Board of Pharmacy
Final Statement of Reasons

Hearing Date: None

Subject Matter of Proposed Regulation: Compounded Drug Preparations

Sections Affected: Amend § 1735.1 of Article 4.5 of Division 17 of Title 16 CCR.
Amend § 1735.2 of Article 4.5 of Division 17 of Title 16 CCR.
Amend § 1735.6 of Article 4.5 of Division 17 of Title 16 CCR.
Amend § 1751.1 of Article 7 of Division 17 of Title 16 CCR.
Amend § 1751.4 of Article 7 of Division 17 of Title 16 CCR.

Updated Information

The Initial Statement of Reasons is included in this rulemaking file. The information contained therein accurately reflects the Board of Pharmacy's (board) position regarding the adoption of the above sections, and is updated as follows:

The 45-day comment period began on August 3, 2018 and ended on September 17, 2018. No request for a hearing was received by the board during the 45-day comment period, and no hearing was held.

During the 45-day comment period, the board received six comments in response to the proposed regulation. The board considered these comments at its meeting held September 26, 2018. In response to the comments received and recommendations by board staff, the board voted to modify the text and initiate a 15-day public comment period.

The modified text was noticed for a 15-day comment period, which began on September 26, 2018 and ended on October 11, 2018. The board received eight comments during this comment period. The comments were reviewed and discussed at the meeting held on October 23 and 24. No additional changes were made in response to the comments received during the 15-day comment period.

On October 15, 2018, the following document was added to the rulemaking file:

- Controlled Environment Testing Associate (CETA) Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015).

This document was added to the rulemaking file as it is referenced within USP Chapter 797 and to ensure that a complete rulemaking record is maintained in one location. The 15-day public comment period to allow the public the opportunity to review the document added to the rulemaking file ended on October 30, 2018. No comments were received.

After having considered all comments in the record, the board adopted the regulation, as noticed on September 26, 2018.

Amend 16 CCR §1735.6

Existing regulations at 16 CCR §1735.6 specify standards for compounding facilities and equipment.

The following updates to the initial statement of reasons are made:

- Subdivision (e)(3) was amended and separated into two subdivisions to clarify the differences between the external exhausting for sterile and nonsterile compounding.
    - New subdivision (e)(3)(A) reads "For sterile compounding, each BSC or CACI shall be externally exhausted."
    - New subdivision (e)(3)(B) reads "For nonsterile compounding, a BSC, a CACI, or other containment ventilated enclosure shall be used and shall either use a redundant-HEPA filter in series or be externally exhausted. For purposes of this paragraph, a containment ventilated enclosure means a full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through high-efficiency particulate air (HEPA) filtration and to prevent their release into the work environment."

In the final version of this language, a Compounding Aseptic Containment Isolator (CACI) is added as an optional device to use in hazardous compounding. The use of a CACI was inadvertently left out of the original proposed text when the language was amended from primary engineering control (PEC) to Biological Safety Cabinet (BSC). The inclusion of a CACI is appropriate within this section because it is also a type of containment device that would appropriately control particulate distribution that might occur during hazardous compounding.

Upon further review of the proposed language, it was identified that the language may have inadvertently prevented the ability to use other types of containment devices when preparing hazardous nonsterile compounds. Under the provisions of USP Chapter 800, an alternative containment device may be used for compounding hazardous nonsterile preparations, and may alternately use a redundant HEPA filter rather than external exhaustion. In recognition of this, the proposed language was further modified to allow those means to control particulate distribution.

Further, the word "also" was deleted from the existing language of subsection (e)(3)(A), so that, if the containment device is itself externally vented, the facility will satisfy main subsection (e) by exhausting the room through the containment device itself. Though this is an unusual method of exhausting the room, any particulates should be adequately removed to protect the products and the compounding staff.

Amend 16 CCR §1751.4(k)

Existing regulations at 16 CCR §1751.4(k) specify the temperature requirements for the sterile compounding area.

The following updates to the initial statement of reasons are made:

Subdivision (k) was further amended to add the word "typically" into the text. The section continues a prior requirement that a pharmacy provide a comfortable and well-lighted working environment to maintain comfortable conditions for compounding personnel when attired in the required compounding garb. As revised, the rule also now clarifies that such comfortable conditions would typically include a room temperature of 20 degrees Celsius (68 degrees Fahrenheit) or cooler. The modification was made to allow some flexibility to account for individuals' needs. The standard remains that the individuals in each environment must be comfortable, because, in general, the compounder's discomfort can distract the compounder from performing their functions appropriately. In addition, if the room is too warm and the compounder perspires, the bacteria-containing perspiration could get into a sterile compounded product and pose a risk to the public.

