May 13, 2021

Lemrey “Al” Carter, MS, PharmD, RPh
Executive Director/Secretary
National Association of Boards of Pharmacy
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Dear Dr. Carter:

The purpose of this letter is to bring to the attention of the National Association of Boards of Pharmacy that FDA is aware of biological products being offered to patients that appear to have been prepared by state-licensed pharmacies, registered outsourcing facilities, and healthcare providers outside the scope of an approved biologics license application (BLA).

Please be advised that federal law does not provide a legal pathway for marketing biological products that have been prepared outside the scope of an approved BLA. Specifically, section 351(a)(1) of the Public Health Service Act (PHS Act) prohibits the introduction into interstate commerce of any biological product unless “a biologics license . . . is in effect for the biological product” (i.e., an approved BLA). Additionally, biological products subject to licensure under section 351 of the PHS Act are not eligible for the exemptions for compounded drugs under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

We note that the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) required that, on March 23, 2020 (10 years after enactment), an approved marketing application for a biological product under FD&C Act was deemed to be a license for the biological product (i.e., an approved BLA) under the PHS Act. This transition pursuant to the requirements of the BPCI Act affects compounding under sections 503A and 503B of the FD&C Act. Beginning on March 23, 2020, biological products that previously could have been submitted in a marketing application under the FD&C Act are subject to licensure under section 351 of the PHS Act and thus are not eligible for the exemptions for compounded drugs under sections 503A and 503B. The "List of Approved NDAs for Biological Products That Were Deemed to be BLAs on March 23, 2020" includes, for example, chorionic gonadotropin (commonly known as HCG) products, hyaluronidase products, and somatropin products. See Notice to Compounders: Changes that affect compounding as of March 23, 2020 and FDA’s webpage on the “Deemed to be a License” Provision of the BPCI Act for additional information.

We also note that, in February 2020, FDA issued a final rule to amend its regulation that defines "biological product" to incorporate changes made by the BPCI Act and the Further Consolidated Appropriations Act, 2020, and to provide its interpretation of the statutory term "protein" (85 FR 10057). Under this rule, the term "protein" means any alpha amino acid polymer with a specific, defined sequence that is *greater* than 40 amino acids in size. A "protein" is a category of "biological product" as defined in section 351(i) of the PHS Act.

As noted, biological products subject to licensure under section 351 of the PHS Act, including biological products that previously could have been submitted in a marketing application under the FD&C Act, are not eligible for the exemptions for compounded drug products under sections 503A and 503B of the FD&C Act. Although biological products are not eligible for the exemptions under sections 503A and 503B, FDA issued guidance in January 2018 explaining the conditions under which FDA does not intend to take action when certain biological products are mixed, diluted, or repackaged outside the scope of an approved BLA . See *Guidance for Industry, Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*.

Biological products that have not undergone premarket FDA review of safety, effectiveness, or manufacturing quality, can pose health risks. In the absence of manufacturing controls, diluting or mixing a biological product with other components or repackaging a biological product by removing it from its approved container-closure system and transferring it to another container-closure system is highly likely to affect the safety or effectiveness of the biological product. Biological products are also particularly susceptible to microbial proliferation in a short period of time if contaminated. Additional health risks include the possibility that patients will use ineffective unapproved biological products instead of FDA-approved products that have been shown to be safe and effective. The policies described in the above-referenced January 2018 guidance are aimed at reducing the risks associated with mixed, diluted, or repackaged biological products while preserving access to these products for patients who have a medical need for them.

We advise that you encourage state boards of pharmacy to submit to FDA any issues or questions involving the preparation of biological products outside the scope of an approved BLA. We are also sending this letter to the Federation of State Medical Boards to facilitate communication among associations with shared goals regarding these matters.

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We look forward to continuing to work with you on matters related to drug compounding. If you have additional questions, please contact the Office of Compounding Quality and Compliance at compounding@fda.hhs.gov.

Sincerely,

Shannon N. Glueck -S

Digitally signed by Shannon N. Glueck -S
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