California State Board of Pharmacy
1625 N. Market Blvd, N219, Sacramento, CA 95834
Phone: (916) 574-7900
Fax: (916) 574-8618
www.pharmacy.ca.gov

BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

To: Board Members

Subject: Discussion and Consideration of Proposal to Modify Pharmacy Compounding Regulations (Title 16, California Code of Regulations, Sections 1735.1, 1735.2, 1735.6, 1751.1, & 1751.4), Including Review of Public Comments

Attachment

Background:

At the July 2017 Board Meeting, the board approved proposed text to amend Sections 1735.1, 1735.2, 1735.6, 1751.1, and 1751.4 of Title 16 CCR, related to Compounded Drug Preparations. This proposal formally amends the board's regulations regarding the establishment of compounding beyond use dates as it relates to sterile and non-sterile compounded drug preparations. Additionally, this regulation allows for the use of a double filtration system and further aligns the board's regulations with The United States Pharmacopeia - National Formulary (USP), which is the professional industry standards used across the nation.

USP contains standards developed by a committee of experts that, among other things, help ensure the quality of compounded medications. USP's General Chapters for compounding establish procedures, methods and practices that are utilized by practitioners to help ensure the quality of compounded preparations. The General Chapters for compounding include Chapter 795 (Pharmaceutical Compounding – Nonsterile Compounding), Chapter 797 (Pharmaceutical Compounding – Sterile Preparations) and Chapter 800 (Hazardous Drugs – Handling in Healthcare Settings). Further, the U.S. Federal Food, Drug, and Cosmetics Act designates the USP as the official compendia for drugs marketed in the United States. All drug products within the U.S. market must conform to the standards in USP to avoid possible charges of adulteration and misbranding.

As required by the Administrative Procedure Act, board staff released the proposed text for the 45-day comment period on August 3, 2018, which ended on September 17, 2018. At the September 26, 2018 Board Meeting, the board approved a modified text to address concerns expressed by stakeholders and initiated a 15-day comment period. The 15-day comment period began on September 26, 2018 and ended on October 11, 2018.

The comments received during the 15-day comment period are included as an attachment. Also included are board staff prepared recommendations in response to the comments.

At this Meeting

The board will have the opportunity to discuss the regulation and determine what course of action it wishes to pursue. Among its options:

1. Amend the regulation to address any concerns raised by stakeholders.
2. Adopt the regulation as noticed by the Board on September 26, 2018.

The Attachment contains the following:

1. Approved regulation text as noticed for public comment on September 26, 2018.
2. A copy of each comment received during the 15-day public comment period for board review.
3. A compilation document of the comments received during the 15-day comment period with staff recommendations. This document summarizes the comments received for reference. The board should also review the comments in section two.

Staff Recommendation: Adopt the regulation language as noticed on September 26, 2018, and delegate to the executive officer the authority to make technical or non-substantive changes as may be required by a Control agency to complete the rulemaking file.

Attachment 1

Approved Modified Regulation
Text as noticed for comment on September 26, 2018

Title 16. Board of Pharmacy
Modified Text

Changes made to the originally proposed language are shown by ~~double strikethrough~~ for deleted language and double underline for added language.

Proposed changes to the current regulation language are shown by ~~strikethrough~~ for deleted language and underline for added language. Additionally, text in [brackets] indicates language that is not being amended.

Note: The board adopted an emergency regulation affecting regulation section 1735.2 effective December 19, 2017. The strikethrough and underline to the text of that section reflects changes from the board's non-emergency regulation.

Amend section 1735.1, subdivisions (c) and (f), in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.1. Compounding Definitions.

[…]

(c) "Biological Safety Cabinet (BSC)" means a ventilated cabinet for compounding sterile drug preparations, having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection. Where hazardous drugs are prepared, the exhaust air from the biological safety cabinet shall be appropriately removed by properly designed external building ~~ventilation~~ exhausting. This external ~~venting~~ exhaust should be dedicated to one BSC or CACI.

