

BEFORE THE U.S. FOOD & DRUG ADMINISTRATION

**Public Hearing, May 13, 2019:
‘The Future of Insulin Biosimilars: Increasing Access and
Facilitating the Efficient Development of Biosimilar and
Interchangeable Insulin Products’**

**FDA Question Number 1: Scientific standards for evaluating the
biosimilarity and interchangeability of an insulin product**

Docket No. FDA-2019-N-1132

**STATEMENT OF MARIANA P. SOCAL, M.D., Ph.D., M.S., M.P.P., and
JEREMY GREENE, M.D., Ph.D.**

Good afternoon. My name is Mariana Socal, and I am a medical doctor. I have a Ph.D. in Health Systems from the Johns Hopkins University and a master’s in Public Policy from Princeton University.

I am currently an Assistant Scientist in the Department of Health Policy & Management at the Johns Hopkins Bloomberg School of Public Health. My primary research interest is how to provide appropriate pharmaceutical coverage for people who need prescription drugs to improve their health and quality of life.

I am speaking today on my own behalf and on behalf of my colleague, Jeremy Greene. Professor Greene is a medical doctor and a Professor of Medicine and the History of Medicine. He is the Elizabeth Treide and A. McGehee Harvey Chair in the History of Medicine at the Johns Hopkins School of Medicine.

Our statement today does not represent Johns Hopkins University. We do want to thank the Arnold Ventures for supporting our research, although Arnold Ventures has had no role in us preparing our remarks today.

We would like to provide commentary on how the FDA could improve the scientific standards for evaluating the interchangeability of insulin products.

We would like to start by defining that human insulin is the first successful product of the modern biotech industry, and has been on the US market since 1982. Human insulins are biological products because they require a living organism – bacteria – to be produced. But in a broader sense, insulins have been biological drugs well before the biotech industry developed.

We view the upcoming transition of insulin products into the regulatory framework established by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act, or BPCIA) in 2020 with concern. We contend that, if exceptions are not made, the transition will deepen the great challenges that currently affect access and affordability of insulin products in America. To encourage the production of high-quality, affordable insulin products, we propose that, as part of the transition, an exception should be made such that proof of biosimilarity should be considered grounds for interchangeability for insulin products.

Transitioning insulin products to the BPCIA framework means that if a generic insulin were to come into the market in or after 2020 it would not be considered a substitute to the existing products, even if they are demonstrated to be the same chemical

molecule, without additional trials. The FDA just issued last week the final guidance explaining these additional requirements that will be placed on biosimilar competitors in order to gain interchangeability. For generic drugs (small molecules) these requirements do not exist.

The coupling of biosimilarity and interchangeability in the FDA's approval process for small-molecule generic drugs has yielded average price reductions of 80% within 5 years after generic introduction.¹ But the disconnection of biosimilarity and interchangeability in the framework established by the BPCIA has prematurely reduced the potential competitiveness of post-patent "large-molecule" drugs, which has resulted in more modest price reductions of about 10-15%.² Were the BPCIA framework to be applied indiscriminately to insulin, it would remove the substitutability that already exists for some insulin products, increase barriers to market entry, increase costs, generate clinical uncertainty and jeopardize the health of millions of Americans. Although insulins have existed for nearly a century we have no dependable supply of affordable insulin in the United States. Indiscriminate application of the BPCIA threatens to make this situation worse.

In our view, there are substantial differences between insulin products and "large-molecule" biotech drugs that provide adequate grounds for considering proof of biosimilarity to be sufficient for interchangeability in the case of insulins.

¹ <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf>

² <https://www.cancernetwork.com/biosimilars/early-insights-biosimilar-cost-savings-united-states>

First, immunogenicity and loss of efficacy—the most substantial concern driving the requirements for interchangeability in large-molecule biologics—have not been a major concern across different insulin products after decades of monitoring. Although insulin is a biologic, it is a relatively small molecule, comprised of about 50 amino acids, much smaller than other biologics such as Humira, which has about 1300 amino acids.³ Even though autoantibodies may be developed by persons utilizing exogenous human insulin, we have seen no evidence to date that these autoantibodies are associated with clinically important changes in glucose control, hypoglycemia rates, or changes in dose requirements for insulin, and there is no evidence that the development of autoantibodies is associated with long-term complications of diabetes.⁴ In fact, these antibodies can also be detected in non-diabetic patients who have never received exogenous insulin. To date, any harms that might be entailed by considering biosimilar insulins to be interchangeable remain entirely theoretical.

Today American Diabetes Association guidelines to the pharmacologic approach to diabetes recommends the use of insulin products according to their therapeutic onset and duration of effect. In other words, the standards of care in diabetes practice already acknowledges that insulin products within the same class (e.g., fast-acting insulins, intermediate acting insulins, and so on) are similarly effective and can be selected at the physician's discretion. While patients may have different preferences and experiences with individual brands, the clinical literature supports equivalence across treatments.⁵

³ crdd.osdd.net/raghava/thpdb/display_thppid_sub.php?details=Th1044

⁴ Fineberg SE1, Kawabata TT, Finco-Kent D, Fountaine RJ, Finch GL, Krasner AS Immunological responses to exogenous insulin. *Endocr Rev.* 2007 Oct;28(6):625-52. Epub 2007 Sep 4.

