COMPOUNDING

Thank you

STATUTORY MANDATE

BPC Section 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 the be promoted, the protection of the public **shall be paramount**."

COMMON QUESTIONS AND ANSWERS

COMMON QUESTIONS AND ANSWERS

Question: Do the Board's proposed regulations ban the compounding of substances such as glutathione and methylcobalamin?

Answer: No. The proposed regulations aim to align with federal law and national compounding standards. The Board's proposed language establishes provisions for compounding of these products while focusing on the purity, quality, and stability of such products for California patients.

PROPOSED TEXT

(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 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 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. The stability data 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) 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

COMMON QUESTIONS AND ANSWERS

Question: Why is the Board making changes to these compounding requirements?

- Answer: Compounding medications can provide California patients with access to medication that may not otherwise be available for a variety of reasons, but not without risk. The Board has conducted investigation of compounding preparations that resulted in harm to patients, including compounded glutathione. It is the Board's goal to protect patients while balancing consumer access.

FDA COMPOUNDING ALERT

FDA highlights concerns with using dietary ingredient glutathione to compound sterile injectables

Compounding Alert: June 7, 2019

FDA COMPOUNDING ALERT

Conclusion

These adverse events were consistent with reactions patients experience with excessive levels of endotoxin, and FDA's testing confirmed higher levels of endotoxin than is appropriate based on the dose of L-glutathione received intravenously. The L-glutathione powder the pharmacies received was labeled with "Caution: Dietary Supplement" and should not have been used to compound sterile injectable drugs. Ingredients not intended for use in compounding sterile injectable drugs can be harmful when administered to patients because they may contain impurities and contaminants, including endotoxins.

It is critical that compounders understand that quality should be built into the drug production, and that testing alone should not be relied on to ensure drug quality. Therefore, compounders should ensure that all ingredients they use to produce sterile injectable drugs are manufactured under conditions and specifications appropriate for the intended route of administration.

COMMON QUESTIONS AND ANSWERS

Question: Do the Board regulations become effective after the Board's discussion today?

Answer: No, the rulemaking process is ongoing. Should changes be approved by the Board, there will be another formal comment period. Should additional comments be received, the Board will consider the comments at a future Board meeting.

COMMON QUESTIONS AND ANSWERS

Question: Is there any oversight of the Board and its rulemaking activities?

Answer: Yes, the Government Code establishes the rulemaking process that the Board and other agencies must following when promulgating regulations. Examples of control agencies include the Department of Consumer Affairs, Business Consumer Services and Housing Agency, Department of Finance and the Office of Administrative Law.

HISTORY OF COMPOUNDING REGULATIONS

HISTORY OF COMPOUNDING REGULATION

November 1986 – Board's first compounding regulations.

Regulations included many of the same elements required both the in Board's current and proposed regulations and addressed items such as:

- Room, equipment, certification requirements
- Labeling requirements
- Recordkeeping requirements
- Garbing requirements
- Training Requirements
- Disposal
- Quality Assurance requirements
- Policies and Procedures
- Reference Materials

HISTORY OF COMPOUNDING REGULATION

May 2001, three vials of betamethasone were compounded and prepared into smaller vials. These smaller vials were sent to different health care facilities. Thirty-eight patients were injected. Of those 13 were hospitalized and three died. Remaining vials tested positive for bacteria.

Senate Bill 293 (Chapter 827, Statutes of 2001) established requirements for pharmacies compounding sterile injectable products and a requirement for the Board to promulgate regulations establishing compounding standards for compounding injectable sterile drug products.

HISTORY OF COMPOUNDING REGULATION

July 2010, Article 4.5 becomes effective establishing provisions for pharmacy compounding. This is in addition to Article 7 related to sterile injectable compounding requirements.

July 2017 Regulations amended.

- 3 Public Comment Periods (45-day and 2- 15-day) and a Regulation Hearing
- 4 Stakeholder meetings between July 2015 and February 2016
- Regulation adopted and approved by OAL in September 2016 with a January 1, 2017 effective date.

CONSUMER PROTECTION

CONSUMER PROTECTION

Death due to pharmacy compounding error reinforces need for safety focus.

June 28, 2017

ISMP Medication Safety Alert! Acute Care Edition. June 15, 2017;22:1-4.

Compounding pharmacies prepare medicines for patients that aren't available as commercial products. Reviewing a case involving a pediatric patient who died after receiving a compounded oral liquid suspension that contained the wrong medication, this newsletter article discusses weaknesses in compounding processes that contributed to the incident. Recommendations for pharmacies to reduce opportunities for error include independent double-checks and designated areas for compounding activities.

CONSUMER PROTECTION

January 31, 2018: New England Compounding Center Pharmacist Sentenced for Role in Nationwide Fungal Meningitis Outbreak

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REGULATION DEVELOPMENT

REGULATION DEVELOPMENT

- 2019 – 8 Meetings
  - Education and Regulation Development
- 2023 – 4 Committee Meetings
  - Education and Regulation Development

INITIAL STATEMENT OF REASONS

New subdivision (d) adds the definition of “Essentially a copy.” A definition is in current section 1735.1(k) of the board’s regulations. It is retained and moved into this definitions section of the new language as it is not included within USP <795> and is used elsewhere in the proposed regulations. The board, however, amended the existing language slightly to provide additional clarity and consistency by amending “comparable” to the “same” active pharmaceutical ingredients (APIs). This change is necessary to align the definition with the FDA guidance document, which says “the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the commercially available drug product (the guidance document is available as underlying data of this rulemaking (item number 9).”

