Federal and California Requirements for Human Drug Compounding: An Overview

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Note and Disclaimer

This presentation contains a brief summary of federal law and guidance, and California state law, governing human drug compounding. Compounding pharmacists should consult their own attorney or other resources to ensure that they are aware of, and in compliance with, current federal and state law.

General Information and Background on Compounding

- Compounding is the long-standing pharmacy practice of mixing, combining, or altering ingredients.
- Compounding may involve altering an existing drug product or creating a new drug product.
- Compounded drugs can serve patients whose clinical needs cannot be met by FDA-approved drugs. However, compounded drugs may pose a higher risk to patients because they are not FDA approved and compounding pharmacies may be exempt from certain manufacturing requirements.

General Information and Background on Compounding

- Compounded drugs can be made for topical, oral, injectable, or inhalable use.
- Drugs administered orally or topically present less danger to patients from residual contaminants than drugs injected or inhaled into the human body – because drugs injected or inhaled into a patient's body bypass the human body's main defense mechanisms to filter out residual impurities.
- Consequently, the acceptable levels of contaminants in injectable and inhalable drug preparations are lower than for topical or oral drugs.
  - Injectable and inhalable preparations must be sterile for this reason.
  - A sterile injectable or inhalable drug preparation compounded from nonsterile ingredients is considered a high-risk preparation due to its route of administration.

General Information and Background on Compounding

- Compounded human drugs are not approved by the FDA, and the FDA does not review such drugs to evaluate their safety, effectiveness, and quality before they are administered to patients.
- However, the FDA has a role in approving the ingredients that may be used in compounding human drugs.
- States are the primary regulators of pharmacists and pharmacies engaged in compounding human drugs.
  - Thus, pharmacists and pharmacies engaged in compounding (sterile or nonsterile) are subject to both federal and state law.

Overview of Federal Law on Compounding

- Similar to other areas of pharmacy law, there is a federal overlay to compounding by state-licensed pharmacists.
- Violation of federal law could subject licensees to potential enforcement by federal agencies as well as discipline of their state-issued licenses or permits.
- FDA has a section on its website devoted to human drug compounding. Human Drug Compounding | FDA

Federal Law Overview:
Need for an Exemption for Compounding

- Generally, compounding a substance would result in a new drug that would require FDA approval and could result in violations of federal provisions, including new drug approval requirements, without an exemption.
- Section 503A of the federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 353a) provides exemption from certain provisions of the FDCA.
- Noncompliance with ANY of the requirements of the 503A exemption could result in violations of one or all of these statutory provisions, or other provisions of the FDCA.

Federal Law Overview: Summary of the 503A Exemption

Section 503A generally provides an exemption from the following provisions of the FDCA for drug products compounded by a state-licensed pharmacist or state-licensed physician:

1) Section 501(a)(2)(B) (concerning the requirement to comply with current good manufacturing practice);
2) Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and
3) Section 505 (concerning the new drug approval process).

Federal Law Overview: Summary of the 503A Exemption

- The 503A exemption DOES NOT provide an exemption from other provisions of the FDCA (*e.g.*, the prohibition against distribution of adulterated drugs set forth in section 301 of the FDCA (21 U.S.C. § 331(a)).)
  - Section 501(a)(1) and (2) of the FDCA (21 U.S.C. § 351(a)(1) & (2)) state that a drug shall be deemed adulterated "If it consists in whole or in part of any filthy, putrid, or decomposed substance; or...if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health..."
  - One insanitary condition FDA identified is using ingredients that have or may have higher levels of impurities compared to compendial or pharmaceutical grade equivalents (e.g., ingredients with potentially harmful impurities, ingredients labeled with "not for pharmaceutical use" or an equivalent statement. (See FDA Guidance for Industry: Insanitary Conditions at Compounding Facilities (November 2020), at p. 5.)

