the current biosimilars market. Currently, it seems as if only big pharmaceutical companies have the necessary financial and legal resources, and since insulins today are largely produced by these same companies, they may paradoxically have little financial incentive to produce biosimilar and interchangeable insulin-products. The group agreed that this problem will likely hamper biosimilar and interchangeable biologic development in the coming years.

In spite of these regulatory challenges, upcoming FDA recategorization of insulins from New Drug Applications (NDAs) to Biologics License Applications (BLAs) in March 2020 promises to lead to further development of biosimilar insulins – and ideally reduced prices. Switching insulins from NDAs to BLAs may spur further development of biosimilars because the newly created BLAs can serve as reference products, encouraging new biosimilars to enter the market.

Regulatory challenges are not unique to biosimilar insulins; interchangeable insulins, too, in spite of their market advantage, face regulatory hurdles hampering their widespread adoption. The biggest challenge of interchangeable insulins is demonstrating for patients, physicians, and regulators that they have identical therapeutic profiles to their reference product biologics. The FDA's May 2019 Final Guidance on demonstrating interchangeability is a much-needed development to legitimizing this therapeutic equivalence. However, there are perhaps additionally steps the FDA can take to assure true interchangeability.

The group discussed whether all follow-on biologics entering the US market should first be marketed as biosimilars. Then, after post-market surveillance of patient switching, biosimilars could be reclassified by the FDA as interchangeable biologics, perhaps without the requirement for additional phase IV clinical studies or randomized "switching studies." We also propose that the FDA find a way to consolidate and publicize conversions between insulin types since there is patient interest in dosage difference between reference products and follow-on biologics.

Sincerely,



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