INITIAL STATEMENT OF REASONS

Underlying Data

1. Relevant Meeting Materials from the Board of Pharmacy meeting held September 12, 2023 – Agenda Item VIII, Minutes Pages ##).
2. Relevant Meeting Materials from the Board of Pharmacy meeting held April 19-20, 2023 – Agenda Item XIV (Enforcement and Compounding Committee Meeting Materials Pages 1-5 and Attachments 1 and 2, Minutes Pages 1, 24-37).
3. Relevant Meeting Materials and Minutes from Board of Pharmacy Enforcement and Compounding Committee Meeting held April 13, 2023 (Meeting Materials Pages 1-4 and Attachments 2 – 5, Minutes Pages 1-29).
4. Relevant Meeting Materials and Minutes from Board of Pharmacy Enforcement and Compounding Committee Meeting held March 23, 2023 (Meeting Materials Pages 1-3 and Attachments 2 and 3, Minutes Pages 1-52).
5. Relevant Meeting Materials and Minutes from Board of Pharmacy Enforcement and Compounding Committee Meeting Held February 15, 2023 (Meeting Materials Pages 1-2 and Attachments 1 and 2, Minutes Pages 1-37).
6. Relevant Meeting Materials and Minutes from Board of Pharmacy Enforcement and Compounding Committee Meeting Held January 23, 2023 – (Meeting Materials Pages 1, 6-7 and Attachments 3 and 4, Minutes Pages 1, 7-41).
7. Food, Drug and Cosmetic Act – Title 21 United States Code Chapter 9, Subchapter V – Drugs and Devices, Part A
8. Food, Drug and Cosmetic Act Guidance Document, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (Revised June 2016)
9. Food Drug and Cosmetic Act Guidance Document, Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act
10. Chapter 795 of the United States Pharmacopeia - National Formulary (Effective November 1, 2023).
11. Chapter 797 of the United States Pharmacopeia - National Formulary (Effective November 1, 2023).
12. Chapter 800 of the United States Pharmacopeia - National Formulary (Effective July 1, 2020).
13. Chapter 825 of the United States Pharmacopeia - National Formulary (Effective December 1, 2020).
14. Chapter 1163 of the Unites States Pharmacopeia – National Formulary (Effective December 1, 2020).
15. CETA Certification Guide for Sterile Compounding Facilities (CAG-003, Revised October 2022).
16. United States Pharmacopeia 795, 797, 800, and 825 FAQs and Commentary

CURRENT VERSUS PROPOSED SECTION

Current:

(k) "Copy or essentially a copy" of a commercially available drug product includes all preparations that are comparable in active ingredients to commercially available drug products, except that it does not include any preparations in which there has been a change, made for an identified individual patient, which produces for that patient a clinically significant difference, as determined by a prescribing practitioner, between that compounded preparation and the comparable commercially available drug product.

Proposed:

(d) "Essentially a copy" of a commercially available drug product means a preparation that includes the same active pharmaceutical ingredient(s) (API(s)) as the commercially available drug product, except that it does not include any

preparation in which there has been a change made for an identified individual patient that produces for that patient a clinically significant difference, as determined by the prescribing practitioner, between that compounded preparation and the comparable commercially available drug product.

CURRENT VERSUS PROPOSED SECTION

Current:

(k) Prior to allowing any drug product preparation to be compounded in a pharmacy, the pharmacist-in-charge shall complete a self-assessment for compounding pharmacies developed by the board (Incorporated by reference is "Community Pharmacy & Hospital Outpatient Pharmacy Compounding Self-Assessment" Form 17M-39 Rev. 1/22) as required by Section 1715 of Title 16, Division 17, of the California Code of Regulations. That form contains a first section applicable to all compounding, and a second section applicable to sterile injectable compounding. The first section must be completed by the pharmacist-in-charge before any compounding is performed in the pharmacy. The second section must be completed by the pharmacist-in-charge before any sterile compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of each odd-numbered year, within 30 days of the start date of a new pharmacist-in-charge or change of location, and within 30 days of the issuance of a new pharmacy license. The primary purpose of the self-assessment is to promote compliance through self-examination and education.

CURRENT VERSUS PROPOSED SECTION

Proposed:

~~(e)~~ (f) Prior to allowing any CNSP to be compounded within a pharmacy, the pharmacist-in-charge shall complete a self-assessment consistent with the requirements established in section 1715.

(f) Prior to allowing any CSP to be compounded within a pharmacy, the pharmacist-in-charge shall complete a self-assessment consistent with the requirements established in section 1715.

CURRENT VERSUS PROPOSED SECTION

Current:

(k) The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which typically includes a room temperature of 20 degrees Celsius (68 degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.

Proposed:

(c)(1) Designated compounding area(s) shall typically be maintained at a temperature of 20° Celsius or cooler.

CURRENT VERSUS PROPOSED SECTION

- Additional Examples:

Current Section	Proposed Section
CCR 1735.6(b)	CCR 1735.6(b) & 1736.6(b)
1751.4(a)	1736.4(f)
1735.5(c)(2)	1735.12(a)(1)
1751.4(f)	1736.5(a)

CURRENT PROVISIONS BEING REMOVED

Examples of requirements being removed. Now covered in USP

- 1735.6(e): Related to HD room requirements
- 1751.7(c): Related to Glove fingertip testing
- 1751.7(b): Related to media fills
- 1751.4(f): Related to Certification every six months
- 1751.4(d)(1): Cleaning schedules

CURRENT VERSUS PROPOSED

Examples of proposed with changes from current requirements providing expansion of flexibility

- 1735.1(c)(3) to 1753.1(d)(2) Related to veterinary compounding
- 1735.3(f) Related to garbing accommodation
- 1736.2 (b) Related to aseptic qualifications used for other premises
- 1751.8(e) to 1736(b)(1) and (b)(2) Related to immediate use provisions

CHANGES MADE IN RESPONSE TO COMMENTS: STAFF RECOMMENDED MODIFIED TEXT

~~(a) At a minimum of every 6 months, air and surface sampling results shall be identified~~

Board of Pharmacy 16 CCR §§ 1735 et seq, 1736 et seq, 1737 et seq, 1738 et seq	Staff Recommended Modified Text Compounded Drug Products	Page 19 of 50 As proposed to be amended August 29, 2024

~~to at least the genus level, regardless of the CFU count to trend for growth of microorganisms. Investigation must be consistent with the deviation and must include evaluation of trends. If the laboratory is unable to identify to the genus level, the facility shall maintain with the sample results written documentation that no identification to that level could be made and an explanation as to why it could not.~~

CHANGES MADE IN RESPONSE TO COMMENTS: STAFF RECOMMENDED MODIFIED TEXT

- Provisions to compounding using bulk drug substances (bulks) on Category 1 Interim Bulks List
- Expanded provisions for veterinary office furnishing
- Exemption for consultation and labeling requirements to an inpatient of a health care facility and others as specified.
- Expanded authority for compounding of "essentially a copy of a commercially available drug product" in a health care facility licensed under specified conditions.
- Hazardous drug provisions
- Failure in training provisions

COMMENT REVIEW

Code Section Section (Subdivision)	Commenter	Comment	Response
1735(a)	National Community Pharmacists Association (NCPA), Scott Brunner Alliance for Pharmacy Compounding	As written this definition assumes that all FDA approved drugs have a diluent, resultant strength, and storage time. This will not always be the case.	Board staff have reviewed the comment and agree that language could be clarified. Staff are offering language to address comment.