Federal Law Overview: Summary of the 503A Exemption

- Section 503A(b)(1) contains the specific substantive requirements to qualify for the exemption.
- In summary, drug products may be compounded using bulk drug substances (*i.e.*, APIs) that:
  1) comply with the standards of an applicable USP or 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 drugs approved by the FDA; or
  3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the FDA, the substance appears on a list developed by the FDA through regulations.
- "[A] bulk drug substance that is not the subject of an applicable USP or NF monograph or is not a component of an FDA-approved drug cannot be used in compounding unless it appears on a list promulgated as a regulation . . . ." (2017 FDA Interim Policy, p. 9, emphasis added.)

Federal Law Overview: 503A Bulks List

- Regarding the third prong: the list developed by the FDA through regulations (the "503A Bulks List") is set forth at 21 CFR § 216.23.
  - This rule was published on February 19, 2019.
  - It (1) establishes the criteria for evaluating substances for future inclusion on the 503A Bulks List (see 21 CFR § 216.23(c); (2) places six substances on the 503A Bulks List (see 21 CFR § 216.23(a)); and (3) identifies four other substances that were evaluated and NOT included on the 503A Bulks List, such that these substances CANNOT be used in compounding (see 21 CFR § 216.23(b)).
  - The rule also notes that additional substances are under evaluation, and may be added to the 503A Bulks List through subsequent rulemaking.

Federal Law Overview: 503A Bulks List

§ 216.23 Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.

(a) The following bulk drug substances can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

(1) Brilliant Blue G, also known as Coomassie Brilliant Blue G–250.

(2) Cantharidin (for topical use only).

(3) Diphenylcyclopropenone (for topical use only).

(4) N-acetyl-D-glucosamine (for topical use only).

(5) Squaric acid dibutyl ester (for topical use only).

(6) Thymol iodide (for topical use only).

(d) Based on evidence currently available, there are inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph (a) of this section, or to establish general recognition of the safety or effectiveness of any such drug product. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the Federal Food, Drug, and Cosmetic Act.

Federal Law Overview: 503A Bulks List

- In Section V of the final rule (Comments on the Proposed Rule and FDA Response), FDA clarified that it interprets the term "an applicable USP or NP monograph" to refer to official **drug substance** monographs, not dietary supplement monographs.
  - "USP monographs for dietary supplements can differ in significant ways from USP monographs for drugs because of the differences between dietary supplements and drug products. For example, dietary supplements are intended for ingestion only, and the standards contained in the USP dietary supplement monographs are likewise intended for dietary supplements that will be ingested; the standards are not appropriate for use in compounding drug products that may have different routes of administration (*e.g.*, intravenous, intramuscular, topical). In addition, the USP limits for elemental impurities are different for drugs and dietary supplements...Furthermore, the bioburden allowable for dietary supplements is considerably higher than that allowed for drug substances. Relying on the standards of a dietary supplement monograph for a substance that will be used in compounding drug products could therefore put patients at risk."

  See 84 FR 4696 at p. 4705.

Federal Law Overview: 503A Bulks List

- As part of FDA's evaluation of substances for possible inclusion on the 503A Bulks List, the FDA must convene and consult with the Pharmacy Compounding Advisory Committee (PCAC). (See section 503A(c)(1) of the FDCA.)
  - PCAC recommendations are not binding on FDA; rather, FDA considers the PCAC's advice but makes an independent judgment regarding whether particular substances should appear on the 503A Bulks List. (See 84 FR 4696 at p. 4704.)
- FDA must also consult with USP when promulgating the regulations. (See section 503A(c)(2) of the FDCA.)

Federal Guidance on Human Drug Compounding

- FDA has issued a lot of written and sometimes changing guidance on human drug compounding. See Regulatory Policy Information | FDA.
- Key guidance documents include:
  - Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance (June 2016).
  - Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry (January 2017)
  - Insanitary Conditions at Compounding Facilities Guidance for Industry (November 2020)

Federal Guidance on Human Drug Compounding: Interim Enforcement Policy

- This guidance document sets forth FDA's non-binding interim enforcement policy concerning compounding using bulk drug substances while the FDA updates the 503A Bulks List, which it last revised in 2019.
- The purpose of the interim policy was to "avoid unnecessary disruption to patient treatment while the Agency considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them." (See Interim Policy at p. 4.)
- The interim policy provides for ongoing categorization of nominated bulk drug substances into three categories.