- The addition of the word "typically" reflects that "20 degrees … or cooler" is a guideline and allows flexibility – some individuals will need it warmer in order to feel their fingers; others will require cooler conditions so that they will not perspire. Additionally, the board chose this construction because it is identical to language in USP Chapter 797, which specifies that facilities provide a comfortable and well lighted working environment, "which typically includes a temperature of 20° or cooler […]." The standard remains that the individuals in each environment must be comfortable, because, in general, the compounder's discomfort can distract the compounder from performing their functions appropriately. In addition, if the room is too warm and the compounder perspires, the bacteria-containing perspiration could get into a sterile compounded product and pose a risk to the public. Although the board will not have a specific temperature range to enforce against, it is important that individuals are comfortable when performing compounding; providing the guideline consistent with USP (that the room typically will be 20 degrees or cooler) makes it clear that California no longer has a different standard. Another benefit of having a guideline consistent with USP is that compliance is simple for compounders, because, in the absence of more stringent board standards, they should already be following national standards.

Local Mandate

A mandate is not imposed on local agencies or school districts.

Small Business Impact

The board believes this regulation will have a minor impact to small businesses. Although the board does not have nor maintain data to define if any of its licensees (pharmacies) are a "small business" as defined in Government Code section 11342.610, the board has made an initial determination that the proposed regulatory action would not have a significant adverse economic impact directly affecting small businesses. This is based on the determination that the regulatory proposal could result

in existing pharmacies, some of which are likely small businesses, offering more nonsterile compounding services, lower costs for those services, patients receiving a larger supply of medication at one time, and fewer patient visits to the doctor and/or pharmacy. Pharmacies that are small businesses may experience cost savings due to decreased testing requirements to extend the duration of a drug preparation's usefulness; it is also possible that they may experience a very minor increase in costs related to record keeping in so doing.

Consideration of Alternatives

The board has determined that no alternative it considered or that has otherwise been identified and brought to the attention of the board would be more effective in carrying out the purpose for which the action is proposed, would be as effective and less burdensome to affected private persons than the proposed action, or would be more cost effective to affected private persons and equally effective in implementing the statutory policy or other provision of law.

The amendments adopted by the board are the only regulatory provisions identified by the board that accomplish the goal of protecting consumers of pharmacy compounding services by setting standards designed to ensure that compounding is performed in a manner and under conditions that ensure the compounded drug preparations dispensed to the public by a pharmacy and pharmacist are safe and effective. Except as set forth and discussed in the summary and responses to comments, no other alternatives have been proposed or otherwise brought to the board's attention.

Objections or Recommendations/Responses

During the 45-day comment period (August 3, 2018 – September 17, 2018), the board received six comments. The comments were provided to the board in the meeting materials for the September 26, 2018 board meeting, and were reviewed and considered by the board at that meeting. A couple of changes were made to address some of these comments and the board voted to initiate a 15-day comment period.

#1 Written Comments from Ayk Dzhragatspanyan, PharmD.

Comment #1.A: Dr. Dzhragatspanyan expressed concern about the inability to use published formulas for beyond use dates with respect to non-sterile preparations. Dr. Dzhragatspanyan indicated that he believes that the regulation is very restrictive and impacts patients. He recommended that the regulations be amended to allow for the use of published literature when compounding for establishing a Beyond Use Date (BUD).

Board response to comment #1.A: The board rejected this comment because his suggestions were already incorporated into the regulation text as proposed (see the adopted text of CCR section 1735.2(i)(1)(G)). The adopted text allows for the use of documentation, literature, research, and analysis by the pharmacist when establishing a beyond use date for non-sterile drug preparations. This change is consistent with USP

Chapter 795, specifically the provisions established under the heading, “Stability Criteria and Beyond-Use Dating.”

Comment #1.B: Dr. Dzhragatspanyan also expressed concern about the 3-day BUD limit for sterile preparations. Dr. Dzhragatspanyan indicated that the sterility testing takes two weeks to complete.