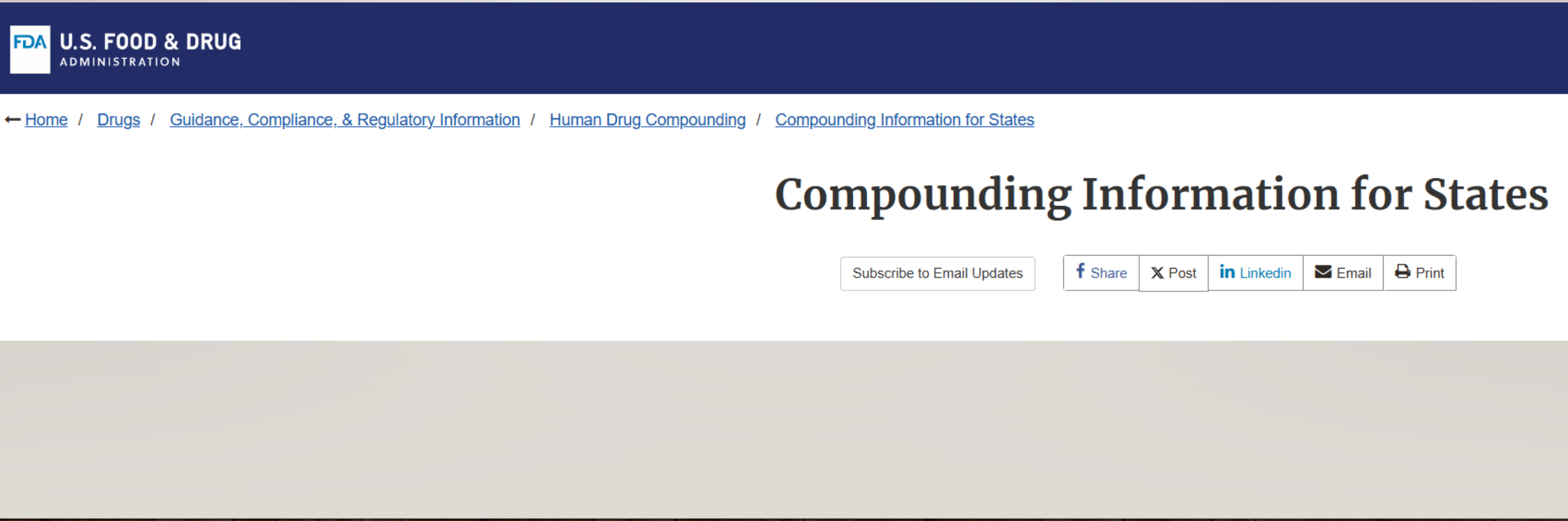
Section	Commenter	Comment	Response
1735.1(f)(1)(B)	A VanOStrand (Hims and Hers) Walgreens Marci Bencomo (Pacific Compounding) Marie Cottman (Pacific Compounding) National Community Pharmacists Association (NCPA) Scott Brunner (Alliance for Pharmacy Compounding) Rheta Silvas (Kaweah Health)	Several commenters expressed concern with the proposed language cited requiring the prescribing practitioner, the compounding pharmacist and the dispensing pharmacist to determine that the compounded preparation produces a clinically significant difference in the patient. The different commenters offered varying proposed text to address their respective comments.	Board staff have reviewed the comments and considered feedback from members. Staff are recommending changes to the proposed text to remove the requirement that could have potentially required two pharmacists to make independent determinations.

EXAMPLES OF ITEMS NOT COVERED IN USP OR WHERE USP DEFERS TO THE STATE

- Recall provisions and notification to the Board
- Adverse event reporting
- Terms lacking definitions
- PIC Responsibility

FDA ACTIONS

FDA: COMPOUNDING INFORMATION FOR STATES



FDA: COMPOUNDING INFORMATION FOR STATES

Collaborating with States

FDA's compounding program closely collaborates with state officials in a variety of ways, including:

- sharing information about compounders who engage in poor practices that could put patients at risk
- sharing information about complaints and adverse events
- sharing findings from inspections
- inviting states to participate in inspections of compounders
- supporting state actions by offering testimony
- hosting an annual intergovernmental working meetings with states to address issues of mutual concern, including continuous improvements to federal/state collaboration

FDA FAQS

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Guidance, Compliance, & Regulatory Information / Human Drug Compounding / Compounding and the FDA: Questions and Answers

Compounding and the FDA: Questions and Answers

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FDA FAQS

Are compounded drugs approved by FDA?

Compounded drugs are not FDA-approved. This means that FDA does not verify the safety, effectiveness or quality of compounded drugs before they are marketed. Consumers and health care professionals rely on FDA's drug approval process for verification of safety, effectiveness and quality.

What are the risks associated with compounded drugs?

Compounded drugs should only be used in patients whose medical needs cannot be met by an FDA-approved drug. Unnecessary use of compounded drugs may expose patients to potentially serious health risks. For example, poor compounding practices can result in serious drug quality problems, such as contamination or a drug that contains too much or too little active ingredient. This can lead to serious patient injury and death.

FDA FAQS

What quality standards apply to compounded drugs?

Quality standards for compounded drugs differ depending on the setting where compounding occurs. Drugs compounded in outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements. By contrast, drugs compounded by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a physician, in accordance with the conditions of section 503A of the FD&C Act, are not.

Regardless of where compounding occurs, in a pharmacy, outsourcing facility or physician's office, other federal law applies, including provisions regarding insanitary conditions. Compounding drugs under insanitary conditions can put patients at risk and lead to widespread patient harm.