Federal Guidance on Human Drug Compounding: Interim Enforcement Policy

- **Category 1**: Substances that may be eligible for inclusion on the 503A Bulks List, were nominated with sufficient supporting information for FDA to evaluate them, and do not appear to present a significant safety risk.
- **Category 2**: Substances that have been identified by FDA as presenting a significant safety risk pending further evaluation.
- **Category 3**: Substances that may be eligible for inclusion on the 503A Bulks List, but were nominated with insufficient supporting information for FDA to evaluate them.
- Current list available on FDA's website at https://www.fda.gov/media/94155/download

Federal Guidance on Human Drug Compounding: Interim Enforcement Policy

- Under the Interim Enforcement Policy:
  - FDA does not intend to take enforcement action for otherwise impermissible compounding of a drug product from a bulk drug substance in Category 1, provided that the bulk drug substance was manufactured by an establishment registered with FDA under section 510 of the FDCA and is accompanied by a valid certificate of analysis (COA) from the entity that originally produced the bulk drug substance and provided that the drug compounded from the bulk drug substance is compounded in compliance with the other conditions of section 503A.
  - FDA will not exercise enforcement discretion for drug substances in Category 2 or Category 3. Substances in those categories cannot be used in compounding, even on a temporary basis, under the FDA interim enforcement policy.

Federal Guidance on Human Drug Compounding: Interim Enforcement Policy

- FDA's interim policy regarding Category 1 substances is an **enforcement discretion** policy. This does not mean that FDA has approved or authorized the compounding of Category 1 substances, or that FDA has stated that compounding with these substances is safe in every instance:

  > "[I]t is FDA's practice to preliminarily assess whether the substance appears to present significant safety risks such that it should be placed in Category 2. However, some risks may not be apparent until FDA conducts the complete evaluation in accordance with the established criteria . . . ." "FDA may, for example, uncover safety risks or effectiveness concerns, or concerns about the physical and chemical characterization of the substance, that could place patients at risk. These concerns may not be apparent until FDA and other experts conduct an in-depth review of the substance for consideration for the 503A bulks list." (2023 Draft Interim Enforcement Policy, p. 11 & n. 25.)

Two Examples of Category 1 Substances: Methylcobalamin and Glutathione

- Neither substance has a USP drug monograph; the only USP monographs for these substances are USP dietary supplement monographs.
- Both substances have been nominated for inclusion on the 503A Bulks List. Both were put on the Category 1 list and then subject to evaluation by the FDA. Thus, both substances are subject to FDA's interim enforcement policy for Category 1 substances and other provisions of the FDCA.

Two Examples of Category 1 Substances: Methylcobalamin and Glutathione

- In a Briefing Document prepared by the FDA for the June 9, 2021 meeting of the PCAC, the FDA **recommended against** including methylcobalamin on the 503A Bulks List.
  - "Methylcobalamin is found in food and is a dietary ingredient in dietary supplements, so exposure from oral ingestion appears to be safe. However, the safety of methylcobalamin administration by intramuscular, subcutaneous or intravenous injections or infusions for a wide variety of uses, as currently promoted online by clinics and compounding pharmacies, is not supported by adequate data…Based on the information the Agency has considered in balancing the four evaluation factors, the lack of effectiveness data and safety data for use of injectable products in patients ***weighs against*** methylcobalamin being added to the 503A Bulks List."

  See Tab 2c, FDA Evaluation of Methylcobalamin, at pp. 46-47, original emphasis.

Two Examples of Category 1 Substances: Methylcobalamin and Glutathione

- Similarly, in a Briefing Document prepared by the FDA for the June 8, 2022 meeting of the PCAC, the FDA **recommended against** including glutathione on the 503A Bulks List.
  - "The safety profile of glutathione includes serious safety issues (e.g., anaphylaxis/hypersensitivity, hepatoxicity, severe wheezing, and breathlessness). Thus, glutathione injections (IV, IM) and glutathione inhalation preparations, which provide rapid, irreversible exposure, are not recommended for addition to the 503A list due to safety concerns...Based on the information the Agency has considered in balancing the four evaluation factors, the lack of effectiveness data and safety data for use of products in patients ***weighs against*** glutathione being added to the 503A Bulks List."

