

HHS Enforcement Discretion Policy Regarding 503A Compounding Using Certain Peptide Bulk Drug Substances

This document describes the Secretary of the Department of Health and Human Services' (HHS) enforcement policy regarding the use of certain peptide bulk drug substances in compounding while the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (the 503A bulks list) is developed through rulemaking (21 U.S.C. § 353a).

Compounding is generally a practice in which a licensed pharmacist, a licensed physician or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.¹ Compounded drugs are not FDA-approved, which means FDA does not review their safety, effectiveness, or quality before they are marketed. Although compounded drugs can serve an important medical need for certain patients, they also may pose risks to patients. However, based on the Pharmacy Compounding Advisory Committee (PCAC) meeting and data regarding utilization of peptides, HHS believes that there is significant interest in the use of these peptides in compounding. HHS also believes based on the PCAC meeting that public comments may provide additional evidence that FDA can consider in rulemaking to address some or all of the substances. Therefore, to expand and improve patient access while FDA reviews these substances, in the circumstances below, HHS does not intend to take enforcement action against a State-licensed pharmacy, Federal facility, or licensed physician compounding a drug product using a bulk drug substance in Appendix A.

HHS may revisit application of this interim policy (in whole or in part) if, among other things, a safety signal or product quality issue arises with a compounded drug product within the scope of this policy.

BACKGROUND

Section 503A of the FD&C Act (21 U.S.C § 353a) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the requirements under section 505 (FDA approval prior to marketing) (21 U.S.C § 355), section 502(f)(1) (labeling of drugs with adequate directions for use) (21 U.S.C. § 352(f)(1)), and section 501(a)(2)(B) (current good manufacturing practice (CGMP) requirements) (21 U.S.C. § 351(a)(2)(B)) .

One of the conditions that must be met for a compounded drug product to qualify for these exemptions is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that: (1) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of FDA-approved drugs; or (3) if such a monograph does not

¹ <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/human-drug-compounding>

exist and the drug substance is not a component of an FDA-approved drug, they appear on a list developed by the Secretary through regulations issued by the Secretary under section 503A(c)(1) (21 U.S.C. § 353a (b)(1)(A)(i)). The Secretary convened and consulted the PCAC as required by statute to issue regulations to implement the 503A bulk peptide list (21 U.S.C. § 353a(c)(1)). FDA must also consult with USP (21 U.S.C. § 353a(c)(2)).

To qualify for the exemptions under section 503A, a drug product must also be compounded using bulk drug substances that are manufactured by an establishment that is registered under section 510 and accompanied by valid certificates of analysis (COAs) for each bulk drug substance (21 U.S.C. § 353a(b)(1)(A)(ii)-(iii)). Additionally, for a drug product to qualify for the exemptions under section 503A, it must be compounded based on the receipt of a valid patient-specific prescription ((21 U.S.C. § 353a(a)).

HHS Interim Enforcement Policy

The Secretary of HHS has determined that this limited enforcement-discretion policy will discourage the continued, widespread use of certain research-use-only peptides supplied by foreign manufacturers that pose a safety risk to US patients. By allowing limited compounding of the substances addressed in this guidance under appropriate safeguards, the policy provides patients with a more controlled alternative. Based on the available evidence, including the recommendations of a recent Pharmacy Compounding Advisory Committee, the Secretary has determined that the policy advances patient choice and freedom while appropriately protecting patient safety. Until a peptide bulk drug substance is addressed in a final rule as being included or not included on the 503A bulks list, HHS does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician compounding a drug product using a peptide bulk drug substance that is not a component of an FDA-approved drug product, the subject of an applicable USP or NF monograph, or on the 503A bulks list codified at 21 CFR 216.23(a), when all of the following circumstances are present:

1. **503A Interim Access List.** The peptide bulk drug substance appears in Appendix A to this policy.
2. **Identity of the Peptide Bulk Drug Substance.** The peptide bulk drug substance has the identity and limitations in route of administration described in Appendix B. The identity includes but is not limited to amino acid sequence, chemical structure, molecular weight, and molecular formula.
3. **Characterization.** The bulk drug substance is from a facility registered under section 510 (21 U.S.C. § 360) and characterized and identified in a valid certificate of analysis (COA) that includes test results consistent with existing guidance-based criteria described by FDA (see Appendix B). This helps provide assurance that what a compounder receives from a supplier is what it claims to be and has been tested for identity, purity, potency, and the absence of harmful contaminants such as endotoxins, heavy metals, microbial contamination, and impurities.
4. The original manufacturer of the bulk drug substance (not a subsequent packer, repacker, labeler, or distributor) is registered with FDA under section 510, is in

compliance with CGMP² and other FD&C requirements and the physical location of the facility is listed on the COA provided to the 503A compounder. If the peptide bulk drug substance is obtained through an FDA-registered repacker, relabeler, or reseller, that entity has itself performed and documented appropriate vendor validation of the bulk drug substance manufacturer and validation of the manufacturer's COA.

5. **Report products compounded, serious adverse events, and product quality issues to FDA and to the States where the products are compounded and sent (if different)**. Compounders report serious adverse events³ associated with the use of the compounded drug product in humans (regardless of whether or not considered drug related) and product quality issues (e.g., information concerning any bacteriological contamination, or any significant chemical, physical, or other change in the distributed drug product, or any failure of a product to meet applicable specifications) to FDA's MedWatch Safety Information and Adverse Event Reporting Program. This provides an opportunity for FDA and States to act on emerging risks. In addition, the procedure for reporting adverse events and issues with the identity, strength, purity, and/or quality of the product should be detailed on the product labeling provided to the patient.

Product reporting for the compounder includes the following

- a. Active ingredient and strength of active ingredient per unit;
 - b. Original manufacturer of the active ingredient, including unique facility identifier for the manufacturing facility; and
 - c. Dosage form and route of administration.
6. **Product labeling**. Product labeling that includes the following statement: "This is a compounded drug product. Not for resale."
 7. **The compounded drug product contains only a single Active Pharmaceutical Ingredient (API) listed in Appendix A**. It will be easier to attribute adverse events or clinical outcomes to a specific substance, which is essential for meaningful safety surveillance and signal detection, if compounded peptide products include a single API.
 8. **Route of administration**. Achieving adequate oral bioavailability of peptides is inherently difficult and complex. Therefore, if a peptide is compounded in an oral dosage form, the compounder is expected to maintain documentation confirming that the specific formulation provided to a patient achieves an adequate level of oral bioavailability in humans.
 9. **Drug delivery device**. The only drug delivery device co-packaged or containing the compounded drug is an FDA 510(k)-cleared syringe. More complex drug delivery devices introduce additional patient risk.

² CGMP expectations for Bulk Drug Substance Manufacturing can be found here: <https://www.fda.gov/media/71518/download>

³ Information about reportable serious events can be found here: <https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event>

10. **The drug product is compounded in compliance with all other applicable requirements of the FD&C Act** including that the drug product not be compounded under insanitary conditions (21 U.S.C. § 351(a)(2)(A)) and section 503A's (21 U.S.C. 353a) patient specific prescription requirement.

Appendix A. List of Peptide Bulk Drug Substances Addressed by HHS Interim Enforcement Policy Regarding 503A Compounding

1. BPC-157
2. Epitalon
3. KPV
4. MOTS-c
5. Semax
6. TB-500