FDA COMPOUNDING ALERT:

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Drug Safety and Availability / FDA warns compounders not to use glutathione from Letco Medical to compound sterile drugs

FDA warns compounders not to use glutathione from Letco Medical to compound sterile drugs

Agency is aware of adverse events related to compounded glutathione injection

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FDA COMPOUNDING ALERT:

FDA highlights concerns with using dietary ingredient glutathione to compound sterile injectables

Compounding Alert: June 7, 2019

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FDA COMPOUNDING ALERT:

FDA Analysis

Accompanying the initial adverse event reports were endotoxin test results from a third-party laboratory, which FDA found concerning. FDA then collected L-glutathione powder samples from Letco and from the pharmacy that compounded the drug associated with the seven adverse events. All samples tested by an FDA laboratory were found to contain excessive bacterial endotoxin with some results as high as five times the appropriate limit, which the agency calculated based on the L-glutathione dose received by the patients.[1] Endotoxin limits should be calculated using the maximum drug dose intended for intravenous (IV) administration. Symptoms associated with exposure to inappropriate endotoxin levels may include fever, chills, myalgia (muscle pain), headache, nausea, vomiting, hypotension (low blood pressure), shock and death.[2, 3]

FDA COMPOUNDING ALERT CON'T

Conclusion

These adverse events were consistent with reactions patients experience with excessive levels of endotoxin, and FDA's testing confirmed higher levels of endotoxin than is appropriate based on the dose of L-glutathione received intravenously. The L-glutathione powder the pharmacies received was labeled with "Caution: Dietary Supplement" and should not have been used to compound sterile injectable drugs. Ingredients not intended for use in compounding sterile injectable drugs can be harmful when administered to patients because they may contain impurities and contaminants, including endotoxins.

It is critical that compounders understand that quality should be built into the drug production, and that testing alone should not be relied on to ensure drug quality. Therefore, compounders should ensure that all ingredients they use to produce sterile injectable drugs are manufactured under conditions and specifications appropriate for the intended route of administration.

FDA COMPOUNDING ALERT

FDA alerts health care professionals of significant safety risks associated with cesium chloride

Summary

Cesium chloride (CsCl) is a mineral salt that is sometimes taken either by mouth, or by injection into the body, by cancer patients who seek alternative treatments. However, no CsCl products have been approved by FDA to treat cancer or other diseases. Furthermore, animal research has shown that taking CsCl can cause irregular heartbeats, also called arrhythmias. There have been reports of humans experiencing serious heart problems after taking CsCl. CsCl is associated with a lower blood level of potassium, which is a mineral that is essential to normal heart function.[1,3]

FDA COMPOUNDING ALERT

FDA investigates two serious adverse events associated with ImprimisRx's compounded curcumin emulsion product for injection

Adverse Events

On March 10, 2017, the U.S. Food and Drug Administration received an adverse event report concerning a 30-year-old female patient who experienced cardiac arrest after IV administration of a curcumin emulsion product compounded by ImprimisRx. The patient reportedly had a history of allergies and was being treated for eczema by a naturopathic doctor. Within minutes of starting the infusion, the patient became pulseless and required CPR. The patient suffered anoxic (depleted oxygen) brain injury and subsequently died. An adverse reaction to infused curcumin solution was identified as a cause of death by the local authorities.

FDA ACTIONS – WARNING LETTER

January 13, 2020

CMS Case # 598303

WARNING LETTER

Mr. Anderson:

From March 26, 2019, to April 5, 2019, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Anderson Compounding Pharmacy, Inc. dba Anderson Compounding Pharmacy, located at 310 Bluff City Hwy, Bristol, Tennessee 37620. The investigators noted serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to your firm on April 5, 2019. FDA acknowledges receipt of your facility's response, dated April 25, 2019, in which you stated that "[e]ffective March 25, 2019, the Pharmacy voluntarily ceased sterile compounding of human and veterinary drugs." FDA also acknowledges your voluntary recall, initiated on April 2, 2019, of all drug products intended to be sterile produced from September 25, 2018, to March 25, 2019, due to lack of sterility assurance.

Based on this inspection, it appears that you produced drug products that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Violations of the FDCA

FDA OBSERVATIONS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949) 608-2900 Fax: (949) 608-4417	3/4/2020-3/11/2020* FEI NUMBER 3009571102

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Christine A. Givant, Co-Owner and Pharmacist in Charge

FIRM NAME	STREET ADDRESS
La Vita Compounding Pharmacy, LLC	3978 Sorrento Valley Blvd Ste 300
CITY, STATE, ZIP CODE, COUNTRY San Diego, CA 92121-1436	TYPE ESTABLISHMENT INSPECTED Producer of Sterile and Non-Sterile Drugs

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

You used a non-pharmaceutical grade component in the formulation of a drug product.

Specifically, the firm purchases Methylcobalamin active ingredient from (b) (4) for use in the production of Methylcobalamin solution for injection. The firm has purchased and used (b) (4) lots of this active ingredient that lacks a description of grade. These ungraded active ingredient batches were used in the production of (b) (4) finished product batches:

(b) (4)

FDA - OBSERVATIONS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612-2445 (949) 608-2900 Fax: (949) 608-4417	11/12/2019-11/22/2019* FEI NUMBER 3005031360

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Si Pham, PharmD, Pharmacist in Charge

FIRM NAME	STREET ADDRESS
McGuff Compounding Pharmacy Services, Inc.	2921 W Macarthur Blvd Ste 142
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Santa Ana, CA 92704-7944	Producer of sterile and non-sterile products

OBSERVATION 7
You used a non-pharmaceutical grade component in the formulation of a drug product.

Specifically,

According to your Raw Material Listing dated 19-Nov-19, you currently use the following dietary grade bulk substances in sterile injectable drug products:

- Choline Chloride
- Alpha Lipoic Acid
- Glucosamine HCl
- Reduced L-Glutathione (Non-Yeast)
- beta-NAD+ [oxidized form]

The following was observed regarding the use of non-pharmaceutical grade bulk substances in your products:

a) On 10-Jan-19, you initiated a recall of Lipoic Acid 40 mg/ml, 30 ml multi-dose vials, lot 18M0991, BUD 15-Jun-19, due to a "filmy/wispy precipitate" found in on-hand vials of released product.

b) You discontinued production of NADH disodium 50 mg/ml after rejecting (b) (4) of this product (produced 25-Apr-19 and 08-Oct-19) due to out of specification (OOS) endotoxin results. You attributed the cause of these results to the raw material, and state in the material review memo (b) (4), dated 18-Oct-19, "NADH raw material is nutraceutical grade", and "it is possible there is variation in presence and quantity of endotoxin from one b-NADH container to the next, within the same vendor's lot".