[…]

(f) "Compounding Aseptic Containment Isolator (CACI)" means a unidirectional HEPA-filtered airflow compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where hazardous drugs are prepared, the exhaust air from the isolator shall be appropriately removed by properly designed external building ~~ventilation~~ exhaust. This external ~~venting~~ exhaust should be dedicated to one BSC or CACI. Air within the CACI shall not be recirculated nor turbulent.

[…]

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4029, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

Amend section 1735.2, subdivision (i), in Article 4.5 of Division 17 of Title 16 California Code of Regulations to read as follows:

1735.2. Compounding Limitations and Requirements; Self-Assessment.

[…]

(i) Every compounded drug preparation shall be given a beyond use date representing the date or date and time beyond which the compounded drug preparation should not be used, stored, transported or administered, and determined based on the professional judgment of the pharmacist performing or supervising the compounding.

(1) For non-sterile compounded drug preparation(s), the beyond use date shall not exceed any of the following:

(A) the shortest expiration date or beyond use date of any ingredient in the compounded drug preparation,

(B) the chemical stability of any one ingredient in the compounded drug preparation~~;~~,

(C) the chemical stability of the combination of all ingredients in the compounded drug preparation,

(D) ~~180 days~~ for non-aqueous formulations, 180 days or an extended date established by the pharmacist's research, analysis, and documentation,

(E) ~~14 days~~ for water-containing oral formulations, 14 days or an extended date established by the pharmacist's research, analysis, and documentation, and

(F) ~~30 days~~ for water-containing topical/dermal and mucosal liquid and semisolid formulations, 30 days or an extended date established by the pharmacist's research, analysis, and documentation.

(G) A pharmacist, using his or her professional judgment may establish an extended date as provided in (D), (E), and (F), if the pharmacist researches by consulting and applying drug-specific and general stability documentation and literature; analyzes such documentation and literature as well as the other factors set forth in this subdivision, and maintains documentation of the research, analysis and conclusion. The factors the pharmacist must analyze include:

(i) the nature of the drug and its degradation mechanism,

(ii) the dosage form and its components,

(iii) the potential for microbial proliferation in the preparation,

(iv) the container in which it is packaged,
(v) the expected storage conditions, and
(vi) the intended duration of therapy.

Documentation of the pharmacist's research and analysis supporting an extension must be maintained in a readily retrievable format as part of the master formula.

(2) For sterile compounded drug preparations, the beyond use date shall not exceed any of the following:
(A) The shortest expiration date or beyond use date of any ingredient in the sterile compounded drug product preparation,
(B) The chemical stability of any one ingredient in the sterile compounded drug preparation,
(C) The chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and
(D) The beyond use date assigned for sterility in section 1751.8.

(3) For sterile compounded drug preparations, ~~E~~ extension of a beyond use date is only allowable when supported by the following:
(A) Method Suitability Test,
(B) Container Closure Integrity Test, and
(C) Stability Studies

(4) In addition to the requirements of paragraph three (3), the drugs or compounded drug preparations tested and studied shall be identical in ingredients, specific and essential compounding steps, quality reviews, and packaging as the finished drug or compounded drug preparation.

(5) Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.

[…]

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4029, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

Amend section 1735.6, subdivision (e), in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.6. Compounding Facilities and Equipment.

[…]

(e) Hazardous drug compounding shall be completed in an externally ~~vented~~ exhausted physically separate room with the following requirements:

(1) Minimum of 30 air changes per hour except that 12 air changes per hour are acceptable for segregated compounding areas with a BSC or CACI when products are assigned a BUD of 12 ~~hrs~~ hours or less or when non sterile products are compounded; and
(2) Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors); and
(3) (A) For sterile compounding, each ~~Each PEC~~ BSC or CACI ~~in the room~~ shall ~~also~~ be externally ~~vented~~ exhausted. ~~except that a BSC used only~~
(B) ~~f~~For nonsterile compounding, a BSC, a CACI, or other containment ventilated enclosure shall be used and shall either ~~may~~ use a redundant-HEPA filter in series or be externally exhausted. ~~; and~~ 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.
(4) All surfaces within the room shall be smooth, seamless, impervious, and non-shedding.