Board response to comment #1.B: The board rejected this comment. The board's current regulations relating to the establishment of a BUD for sterile preparations are consistent with USP Chapter 797 provisions relating to sterile preparations. The primary focus of this regulation proposal relates to modifying the BUDs for nonsterile compounded preparations. In this rulemaking, changes to the standard for sterile BUDs have not been explored.

#2: Written Comments from Corbin Bennett, Pharm.D.

Comment #2: Dr. Bennett recommended adding “CACI” following the term “BSC” to section 1735.6(e)(3).

Board response to comment #2: The board accepted this comment. As previously indicated, the use of a CACI was inadvertently left out of the original proposed text when the language was amended from PEC to BSC. The inclusion of a CACI is appropriate within this section because it is also a type of containment device that would appropriately control particulate distribution that might occur during hazardous compounding.

#3: Written Comments from Sarah Han-Yoo, Pharm.D.

Comment #3: Dr. Han-Yoo expressed concern about that the temperature change from 68-75 degrees Fahrenheit (20-24 degrees Celsius) to a maximum of 68 degrees Fahrenheit (20 degrees Celsius) in section 1751.4. Dr. Han-Yoo indicated that 68 degrees Fahrenheit was too cool for hospital patients and portable air conditioners cannot be used within a sterile environment. She recommends the board reconsider the change, inferring that the board keep existing language.

Board response to comment #3: The board accepted this comment in part. The board modified the text of this section to allow more flexibility in the temperature, as long as compounding staff are comfortable. The change is consistent with the temperature recommendations within USP Chapter 797. Further, board compounding experts note that because of the garbing requirements for staff engaging in compounding, individuals may perspire in the higher temperatures expressly permitted by the existing text. Perspiration contains bacteria which can ultimately compromise the sterility of the environment and of the compounded drug preparations.

Regarding the concern expressed by Dr. Han-Yoo about the temperature in patient care areas, the board’s proposed regulation applies to compounding areas, not patient care rooms.

#4: Written Comments from Dale Costantino, Pharm.D.

Comment #4: Dr. Costantino agreed that lowering the temperature requirement within section 1751.4 was beneficial for compounding personnel; however, he expressed concern about the ability to implement the reduced temperature requirement within hospitals. Dr. Costantino requested that the temperature change be delayed or that the board allow a waiver to hospitals to make the appropriate changes to the facilities.

Board response to comment #4: The board accepted this comment in part (accept his agreement with raising the maximum temperature) and rejected in part (reject his request to delay adoption of the change). USP Chapter 797, though for different reasons, specifies that the temperature should typically be 20 degrees C (68 degrees F) or cooler.

With respect to Dr. Constantino's request for a temporary waiver and its rationale, the board rejected that comment because if the modified temperature poses a risk to compounded sterile products, it cannot be allowed to continue.

#5: Written Comments from Michael Tou, Pharm.D.

Comment #5: Dr. Tou expressed concern about that ability to implement the reduced temperature requirement within hospitals. Dr. Tou indicated that some hospitals will require building modifications to comply. Additionally, Dr. Tou expressed concern that certain drugs used in compounded products are required (by other provisions of USP and by manufacturer specifications) to be stored at controlled room temperatures of 68 degrees Fahrenheit to 77 degrees Fahrenheit. He indicated that reducing the temperature of the sterile environment to 68 degrees or below would conflict with drug storage requirements and would prevent the hospital from storing drugs in the compounding area. Dr. Tou requested that (A) the temperature be modified to include a range from 20 – 22 degrees Celsius (68-72 degrees Fahrenheit) to allow for a comfortable working environment for compounding staff and allow for the storage of specific drugs within the compounding area, or (B) that implementation of any modified temperature range be delayed, or that the board grant a waiver to hospitals in order to allow hospitals to make the appropriate physical changes to their facilities.

Board response to comment #5: The board rejected this comment in part. USP Chapter 797 specifies that the temperature where sterile compounding occurs should typically be 20 degrees C (68 degrees F) or cooler. In response to comment #5(A), the board amended the language to add the term "typically" to further align with the terminology of USP Chapter 797, which will provide some flexibility for the storage of specific drugs as well as for the compounding personnel. With respect to Dr. Tou's request (#5(B)) for delayed implementation or a temporary waiver, the board rejected that comment because if the higher temperature poses a risk to compounded sterile products, it cannot be allowed to continue.

#6: Written Comments from Lauren Eichstadt-Forsythe, Pharm.D.

