Addendum 1

Board Response to Comments Received Specifically Related to Proposed Regulation Text Sections 1736.9 and 1736.17 (FDA Category 1 Bulk Drug Substances)

Board staff believe that the commenters may, in part, be referring to proposed regulation sections 1736.9 and 1736.17 related to FDA Category I bulk drug substances discussed in the FDA's guidance related to bulk drug substances. Board staff note that the Board has confirmed the continued availability of compounded glutathione and methylcobalamin for California patients. These findings are consistent with public comment that suggests that treatments using compounded glutathione continue in California.

After further consideration of the issue, Board staff believe that an approach that relies on a pharmacist's knowledge of compounding, including an understanding of federal law, guidance documents, and the national standards is appropriate. Following is the recommended text, the Board's response provides additional information in response to this and other comments on the same topic.

Recommended changes as follows:

1736.9(e) and (f)

~~*(e)(1)Except as provided in (2), When when a bulk drug substance or API is used to compound a CSP, it shall comply with a USP drug monograph, be the active substance of an FDA-approved drug, or be listed in 21 CFR section 216, or unless authorized by a public health official in an emergency use situation for a patient-specific compounded sterile preparation.*~~

~~*(2) A bulk drug substance nominated for inclusion in 21 CFR section 216.23(a) and for which the FDA determined that the nomination included adequate information for the FDA to evaluate the substance and that the substance does not appear to present significant safety risks, and accordingly included in the published 503A Category 1 bulk drug substances list, may be used in compounding in accordance with this article if all of the following conditions are satisfied.*~~

~~*(A) Any facility using a bulk drug substance permitted by this subdivision shall:*~~

~~*(i) Assign a beyond-use date, supported by stability data obtained using stability-indicating analytical methods consistent with the provisions established in USP 797 Section 14.4.3, or stability information for a patient enrolled in a clinical trial that is approved by a U.S. Department of Health and Human Services (HHS) registered Institutional Review Board (IRB). The stability data or information is required regardless of the USP Category of CSP.*~~

~~*(ii) Dispense pursuant to a patient-specific prescription that documents the clinical circumstances that require the use of a bulk drug substance currently on the 503A Category 1 bulk drug substance list.*~~

~~*(iii 3) Failure to compound pursuant to this subdivision and the facility's SOPs constitutes unprofessional conduct and shall be deemed as posing an immediate threat to the public health as established subject to the provisions in Business and Professions Code section 4127.3*~~

(e) All APIs and other components used must be evaluated for suitability for use in sterile

drug preparations, as provided in USP 797, Section 9.3 Components, and follow the USP drug monograph if one exists. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes.

(f) If a component included on the published 503A Category 1 interim bulk drug substances list is used, it must be found suitable for sterile drug preparations following USP Chapter 797, Section 9.3 Components. The facility's SOPs must establish a process to determine the quality of the API.

1736.17(a)(2)(C), (E), and (F)

(C) The methods ~~**a pharmacist will**~~ use**d** to determine and approve the ~~***ingredients***~~ ***components*** and the compounding process for each preparation before compounding begins~~***;***~~ ***including components referenced in section 1736.9(f),***; and

(D) The method for complying with all other requirements specifically defined in the SOPS.s

~~***(E) The methods by which the pharmacist compounding or supervising the compounding pursuant to section 1736.9(f)(2)(e) related to use of a bulk drug substance published in the section 503A Category 1 bulk substances list, will ensure each lot of the bulk drug substance is representatively sampled per USP Chapter 1097 (bulk powder sampling procedures), tested, and found to be in compliance with at least:***~~

~~***(i) USP Chapter 1, Injections and Implanted Drug Products (Parenterals) – Product Quality Tests***~~

~~***(ii)USP Chapters 232 and 233 related to Elemental Impurities.***~~

~~***(iii) USP Chapter 467 – Residual Solvents.***~~

~~***(iv)USP Chapter 85 – Bacterial Endotoxins, and***~~

~~***(v) any other USP Chapters deemed appropriate based on the clinical judgment of the pharmacist developing the SOPs.***~~

~~***(F) Nothing in paragraph (E) requires the facility to perform this testing when it is performed by the manufacturer, repackager, or wholesaler and appropriate documentation***~~

Staff note that in response to previous comments the Board has been discussing this issue throughout the formal rulemaking process and has made significant changes to the proposed text to provide a legal pathway in California to compound using bulk drug substances included on the FDA Category 1 bulk drug substances list that meets the requirements of federal law, federal guidance and national standards.

The Board respectfully refers the commenter to the Board's response to prior similar comments that include the provisions of federal law established in section 503A of the federal Food, Drug, and Cosmetic Act (FDCA), relevant FDA guidance documents, and relevant sections of the national standards, especially those sections related to components. The Board notes that, contrary to what some public comment has stated, the FDA has not approved or authorized the

compounding of Category 1 bulk drug substances, nor has the FDA stated that compounding with these substances is safe in every instance. Rather, the FDA has released guidance that articulates an interim enforcement discretion policy that applies if an authorized facility or individual compounds using certain unapproved bulk drug substances, such as glutathione or methylcobalamin, but only under very specific conditions. Such conditions include that the original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under section 510 of the FDCA; that the bulk drug substance is accompanied by a valid Certificate of Analysis; and that the drug product compounded using the bulk drug substance is compounded in compliance with all other conditions of section 503A (including, for example, that the compound has not been produced or held under insanitary conditions). As the Board has noted previously, until the FDA formally makes a determination of approval of these bulk drug substances nominated for inclusion in 21 CFR 216.23, a pathway to allow for such compounding and continue access to these substances is needed.

Board staff respectfully also refer the commenters to USP Chapter 797, Section 9.3 Components, which specifically provides: "All APIs and other components used must be evaluated for suitability for use in sterile drug preparations. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes." The Chapter continues: "Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated…Any other lots of that component from that vendor must be examined to determine whether other lots have the same defect."

Further, the FDA Guidance Document, Insanitary Conditions at Compounding Facilities (dated November 2020) provides examples of insanitary conditions that the FDA has observed. The following is an example of an insanitary condition: "Using active ingredients, inactive ingredients, or processing aides, 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)."

The Board's underlying data included in the Modified Initial Statement of Reasons contains additional information specifically related to this issue, including, as an example, item 21, "FDA highlights concerns with using dietary ingredient glutathione to compound sterile injectables."

The Board continues to monitor information released from the FDA and evaluate compounding facilities during inspections for insanitary conditions and compliance with state and federal law and national standards.