  See Tab 2c, FDA Evaluation of Glutathione, at p. 65, original emphasis.

Two Examples of Category 1 Substances: Methylcobalamin and Glutathione

- Ultimately, the PCAC voted to recommend the inclusion of both substances on the 503A Bulks List, although the votes were not unanimous. As noted, the FDA is not bound by these recommendations and the FDA's decision on both substances is still pending.

California Law

- BPC § 4001.1
  - “Protection of the public shall be the highest priority for the California State Board of Pharmacy in exercising its licensing, regulatory, and disciplinary functions. Whenever the protection of the public is inconsistent with other interests sought to be promoted, the protection of the public shall be paramount.”

California Law

- BPC § 4126.8
  - “The compounding of drug preparations by a pharmacy for furnishing, distribution, or use in this state shall be consistent with standards established in the pharmacy compounding chapters of the current version of the United States Pharmacopeia-National Formulary, including relevant testing and quality assurance. The board may adopt regulations to impose additional standards for compounding drug preparations.”
- BPC § 4342(a)
  - “The board may institute any action or actions as may be provided by law and that, in its discretion, are necessary, to prevent the sale of pharmaceutical preparations and drugs that do not conform to the standard and tests as to quality and strength, provided in the latest edition of the United States Pharmacopoeia or the National Formulary, or that violate any provision of the Sherman Food, Drug, and Cosmetic Law (Part 5 (commencing with Section 109875) of Division 104 of the Health and Safety Code).”
- BPC § 4301
  - “The board shall take action against any holder of a license who is guilty of unprofessional conduct or whose license has been issued by mistake. Unprofessional conduct includes, but is not limited to, any of the following:...(o) Violating or attempting to violate, directly or indirectly, or assisting in or abetting the violation of or conspiring to violate any provision or term of this chapter or of the applicable federal and state laws and regulations governing pharmacy, including regulations established by the board or by any other state or federal regulatory agency.”

California Law

- Similar to federal law, Health and Safety Code section 111550, subdivision (a), prohibits the sale, delivery, or giving away of a new drug that has not had a new drug application approved under section 505 of the FDCA.
- Thus, the delivery of a new drug that does not comply with section 503A's exemption from section 505 approval would violate both federal and California law.

California Law

- Also like federal law, California law makes it unlawful for any person to manufacture, sell, deliver, hold, or offer for sale any drug that is adulterated. (Health & Saf. Code, § 111295.)
  - Health & Safety Code sections 111250, 111255, and 111260 define "adulterated" similar to federal law.

California Law

- Unlike the FDA (which has released the Interim Enforcement Policy), the Board has not issued guidance declining to enforce state law concerning compounding with substances that are not permitted under section 503A.

Proposed Regulations

- The proposed new regulations would create a pathway in state law to expressly allow Category 1 bulk drug substances to be used in sterile compounding under specified conditions. (See proposed new section 1736.9(e)(2); see also proposed new section 1736.17(a)(2)(E).)
- Since Category 1 substances lack a USP or NF drug monograph, they also lack a recognized uniform sampling and testing standard for use in sterile drug compounding.
- Consistent with the Board's public protection mandate, the conditions set forth in the proposed regulations include sampling and testing requirements to help ensure that the specific bulk substances being used are pure and appropriate for the intended route of administration.

Recap of FDA Statement from Preamble to 503A Bulks List Regulation

- "USP monographs for dietary supplements can differ in significant ways from USP monographs for drugs because of the differences between dietary supplements and drug products. For example, dietary supplements are intended for ingestion only, and the standards contained in the USP dietary supplement monographs are likewise intended for dietary supplements that will be ingested; the standards are not appropriate for use in compounding drug products that may have different routes of administration (*e.g.*, intravenous, intramuscular, topical). In addition, the USP limits for elemental impurities are different for drugs and dietary supplements…Furthermore, the bioburden allowable for dietary supplements is considerably higher than that allowed for drug substances. ***Relying on the standards of a dietary supplement monograph for a substance that will be used in compounding drug products could therefore put patients at risk***."

See 84 FR 4696 at p. 4705 (emphasis added).

Thank you