Comment #6: Dr. Eichstadt-Forsythe recommended that the proposed changes not be implemented and instead, recommended that the board incorporate USP by reference to eliminate confusion. Dr. Eichstadt-Forsythe notes that USP is currently being amended and the amendments will not be finalized until December 2019.

Board response to comment #6: The board rejected this comment. The board notes that it is working toward incorporating USP into California statute; however, the current proposed changes are necessary to address some immediate issues within existing regulation text. In addition, changes to California law and to USP are, at this point, speculative and delaying these changes will impact patient safety within California. The board further notes that the changes being made are consistent with existing USP compounding provisions.

Modified Text – Response to Comments

During the 15-day comment period (September 26, 2018 – October 11, 2018), the Board received eight comments. The comments were provided to the board in the meeting materials for the October 23-24, 2018 board meeting, and were reviewed and considered by the board at that meeting. No changes were made in response to these comments.

#1 Written Comments from Christine Givant, La Vita Compounding Pharmacy
Comment #1: Ms. Givant indicated that she felt that biannual video smoke studies was extremely excessive. She indicated that a hood tested upon purchase should not require additional studies unless the hood is moved or the type of compounding changes. Ms. Givant added that she didn't feel biannual smoke studies was warranted.

Board response to comment #1: The board rejected this comment as it is outside the scope of this comment period. The comment was specified to a section that was not modified following the 45-day comment period. However, the board notes that smoke studies are a requirement for biannual certification of ISO class five areas within USP Chapter 797. Further, CETA (Controlled Environment Testing Association) guidelines require that a smoke pattern test be completed at every certification (13.2.1 and 13.2.4) and that certifications be completed consistent with USP Chapter 797 (9.0). As the certification must be completed at least once every six months, it is appropriate to require biannual smoke studies.

#2: Written Comments from Narwan Yakubi, CPHT, Stanford Healthcare
Comment #2: Mr. Yakubi states that section 1735.6(e)(3) does not state that the BSC and HD room must be separately vented by their own exhaust. He inquired if the room external vent and the BSC external vent could be combined. Additionally, he asked if the externally exhausted BSC could be used to exhaust room air.

Board response to comment #2: The board rejected this comment. His comments are understood to suggest that his questions should be answered by the regulation text. The board believes that Mr. Yakubi's questions are answered within the modified regulation text. Specifically, sections 1735.1(f) and 1735.6(e)(3)(B) address Mr. Yakubi's questions, which allow the entire room to be exhausted through the device designed to contain the particulate matter.

#3: Written Comments from Sean O'Rourke, Dignity Health

Comment #3: Mr. O'Rourke expressed concern about the temperature in section 1751.4. He indicated that hazardous drugs stored in a negative pressure room must be stored at a standard temperature of 68-77 degrees (Controlled Room Temperature), which conflicts with the proposed 68 degrees or lower.

Board response to comment #3: The board rejected this comment. The change is consistent with the temperature recommendations within USP Chapter 797, and the use of the word "typically" was from USP Chapter 797. As written, the standard will be to maintain comfortable conditions and 68° is a guideline, but not a requirement, so variation will be permitted. Further, board compounding experts note that because of the garbing requirements for staff engaging in compounding, individuals may perspire at various temperatures. Perspiration contains bacteria which can ultimately compromise the sterility of the environment and of the compounded drug preparations. It is the board's position that it is critical that the comfort of the individual compounding be ensured to avoid possible contamination and ensure patient safety.

#4: Written Comments from Cindy Del Buono, Pharm.D., St. Joseph Health Petaluma

Comment #4: Dr. Del Buono expressed concern about the temperature requirements of 1751.4. She indicated that it can be warm wearing the required compounding garb and recommends that the temperature be specified at 68 – 72 degrees. Dr. Del Buono further expressed concern about the addition of the word "typically" within the text. She indicated that facilities need to adhere to a temperature and the word "typically" would allow them to not adhere to a temperature range that is comfortable for employees doing the compounding.

Board response to comment #4: The board rejected this comment as the change and the use of the term "typically" is consistent with the language and temperature recommendations within USP Chapter 797. The use of the term "typically" may permit the storage of specific drugs within the room, as long as there is a comfortable work environment for staff. Perspiration contains bacteria which can ultimately compromise the sterility of the environment and of the compounded drug preparations. It is the board's position that it is critical that the comfort of the individual compounding be ensured to avoid possible contamination from perspiration and to ensure patient safety. If individuals in the compounding room are comfortable at 70°F, for example, that would be allowed, because if the individuals are comfortable, there is little likelihood of perspiration and more focus on the compounding, and therefore less risk to the public.