⁵ Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review.

Tieu C, Lucas EJ, DePaola M, Rosman L, Alexander GC. Efficacy and safety of biosimilar insulins compared to their reference products: A systematic review. *PLoS One.* 2018 Apr 18;13(4):e0195012.

Second, in the case of insulin, even if a theoretical risk of non-interchangeability were to become a concern, the nature of diabetes management with robust biomarkers - especially the measurement of blood glucose levels - mitigates the possibility of clinical failure going unnoticed. The day-to-day, hour-to-hour effectiveness of insulins is quickly and easily measured via blood glucose levels by patients and their physicians. Many patients also have continuous glucose monitors that can provide immediate feedback. If, in theory, a biosimilar insulin were for some reason not to provide an adequate clinical effect, patients should be able to identify it within the hour and correct it. This is not the case of other biologic drugs for which, if a clinical failure occurs, by the time it is identified it may be too late to address it, as complications may have already ensued.

Therefore, in the case of insulin, there is no justification or credible evidence mobilized for requiring additional studies for interchangeability. There is no reason to indiscriminately apply a principle of the BPCIA that in the case of insulin would apply to concerns that are merely theoretical.

In addition, we believe that the regulatory framework established by the BPCIA has multiple provisions that are undesirable in the case of insulins. The differentiation between biosimilarity and interchangeability that will be imposed by transitioning insulins into the BPCIA regulatory framework has unintended consequences that can be harmful to patients, providers, and the broader pharmaceutical market.

To patients, the negative consequences will be as follows: Under the current regulation, there is substitutability across insulin products as long as prescribers do not indicate a

proprietary name and no proprietary administration device like a pen is involved. When a provider prescribes a human insulin by its non-proprietary name – for example NPH human insulin - the pharmacy may dispense any of the existing brands of insulin to fill that prescription.

This substitutability prerogative is important in light of the very real harm that already comes from rationing due to unaffordable prices in the insulin market. An insulin-dependent patient who ran out of their drug may not afford the time needed to go back to their doctor and procure a new prescription. In some cases, just a few hours without insulin may be enough to send a person to the emergency room for a serious diabetes exacerbation. Patient safety would suffer if this pattern of direct substitutability were to change. It is also unclear if, under the new regulation, the availability of insulin products “over the counter” or without a medical prescription, would be maintained.

Diabetes is a life-long condition and patients are well educated to its management and adverse occurrences. They know that fast-acting insulins share a given therapeutic profile and long-acting insulins share a different one. Introducing the intricate and arbitrary divide between biosimilarity and interchangeability to insulin products will increase complexity, decrease patient autonomy and decrease self-management abilities. This can have serious consequences for treatment adherence and overall glycemic control.

Insulin products are used by vastly more patients than any biologic drug. Nearly two million Medicare beneficiaries use glargine alone, a long-acting insulin.⁶ This is five

⁶ Medicare part D and B dashboards combined.

times more than the users of the top five biologics (Humira, Rituxan, Enbrel, Herceptin, and Avastin) combined. If, due to increased barriers to access, the hospitalization risk were increased by even a minor percentage, given the immense population of insulin users the additional costs to the system and the loss of quality of life would be significant.

To providers familiar with the current practice, adding an arbitrary divide between biosimilarity and interchangeability for insulins will generate confusion and uncertainty, and also has the potential to generate liability concerns for prescribers and insurers without any clinical benefit. The addition of four-letter suffixes will further add complexity to prescribing and de facto restrict competition.

To the pharmaceutical market, increasing complexity would increase uncertainty regarding new products and would further increase barriers to new entrants. The interchangeability requirements would increase the spending necessary to bring a new product into the market without adding real clinical gains. This may contribute to increasing prices even further.

Instead, we suggest that the FDA has enough authority to issue guidance in its own modifying the criteria for insulin's biosimilarity and interchangeability. While the criteria established by the BPCIA may be important in order to monitor and safeguard the public in relation to the use of new complex molecules of larger sizes, we contend that these criteria should not be blindly applied to older and smaller molecules that happen to be produced through biological pathways like insulin. Insulin is not Humira.

We contend that to both patients and providers there is more harm than good in increasing regulatory complexity and barriers to generic competition by applying without further consideration the BPCIA interchangeability framework intended for “large molecules” to a molecule that is not large and which has nearly a century of safe manufacturing experience, especially given that there is no evidence that this increased complexity would increase safety or effectiveness for insulin users as compared to current standards. The FDA can and should consider insulin to be an exceptional product to which the interchangeability rules of the BPCIA should be carefully reinterpreted (if applied at all) in order to maximize benefit, affordability, and access to insulin for all Americans living with diabetes.