[…]

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4029, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code.

Amend section 1751.1, subdivision (a)(5), in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.1. Sterile Compounding Recordkeeping Requirements.

(a) In addition to the records required by section 1735.3, any pharmacy engaged in any compounding of sterile drug preparations shall maintain the following records, which must be readily retrievable, within the pharmacy:
[…]
(5) Biannual ~~V~~ video of smoke studies in all ISO Class 5 certified spaces.
[…]

[…]

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4029, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

Amend section 1751.4, subdivision (k), in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.4. Facility and Equipment Standards for Sterile Compounding.

[…]

(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~~-24~~ degrees Celsius (68~~-75~~ degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.

[…]

Note: Authority Cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4029, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code; and Section 18944, Health and Safety Code.

Comments received during the 15-day comment period (9/26/18 – 10/11/18)

Martinez, Lori@DCA

From: Chris Givant <chris@lavitarx.com>
Sent: Thursday, September 27, 2018 8:32 AM
To: Martinez, Lori@DCA
Subject: Comments regarding.: Modified text Title 16 CCR 1735.1, 1735.2, 1735.6, 1751.1, 1751.4

Hi Lori,

I have a comment regarding 1751.1 (a) (5) referencing Biannual video smoke studies of all ISO Class 5 certifed spaces. In my opinion, this is extremely excessive. If a hood has been tested upon purchase with a smoke study under dynamic conditions that should be sufficient unless the hood is moved or the type of compound that is being made changes. There is nothing to indicate that twice yearly smoke studies are warranted. I would ask for the study that shows twice yearly smoke studies increase safety.

Thank you

Christine Givant
Co-Founder

La Vita Compounding Pharmacy
P-858-453-2500
F-858-453-2501
www.lavitarx.com

laVITA
COMPOUNDING PHARMACY

PCAB ACCREDITED®
Compounding Pharmacy

Martinez, Lori@DCA

From: Yakubi, Narwan <NYakubi@stanfordhealthcare.org>
Sent: Thursday, September 27, 2018 9:14 AM
To: Martinez, Lori@DCA
Subject: section 1735.6

Good Morning Lori,
In Section 1735.6 e (3)
It does not specify that BSC and HD room must be separately vented (by their own separate exhaust).
Can room external vent and BSC external vent be combined ?
Can BSC that is externally exhausted be used to exhaust room air ?

Thank you,
Narwan Yakubi CPHT
Pharmacy Compliance Technician
300 Pasteur Drive Suite H0301
Stanford, CA 94305
Mail Code: 5616

Martinez, Lori@DCA

From: O'Rourke, Sean - MRMC <Sean.ORourke@DignityHealth.org>
Sent: Thursday, September 27, 2018 9:55 AM
To: Martinez, Lori@DCA
Subject: FW: Corrected - Notice of Modified Text
Attachments: mg_info.txt

Hi Lori, in regard to clean room temperature. Will there be any changes to the drug storage temperature range? Specifically for hazardous drugs which are stored in a negative pressure room? This has been a discussion topic since the standard of 68-77 (controlled room temperature) conflicts with the proposed 68 or lower.