#5: Written Comments from Michael Tou, Pharm.D., Providence Health

Comment #5: Dr. Tou requested that the board provide guidance to inspectors on how the term "typical" will be interpreted if the temperature is above 20 degrees Celsius at the time of inspection. Dr. Tou recommended that inspectors consider temperature logs, drug storage, and seasonal temperature to ensure consistent application. Dr. Tou recommended defining what is *atypical*.

Board response to comment #5: The board rejected this comment. The board noted that the language is clear that 20°C or less is the typical temperature; however, the

temperature could fluctuate based on the comfort of garbed individuals performing the compounding. Atypical need not be defined as the standard will be variable based on the facility and the compounding staff.

#6: Written Comments from Anthony Grzib, Wedgewood Pharmacy

Comment #6: Mr. Grzib expressed concern that the modifications to the proposed text do not extend the beyond use date requirements for sterile compounded drug preparations. He indicates that the regulations incorrectly combine that terms "stability" and "sterility" and creates confusion about when to apply the standards. Mr. Grzib recommends that section 1735.2(i)(2) and 1735.2(i)(3) be amended to clarify the terms "stability" and "sterility" and allow the same beyond use date extension procedures that apply to non-sterile compounded drug preparations.

Board response to comment #6: The board rejected this comment as it is outside the scope of the proposed modifications. Nevertheless, the standards for sterile preparations are consistent with USP Chapter 797. The primary focus of this regulation proposal relating to BUDs is on nonsterile compounded preparations. Additionally, the board determined that the specific beyond use date requirements for sterile compounded drug preparations are defined in section 1751.8, which has not been considered as a part of this proposal.

#7: Written Comments from BJ Bartleson, CA Hospital Association

Comment #7: Ms. Bartleson expressed concern about the addition of the word "typically" within the text. She recommended that the board use the term "approximately" to align with fluctuations in hospital temperatures.

Board response to comment #7: The board rejected this comment as the term "typically" is the exact term used within USP Chapter 797 for facility design and environmental controls and already permits some flexibility. The use of the term "typically" may permit the storage of specific drugs within the room, as long as there is a comfortable work environment for staff. It is the board's position that it is critical that the comfort of the individual compounding be ensured to avoid possible contamination from perspiration to allow the compounder to focus and retain attention on the compounding and to ensure patient safety.

#8: Written Comments from Katherine Palmer, Pharm.D. and Rita Shane, Pharm.D. Cedars-Sinai

Comment #8.A: Dr. Palmer and Dr. Shane expressed concern about the definition of Compounding Aseptic Containment Isolator (CACI) in section 1735.1(f). They indicated that USP Chapter 800 does not require that each BSC be separately exhausted.

Board response to comment #8.A: The board rejected this comment as the board's regulation does not require that each BSC be separately exhausted. The regulation text indicates "should" and as such, it is recommended, but not required. Additionally, the comment is outside the scope of this comment period, because the language is in existing text not being amended.

Comment #8.B: Dr. Palmer and Dr. Shane recommended that the board use the term "approximately" in place of "typically" in section 1751.4 to be consistent with USP Chapter 797.

Board response to comment #8.B: The board rejected this comment as the term "typically" is the exact term used within USP Chapter 797 multiple times for facility design and environmental controls. The use of the term "typically" permits the storage of specific drugs within the room, as long as there is a comfortable work environment for staff. It is the board's position that it is critical that the comfort of the individual compounding be ensured to avoid possible contamination, maintain focus on the compounding, and ensure patient safety.

Comment #8.C: Dr. Palmer and Dr. Shane recommended that the board remove the term "above ceiling" from section 1735.6(e)(2) as it is not required by USP Chapter 800.

Board response to comment #8.C: The board rejected this comment as it is outside the scope of this proposal. The primary focus of this regulation proposal is the BUDs for nonsterile compounded drug preparations other more urgent conflicts with current regulation. The board determined that "above ceiling" is an example given for clarity and this requirement has been in place since January 2017 and there have not been any issues with compliance.

On October 23, 2018, after having reviewed all the comments submitted, the board voted to adopt the compounded drug preparation regulation text as it was noticed on September 26, 2018.