FDA Reduces Regulatory Uncertainty with New Finalized Rule Defining "Biological Product" under BPCIA to Include Insulin and Other "Protein"-Based Products

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KEY POINTS

In February, the U.S. Food and Drug Administration issued a "bright-line rule" redefining "biological products" under the Biologics Price Competition and Innovation Act (BPCIA) to include insulin and other "protein"-based products.

- The purpose of the final rule is to reduce regulatory uncertainty under the BPCIA for companies looking to develop biosimilars of proteins.
- Both insulin and Human Growth Hormone (HGH) will transition to BPCIA/PHSA regulation in March.
- The transition of these biological products should not affect (a) health care providers' existing prescribing or dispensing practices or (b) how patients use medications, but may lower the price of certain medications.
- Pharmaceutical and biotech companies involved in or considering expansion into insulin and/or other proteins and biologics should assess if the FDA's changes will affect their patent portfolios and business decisions.

On February 20, the U.S. Food and Drug Administration (FDA) took additional steps to prepare for the March 2020 transition of insulin and other older biological products from a small molecule-like regulatory scheme to one where they are treated as follow-on biologics under the Biologics Price Competition and Innovation Act of 2009 (BPCIA or BPCI Act).

Defining "biological product" and "protein"

One of the steps the FDA took was to issue a final rule defining "biological product" to include the FDA's previous interpretation of "protein" in an attempt to avoid confusion and clarify the statutory framework.[1] More specifically, under the Public Health Service Act (PHSA), as amended by the BPCIA and the Further Consolidation Appropriations Act of 2020 (FCAA or FCA Act)[2], a "biological product" is defined as "a virus, therapeutic serum,

[1] *See* https://www.federalregister.gov/documents/2020/02/21/2020-03505/definition-of-the-term-biological-product (last visited on Feb. 25, 2020).

[2] The Further Consolidated Appropriations Act of 2020 (FCAA or FCA Act).

toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." (*See* PHSA §351(i)(1)). The FDA's final rule defines "protein" as "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size." (*See* 21 CFR §600.3(h)(6)). This establishes a clear line for companies looking to develop biosimilars of proteins, as there is no real consensus definition of the term in scientific literature.

The FDA chose this definition despite comments that proteins can be smaller than 40 amino acids in size and stated their definition "establishes a scientifically reasonable, bright-line rule that provides regulatory clarity and facilitates the implementation of the BPCI Act, as further amended by the FCA Act. A clear rule facilitates efficient use of time and resources by both [the] FDA and applicants and reduces regulatory uncertainty. In deciding where to draw this bright-line rule, one of the factors that [the] FDA considered is the number of amino acids understood to be generally necessary for an amino acid polymer to exhibit characteristics that are generally associated with 'proteins,' lending a higher level of complexity to these products." The FDA also considered but rejected including structural or functional abilities (e.g., folding, catalyzation, molecular transport) in the definition of "protein" because such abilities would not aid in providing clarity and regulatory certainty.

Importantly, the FDA clarified that even chemically synthesized polypeptides over 40 amino acids in size would be included in the definition of "biological product." This is due to the FCAA removing the exclusion of "chemically synthesized polypeptide" from the BPCIA's definition of "biological product" that included, *inter alia*, "a protein (except any chemically synthesized polypeptide)." Thus, "an amino acid polymer that previously would have fallen within the term 'chemically synthesized polypeptide' as interpreted by [the] FDA" will be considered within the statutory definition of "biological product."

Finally, the FDA clarified that insulin clearly is a "protein" as defined in the final rule. One commenter argued that insulin is composed of two polypeptide chain subunits, neither of which is over 40 amino acids long (though the two subunits together contained over 40 amino acids). The FDA clarified that it was going to count the total number of amino acids in all of the subunits to determine if it met the "greater than 40 amino acid" part of the definition (at least as long as the subunits are "associated in a manner that occurs in nature").

FAQs for patients and health care providers

The FDA also released two "Frequently Asked Questions" documents (FAQs) — one directed toward patients[3] and the other toward Health Care Providers (HCPs)[4] — with information on what the regulatory scheme transition of these older biologic products means to each group. Both of these FAQs intend to "clarify that the transition should not affect existing prescribing or dispensing practices and that patients should not notice any difference in their medications, or how they receive their medications, among other topics." Also, both of these FAQ documents highlight insulin and Human Growth Hormone (HGH), among others, as biological products that are transitioning to BPCIA/PHSA regulation on March 23. The FDA also indicates that this transition will allow these older biological products to serve as reference products for biosimilar applications, which may ultimately lead to lower prices for these medicines. The FDA also highlighted the availability of the Purple Book (the nickname for the FDA's List of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations) as a reference source for FDA-approved biological products that HCPs can use to aid their practice of medicine.

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In light of the FDA's recent actions, both patent owners and alleged infringers of patents related to insulin and other proteins and biologics should reassess whether these FDA changes affect their portfolio and business decisions.

[3] Available at https://www.fda.gov/media/135341/download (last visited on 2/25/20).

[4] Available at https://www.fda.gov/media/135340/download (last visited on 2/25/20).

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