From: General Board of Pharmacy Subscriber List [mailto:PHARM-GENERAL@DCALISTS.CA.GOV] **On Behalf Of** California State Board of Pharmacy
Sent: Wednesday, September 26, 2018 2:16 PM
To: PHARM-GENERAL@DCALISTS.CA.GOV
Subject: Corrected - Notice of Modified Text

NOTICE IS HEREBY GIVEN that the Board of Pharmacy has proposed additional modifications to the text of Title 16 CCR §§ 1735.1, 1735.2, 1735.6, 1751.1, and 1751.4, related to Compounded Drug Preparations. Any person who wishes to comment on the proposed modifications may do so by submitting written comments beginning September 26, 2018 and ending at 5pm on October 11, 2018, to the following:

Contact Person:	Lori Martinez
Agency Name:	California State Board of Pharmacy
Address:	1625 North Market Blvd, Suite N 219 Sacramento, CA 95834
Email:	Lori.Martinez@dca.ca.gov
Fax:	(916) 574-8617

Please limit your comments to the new modifications to the text.

Any responses to comments directly concerning the proposed modifications to the text of the regulations will be considered and responded to in the Final Statement of Reasons.

All information and documents related to this and other pending regulations can be found on the Board's website https://www.pharmacy.ca.gov/laws_regs/pending_regs.shtml.

---------- To unsubscribe from this email list please click on the link below and follow the instructions on the web page.

https://www.dca.ca.gov/webapps/pharmacy/subscribe.php

Martinez, Lori@DCA

From: Del Buono, Cynthia <Cynthia.DelBuono@stjoe.org>
Sent: Monday, October 1, 2018 2:30 PM
To: Martinez, Lori@DCA
Subject: Feedback to proposed regulation

Dear Lori, I would like to provide feedback on the following proposed update in regulations for sterile compounding:

"The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which includes a room temperature of 20-~~24~~ degrees Celsius (68-~~75~~ degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb."

As a pharmacist that prepares chemotherapy, I think this is an important addition to the regulations. It can be uncomfortably warm wearing required compounding garb in a room that is not temperature controlled. I set our thermostat so that it goes no higher than 72 degrees F. I suggest a 68 to 72 degree range. Also I am hearing that you may be contemplating addition of the word "typically" to this sentence. If addition of the word "typically" can be interpreted by the facility that they do not need to adhere to this temperature range, I would ask the word "typically" not be added. We need employers to ensure the working conditions/temperature are comfortable for employees.

Thank you, Cindy

Cindy Del Buono, PharmD, BCOP
Oncology Pharmacist
Advanced Practice Pharmacist
St. Joseph Health Petaluma Cancer Center
110A Lynch Creek Way
Petaluma, CA 94954
(707) 521-3819
cynthia.delbuono@stjoe.org

Providence
St. Joseph Health

Martinez, Lori@DCA

From: Tou, Michael P <Michael.Tou@providence.org>
Sent: Monday, October 8, 2018 2:38 PM
To: Martinez, Lori@DCA
Subject: Providence St. Joseph Health - Notice of Modified text: Compounded Drug Preparations
Attachments: Providence St. Joseph Health_Compounded Drug Preparations-Modified Text_100818.pdf

Importance: High

Good afternoon,

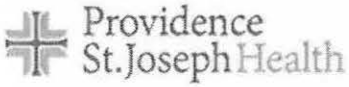
On behalf of Providence St. Joseph Health and our pharmacy directors, I am submitting comments in response to the Notice of Modified Text, related to compounded drug preparations.

Thank you for the opportunity to comment on the modified text.

Best regards,

Michael

Michael Tou, MPA | Director, Government Relations – California
Providence St. Joseph Health
20555 Earl Street | Torrance, CA 90503
Work: (310) 793-8093 | Mobile: (818) 512-4837 | Email: michael.tou@providence.org



Providence St. Joseph Health
20555 Earl Street
Torrance, CA 90503

Providence St. Joseph Health

October 8, 2018

California Board of Pharmacy
Attn: Ms. Lori Martinez
1625 N. Market Blvd., N219
Sacramento, CA 95834

SUBJECT: Compounded Drug Preparations, Notice of Modified Text, Title 16 of the California Code of Regulations, Sections 1735.1, 1735.2, 1735.6, 1751.1, 1751.4. Comment Period: September 26, 2018 to October 11, 2018.