RECENT FDA ALERT: OCTOBER 30, 2024

FDA reminds compounders to use ingredients suitable for sterile compounding

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FDA is reminding compounders to only produce sterile drugs using components that are suitable for compounding drugs intended to be sterile.

The agency is aware of compounders using food-grade nicotinamide adenine dinucleotide (NAD+) sold by repackagers to make intravenous products. Ingredients identified as food grade are not suitable for compounding sterile drugs without appropriate processing, due to the high risk of contamination with microbes and endotoxins, which can harm patients.

FDA also reminds compounders to only use appropriate ingredients when compounding drugs intended to be sterile to help ensure patient safety.

The agency urges manufacturers, including repackagers, to clearly identify any ingredients intended for use in foods or dietary supplements on the label. Providing this information on ingredient labels could help prevent compounders from using ingredients that are not appropriate for sterile drugs and may help prevent patient harm.

FDA has received adverse event reports following use of NAD+ injectable drugs, including severe chills, shaking, vomiting and fatigue with some requiring medical treatment. These reactions are consistent with excessive levels of endotoxins.

The agency encourages compounders to know your bulks and excipient suppliers and

Content current as of:
10/30/2024

Regulated Product(s)
Drugs

RECENT FDA: MEDWATCH

TOPIC: FDA Reminds Compounders to Use Ingredients Suitable for Sterile Compounding - CDER Alert

AUDIENCE: Patient, Health Care Professional, Pharmacy

ISSUE: FDA is reminding compounders to only produce sterile drugs using components that are suitable for compounding drugs intended to be sterile. The agency also reminds compounders to only use appropriate ingredients when compounding drugs intended to be sterile to help ensure patient safety.

FDA urges manufacturers, including repackagers, to clearly identify any ingredients intended for use in foods or dietary supplements on the label. Providing this information on ingredient labels could help prevent compounders from using ingredients that are not appropriate for sterile drugs and may help prevent patient harm.

FDA has received adverse event reports following use of NAD+ injectable drugs, including severe chills, shaking, vomiting and fatigue with some requiring medical treatment. These reactions are consistent with excessive levels of endotoxins.

Previously, FDA highlighted concerns with using dietary ingredient glutathione to compound sterile injectables.

For more information about this alert, click on the red button **"Read Alert"** below.

INTERIM GUIDANCE – BULK SUBSTANCES

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

monograph" to mean an official USP or NF **drug substance** monograph. Accordingly, FDA does not consider USP monographs for dietary supplements to be "applicable" USP or NF monographs within the meaning of section 503A(b)(1)(A)(i)(I).

INTERIM GUIDANCE – BULK SUBSTANCES

1. The bulk drug substance appears in 503A Category 1 on FDA's website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf. A Category 1 substance may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information for FDA to

[21] See the Appendix for a chart summarizing FDA's interim policy.

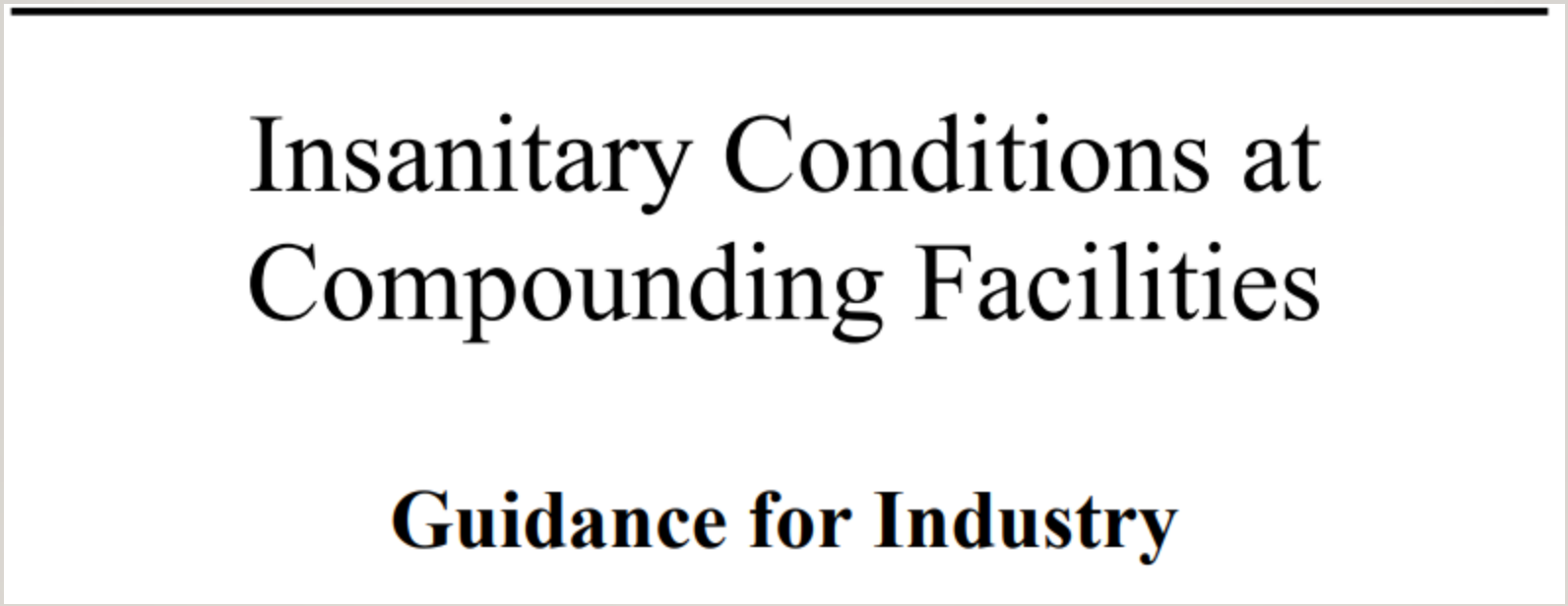
evaluate it and has not been identified by FDA as a substance that presents a significant safety risk in compounding prior to the publication of a final rule.

2. The original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under section 510 (including foreign establishments that are registered under section 510(i)) of the FD&C Act);

3. The bulk drug substance is accompanied by a valid COA; and

4. The drug product compounded using the bulk drug substance is compounded in compliance with all other conditions of section 503A of the FD&C Act.

INTERIM GUIDANCE: INSANITARY CONDITIONS



INTERIM GUIDANCE: INSANITARY CONDITIONS

Under sections 503A and 503B of the FD&C Act (21 U.S.C. 353a and 353b), compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section provides an exemption from section 501(a)(2)(A) of the FD&C Act. Drugs (including biological products) prepared, packed, or held (hereinafter referred to as "produced") under insanitary conditions are deemed to be adulterated, regardless of whether the drugs qualify for exemptions set forth in sections 503A or 503B of the FD&C Act.

- 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)

FDA: KNOW YOUR BULKS SUPPLIER

U.S. FOOD & DRUG ADMINISTRATION

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FDA to Compounders: Know Your Bulks and Excipients Suppliers

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FDA: KNOW YOUR BULKS SUPPLIER

Quality Matters Related to Components of a Drug

FDA continues to identify several issues related to repackagers of bulk drug substances, also called active pharmaceutical ingredients (APIs), and excipients used to compound drugs that have resulted in patient harm.

The agency urges compounders to know your bulk drug substance, or API, and excipient suppliers and know if the supplier is testing the component to ensure it is of appropriate quality to use in drugs. The quality of bulk drug substances and excipients can affect the quality of compounded drugs.

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FDA Urges Compounders to:

- know your bulk drug substance and excipient suppliers
- know the quality of the materials you get from your suppliers, including what testing the supplier does to determine the quality of the components you purchase
- meet the conditions regarding bulk drug substances in sections 503A and 503B of the Federal Food, Drug and Cosmetic Act, including:
    - API compliance with applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph standars
    - sourcing API from FDA-registered facilities
    - valid certificates of analysis
    - excipient compliance with applicable USP or NF monograph standards

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Repackagers should:

- ask compounders how they intend to use the ingredient to help ensure the ingredient is appropriate for use in a drug
- follow all quality standards pertaining to API you repackage
- ensure you have sufficient supply chain transparency to mitigate risks to patients
- clearly identify the original API manufacturer to customers who use them to make the finished drugs
- report quality problems to FDA
- do not have false or misleading labels regarding the identity of the manufacturer of the component you are selling (21 CFR 201.1(h)(2))

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Examples of Quality Issues with Bulk Drug Substances and Excipients

The agency has issued alerts regarding several quality issues:

- baclofen API
- dietary ingredient nicotinamide adenine dinucleotide (NAD+)
- dietary ingredient glutathione
- curcumin emulsion found to contain diethylene glycol (DEG) toxin

Additionally, Darmerica recalled bulk API, which shipped API labeled as quinacrine dihydrochloride to compounders nationwide, but subsequent tests identified the API as artemisinin.

original manufacturer, Supriya. The Supriya certificate of analysis (COA) for this

ingredient[21] indicates that the applicable specifications for heavy metals were less than one part per million (ppm) of lead, arsenic, and cadmium, and less than 0.1 ppm of mercury. The Supriya COA states that none of those metals were detected, except 0.03 ppm arsenic (3 percent of the specified allowable amount). However, significantly, [redacted] did not have the Supriya COA at the time he was compounding using the methylcobalamin from Medisca lot number 155828; rather, he had and was relying on a Medisca COA, which did not indicate the grade or original manufacturer of the methylcobalamin.[22]

OTHER REGULATORS AND AGENCIES

NABP – COMPOUNDING INSPECTION FORM

51.1	APIs or other components have been evaluated for use in sterile drug preparation. ***Inspector note: Per USP <797>, "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."*** ***If no, photograph and describe in the notes column. Request copies of the invoices for products with these types of labels.***	

KENTUCKY: ACTIONS TAKEN

From December 1, 2020 through May 25, 2021, the following were shipped into Kentucky that were compounded preparations compounded with bulk substances that:

- Do not have an USP or NF monograph;
- Are not a component of an FDA approved human drug;
- Do not appear on the FDA's 503A Bulk Drug Substances list; and/or
- Are considered biologics

Compound	Number of times shipped	Issue
Urofollitropin (FSH)	3	Biological Product
Human Chorionic Gonadotropin (HCG) Oral	210	Biological Product
Human Chorionic Gonadotropin (HCG) Injectable	1351	Biological Product
Ibutamoren (MK-677)	43	No USP/NF monograph, not component of FDA approved human drug, not on Bulk Substance list
Ipamorelin	112	No USP/NF monograph, not component of FDA approved human drug, not on Bulk Substance list
Menatropins	4	Biological Product

KENTUCKY: COMPOUNDING REGULATIONS

Section 3. Standards.

(1) All non-sterile compounded preparations shall be compounded pursuant to USP 795.

(2) All sterile compounded preparations shall be compounded pursuant to USP 797.

(3) All preparation, compounding, dispensing, and repackaging of radiopharmaceuticals shall be pursuant to USP 825.

(4) All non-sterile or sterile compounded preparations containing hazardous drugs shall be compounded pursuant to USP 800, unless specified portions submitted by a p
the board.

(5) Non-sterile and sterile preparations compounded for human use shall:[

(a)

1. Comply with the standards of an applicable USP or National Formulary monograph;
2. Be compounded from a component of a human drug approved by the United States Food and Drug Administration (FDA); or
3. Be compounded from a component that appears on the FDA's list of bulk drug substances established in 21 C.F.R. 216.23 that can be used in compounding; and

(b) Not be essential copies of a commercially available drug product unless authorized by 21 U.S.C. 353(a).

KANSAS: PROPOSED COMPOUNDING REGULATIONS

~~specified in this subsection:~~ "⟨797⟩ PHARMACEUTICAL COMPOUNDING-STERILE PREPARATIONS," published by the U.S. pharmacopeia (USP), dated November 1, 2023, is hereby adopted by reference with the following modifications:

(1) General changes:

(A) Each "must" shall be replaced with "shall."

(B) Each "should" shall be replaced with "shall" except in section 4.2.1 Types of SECs and design, in the fifth paragraph, in the third sentence, "should" shall be replaced with "may."