Dear Ms. Martinez:

Providence St. Joseph Health appreciates the efforts by the California Board of Pharmacy to develop a temperature standard that seeks to address the concerns we raised in our original comment letter. We are submitting additional comments on the modified text for your consideration.

PSJH Recommendation

In reference to the proposed modifications to Section 1751.4(k), Providence St. Joseph Health urges the Board to provide guidance to inspectors on how they will interpret a "typical" temperature if the cleanroom is measured above 20 degrees Celsius during an inspection. Inspectors should consider a variety of factors, including a daily temperature log, drug storage requirements, and seasonal temperatures, to ensure consistency in the application of the new standard. It may be helpful to consider what is *atypical* when defining and/or interpreting the room temperature standard.

Thank you for carefully considering our comments on the modified text.

Sincerely,

Michael Tou
Director, Government Relations

cc: Providence St. Joseph Health Pharmacy Directors
BJ Bartleson, California Hospital Association

Martinez, Lori@DCA

From: Anthony Grzib <AGrzib@wedgewoodpharmacy.com>
Sent: Wednesday, October 10, 2018 3:10 PM
To: Martinez, Lori@DCA
Subject: Comments to Proposed Modifications to Text of Title 16 CCR Sections 1735.1, 1735.2, 1735.6, 1751.1, and 1751.4 Related to Compounded Drug Preparations
Attachments: Calliforma Comments-signed.pdf; Proposed Text Amendments to CA BOP 10-10-18.pdf

Dear Ms. Martinez,

Please find attached Wedgewood Pharmacy's comments to the above referenced regulations related to compounded drug preparations. Please feel free to contact me with any questions.

Thank you,

Anthony Grzib, R.Ph
Director of Pharmacy Compliance
Wedgewood Pharmacy
(856) 832-1315

Sent via Email to: Lori.Martinez@dca.ca.gov

October 10, 2018

Ms. Lori Martinez
California State Board of Pharmacy
1625 North Market Blvd, Suite N 219
Sacramento, CA 95834

Re: Proposed Modifications to the Text of Title 16 CCR §§ 1735.1, 1735.2, 1735.6, 1751.1, and 1751.4 Related to Compounded Drug Preparations

Dear Ms. Martinez:

Wedgewood Pharmacy would like to thank the California State Board of Pharmacy (the "Board") for this opportunity to present comments on proposed modifications to regulations applicable to compounding pharmacies. Wedgewood Pharmacy supports the Board's mission to ensure that patients throughout the State of California receive safe, effective and quality compounded medications. Wedgewood Pharmacy understands and supports the need to protect public health. However, when developing and implementing regulations, it is essential to preserve patient access to vital compounded medications. Patient safety and public health are jeopardized when compounded medications that best fit the medical needs of patients become unavailable.

We commend the Board for taking action to make permanent the amendments to Section 1735.2(i)(1) related to the Beyond Use Date (BUD) requirements for non-sterile compounds to align California regulation with the nationally recognized standards of USP Chapter <795>. Unfortunately, these amendments do not extend to the sterile compounding Beyond Use Date requirements of Sections 1735.2(i)(2), 1735.2(i)(3), and 1735.2(i)(4).

As currently written, Sections 1735.2(i)(2), 1735.2(i)(3), and 1735.2(i)(4) incorrectly intermingle *stability* and *sterility* criteria in establishing the BUD for sterile compounded preparations.