MASSACHUSETTS: PROPOSED COMPOUNDING REGULATIONS

Section

17.01: Authority and Purpose
17.02: Licensure Requirements
17.03: General Requirements
17.04: General Facility Requirements
17.05: Heating, Ventilation, and Air Conditioning (HVAC) Systems
17.06: Primary Engineering Controls (PEC) including Containment Primary Engineering Controls (C-PEC)
17.07: Secondary Engineering Controls (SEC)
17.08: Certification of ISO Classified Areas
17.09: Pressure Differential Monitoring
17.10: Temperature and Humidity
17.11: Smoke Studies
17.12: Environmental Monitoring (EM)
17.13: Environmental Monitoring Action Levels
17.14: Cleaning and Disinfecting
17.15: Hand Hygiene and Garbing
17.16: Training and Qualification
17.17: Sterility and Endotoxin Testing
17.18: Beyond Use Date (BUD)
17.19: Master Formulation Records
17.20: Compounding Records
17.21: Labeling
17.22: Counseling

17.01: Authority and Purpose

247 CMR 17.00 is promulgated under the authority granted to the Board by M.G.L. c. 112, §§ 39F, 39G, 39I, 39J, and 42A. The purpose of 247 CMR 17.00 is to establish minimum professional standards for sterile compounding in order to safeguard the public health and welfare. 247 CMR 17.00 applies to pharmacies that hold a sterile compounding pharmacy license, non-resident sterile compounding pharmacy license, or institutional sterile compounding pharmacy license.

MASSACHUSETTS: PROPOSED COMPOUNDING REGULATIONS

17.03: General Requirements

(1) A pharmacy licensed by the Board that performs sterile compounding, including veterinary compounding, shall comply with all state and federal laws and regulations and all chapters of the most current United States Pharmacopeia (USP).

(2) A pharmacy shall maintain written policies and procedures on all aspects of the sterile compounding operation and a formal, written Quality Assurance Program in accordance with USP <1163>.

MASSACHUSETTS: PROPOSED COMPOUNDING REGULATIONS

17.10: Temperature and Humidity

(1) SECs shall maintain a temperature of 68 degrees Fahrenheit (20 degrees Celsius) or lower.

(2) SECs shall maintain a relative humidity of 60% or lower.

(3) A pharmacy shall have a system to continuously measure the temperature and humidity of each SEC. The quantitative results shall be reviewed and documented at least daily on all days the pharmacy is open.

(4) A pharmacy shall respond to out-of-range temperature or humidity levels in a timely manner and document the response.

MASSACHUSETTS: PROPOSED COMPOUNDING REGULATIONS

17.13: Environmental Monitoring Action Levels

(1) A Manager of Record or Designated Pharmacist-in-Charge shall notify the Board, in the manner and format determined by the Board, of any action level EM results.

(2) Action levels shall be defined by USP <797> or Board policy, whichever is stricter.

(3) A pharmacy shall immediately respond to and properly remediate action level EM results.

(4) A pharmacy shall maintain a written policy and procedure for response and remediation of action level EM results.

MASSACHUSETTS: PROPOSED COMPOUNDING REGULATIONS

17.16: Training and Qualification

(1) After initial qualification, garbing competency and a media-fill test followed by gloved fingertip/thumb sampling and surface sampling of the direct compounding area shall be performed by personnel who physically compound or directly supervise compounding:
  (a) at least once every six months; or
  (b) at least once every three months if sterile compounding includes any non-sterile starting components or involves the assignment of a BUD that requires sterility testing and / or terminal sterilization.

(2) In the event an individual fails a written sterile compounding assessment exam, gloved fingertip/thumb sampling, media-fill test, or surface sampling, they may not compound until retrained and requalified.

(3) Compounding personnel shall be retrained and requalified if a pause in sterile compounding practice exceeds six months.

PATIENT HARM

PATIENT HARM

42. In 2017 and 2018, [redacted] received reports of adverse drug effects (i.e., headaches, high fevers, diarrhea, extreme fatigue, loss of consciousness, chills and nausea) suffered by patients after being administered infusions of lipoic acid compounded and dispensed by [redacted].

PATIENT HARM

57. Despite the filing of the Accusation, the discussions with the FDA and Board about safety risks associated with using inappropriate ingredients, the receipt of the FDA Form 483, the receipt of the Board's Order of Correction and the Written Notice and Respondents' promises to cease compounding and dispensing sterile injectable drugs with dietary grade and non-compendial substances, from at least June 1, 2021 through December 1, 2021, [redacted] continued to compound and dispense sterile injectable drugs, methylcobalamin 5mg/mL, glutathione 200mg/mL, taurine, lipoic acid and DMPS using inappropriate ingredients (i.e., dietary grade and ungraded bulk substances) likely containing higher levels of contaminates or impurities, including heavy metals, bacteria and mold and higher bioburden levels (i.e., the number of bacteria living

58. In 2021, [redacted] received reports of at least six adverse drug effects, including headaches, fever, chills and nausea from sterile injectable drugs compounded and dispensed, but failed to timely report at least four of those adverse drug effects to the Board. It also failed to report at least four of the adverse drug effects immediately to the MedWatch Program of the FDA.

PATIENT HARM

Institute for Safe Medication Practices Canada

REPORT MEDICATION INCIDENTS
Online: www.ismpcanada.ca/report/
Phone: 1-866-544-7672

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ISMP Canada Safety Bulletin

Volume 23 • Issue 10 • October 11, 2023

ALERT: Clonidine Compounding Errors Continue to Harm Children

INCIDENT EXAMPLES

- A child received 1000 times the intended clonidine dose because of a mix-up between units of measure (micrograms vs milligrams) during the process of preparing a suspension. The child required admission to a pediatric intensive care unit.
- A child experienced severe drowsiness, leading to hospitalization, after receiving a dose of compounded clonidine suspension. Testing of the prepared product determined that it was over 10 times more concentrated than intended. Inaccurate trituration of clonidine powder was reported as a contributing factor.

PATIENT HARM

Parents of children hospitalized after taking meds from Eminence pharmacy want answers

Darby Beane Aug 27, 2024 Updated Aug 29, 2024

"It's a compounded medicine and there's not many pharmacies in the area that do compounding," he said. "I mean, we have two or three pharmacies in Eminence that are available to us and Med Save is the only one that can fulfill that prescription."

5-year-old Kentucky girl remains in ICU after taking potentially bad batch of clonidine

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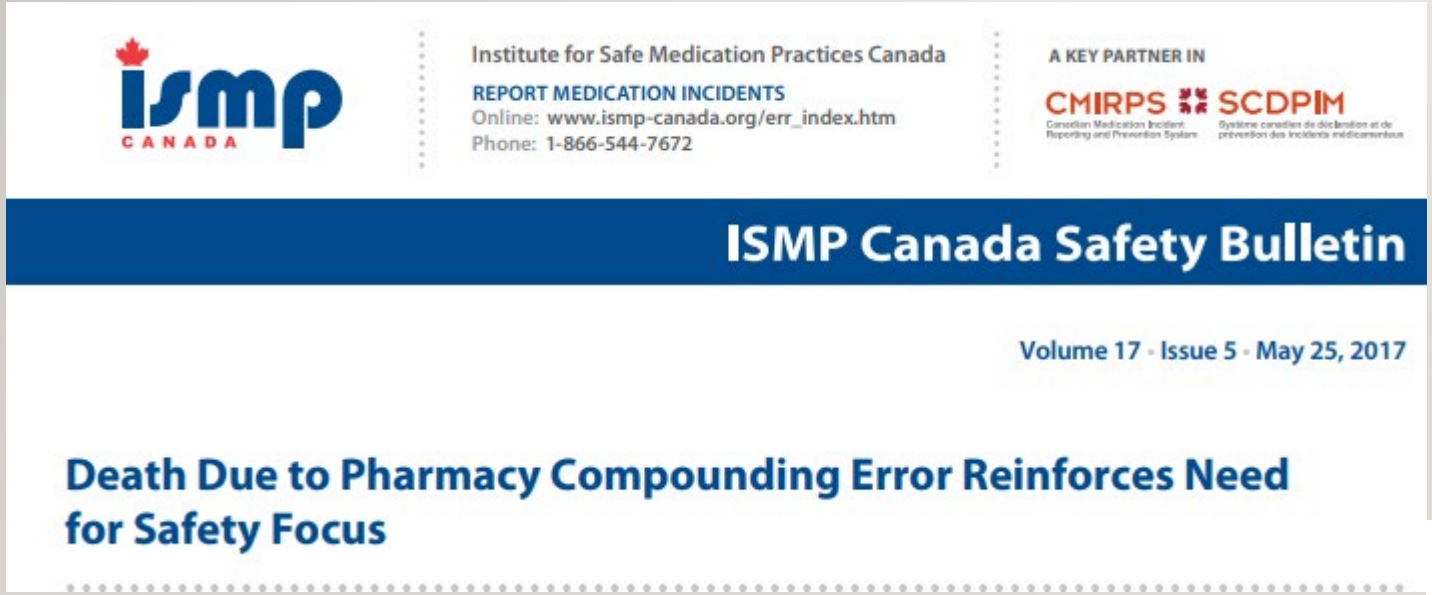
WLKY

Updated: 7:10 PM EDT Aug 27, 2024

PATIENT HARM



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ISMP Canada Safety Bulletin

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Death Due to Pharmacy Compounding Error Reinforces Need for Safety Focus

Case Description

For about 18 months, a young child had been receiving a 3 gram (20 mL) dose of tryptophan 150 mg/mL suspension by mouth at bedtime to treat a complex sleep disorder. A refill of the tryptophan prescription was ordered and picked up from the compounding pharmacy that had prepared the suspension in the past. That night, the child was given the usual dose of medication; the next morning, the child was found deceased in bed.

PATIENT HARM

Possible Risks of Drug Compounding Seen in Vision Loss Cases

Strong and well-enforced quality standards can protect patients

ARTICLE | October 25, 2018 | By: Elizabeth Jungman | Read time: 2 min

Projects: Drug Safety

Last year, dozens of people in the Dallas, Texas, area reported symptoms such as vision impairment, poor night vision, and loss of color perception after they received eye injections of compounded antibiotics during cataract surgery. The Food and Drug Administration (FDA) later issued a safety alert that said the drug was made with a large amount of an inactive ingredient that apparently degraded as the drug was prepared.

PATIENT HARM

Data Table — THE PEW CHARITABLE TRUSTS — March 2020

U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-19

Year	Reported cases	Reported deaths	Adverse event(s)	Compounding error	Product	State where compounding occurred	State(s) where adverse event(s) occurred	Notes
2018-2019[3]	8		Nausea, vomiting, lightheadedness, chills, fever, shaking, body aches, sneezing, low blood pressure, difficulty breathing, hospitalization	Product was labeled for use in dietary supplements, not injectable drugs; contained excessive levels of bacterial endotoxin	Injectable drug compounded with L-glutathione 200mg/mL powder	Not reported	Not reported	The distributor of the ingredient L-glutathione was located in Alabama, but the location of the compounders was not reported.
2001-2018[4]	23	At least 2	Irregular heart rhythm, seizures, potentially lethal arrhythmias, fainting, cardiac arrest, and death	Products contained cesium chloride, which is not approved by FDA to treat disease.	Compounded products containing cesium chloride	Not reported	Not reported	Patients were administered cesium chloride to treat their cancer. It is not approved for this indication, and FDA subsequently issued a compounding risk alert and banned its use in compounded products.
2016-2018[5]	46		Eye inflammation, eye infections, high eye pressures, color variation, spots over vision	Not reported	28 adverse events were related to eye injections of repackaged sterile Avastin (bevacizumab); source of remaining 18 adverse events not reported.	FL	Not reported	Adverse events were identified upon inspection. Compounding facility failed to report these adverse events to FDA, and did not conduct an appropriate investigation.

POTENTIAL BOARD ACTIONS

1. Do nothing, allow the currently noticed proposed regulation to expire.
2. Withdraw the current rulemaking.
3. Move forward with the current rulemaking for another comment period.

STATUTORY MANDATE

BPC Section 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 the be promoted, the protection of the public **shall be paramount**."

RECOMMENDATION

Staff Recommendation: Option 3

Specifically release the proposed modified text included in the meeting materials, for another comment period.

Opens the rulemaking for public comment. It does not adopt regulation requirements.

POSSIBLE MOTION

Possible motion:

1. Accept the Board staff recommended responses as included in the packet, including the updated supplemental responses, to the initial comments from the 45-day comment period and regulation hearing as the responses of the Board and

2. Approve the recommended modified regulation text [either "dated August 29, 2024 as presented" or "as discussed by the Board] for a [either "15-day public comment period" or "[insert different time frame] day public comment period"

3. Additionally, delegate to Members Serpa and Barker the authority to review comments received to the modified text during the public comment period with staff to present recommended changes and responses at a future Board meeting.