PHONE: 800.331.8272
FAX: 800.589.4250
ADDRESS: 405 HERON DRIVE, STE. 200 | SWEDESBORO, NJ 08085
WEDGEWOODPETRX.COM

While stability and sterility are both important in the establishment of a BUD for a sterile compounded preparation, they are two distinct attributes that are independent of each other regarding the type of information needed to establish them. *Stability* relates to the preparation's ability to retain its labeled potency of active ingredient during its established use period. *Sterility* relates to the preparation's ability to remain sterile during its established use period. A preparation's chemical stability has no impact on its ability to remain sterile, and the length of time a preparation remains sterile has no impact on the length of time that preparation remains chemically stable. Therefore, the information the compounder uses to determine the length of time a sterile compounded preparation remains chemically stable is separate and unrelated to the information the compounder uses to determine the length of time that preparation remains sterile. Furthermore, the information used to establish the stability of a compounded preparation is the same, regardless of whether the preparation is sterile or non-sterile.

Section 1735.2(i)(1), as amended, is very clear about the information the compounder must consider when establishing the BUD of non-sterile compounded preparations. This section also provides specific maximum BUDs for various non-sterile dosage forms, along with an allowance to exceed these maximum BUDs if the compounder applies relevant information supporting longer stability.

As currently written, Section 1735.2(i)(2) and Section 1735.2(i)(3) create confusion regarding where to apply *stability* criteria and where to apply *sterility* criteria in establishing maximum and extended BUDs for sterile compounded preparations. For example, (A), (B), and (C) of Section 1735.2(i)(2) address some of the stability criteria for establishing a BUD for a sterile compounded preparation, but this section does not specify any maximum allowable BUD assignment for sterile preparations based on *stability*. Section 1735.2(i)(2)(D) specifies the maximum BUDs for sterile compounds are based on the criteria of Section 1751.8, but the maximum BUDs specified in Section 1751.8 are based only on *sterility*. Additionally, the maximum BUDs specified in Section 1751.8 are only applicable when the sterile preparations do not undergo sterility testing, meaning these maximum BUDs are *not* applicable to sterile items that are tested for sterility. Because neither Section 1735.2(i)(2) nor Section 1751.8 provide specific maximum BUDs based on stability criteria, and because neither section specifies a maximum allowable BUD assignment for sterile compounded preparations that *do* undergo sterility testing, compounders who test preparations for sterility are left to guess what the allowable maximum BUDs are for these preparations. The maximum BUDs specified in 1735.2(i)(1)(D through F) are based on chemical stability, even though these appear to only apply to non-sterile preparations. The maximum BUDs specified in Section 1751.8 are based solely on sterility, do not account for the chemical stability of the preparation, and are not applicable to sterile compounded preparations that undergo sterility testing. Finally, it is not known when the criteria in Section 1735.2(i)(3) becomes applicable because sterility testing is not a prerequisite for this section and this section appears only to be applied when there is an "extension" of the BUD of a sterile compounded preparation beyond some unknown maximum. Amending Section 1735.2(i)(2) to incorporate maximum allowable BUDs based on stability, like those found in Section 1735.2 (i)(1)(D through F), is essential for the Board to effectively establish BUD expectations for sterile compounded preparations that undergo sterility testing.

It is essential for the Board to amend Section 1735.2(i)(3)(C) and Section 1735.2(i)(4) in addition to the amendments to Section 1735.2(i)(2). By making the above-recommended amendments to Section 1735.2(i)(2) to specify maximum allowable BUDs for sterile compounded preparations, Section 1735.2(i)(3) would then be applicable only when a compounder wishes to exceed those maximum allowable BUDs. While the criteria currently required in (A) and (B) of Section 1735.2(i)(3) seem

appropriate for establishing longer *sterility* timelines, the stability studies currently required in 1735.2(i)(3)(C) are not appropriate for establishing longer *stability* timelines for sterile compounded preparations. As stated earlier, the stability information used to establish the stability of a compounded preparation is the same, regardless of whether the compound is a sterile preparation or a non-sterile preparation. Section 1735.2(i)(1)(G), as amended, establishes the criteria needed to establish extended stability timelines for non-sterile compounds. **There is no scientific basis for not applying these same criteria to establish extended stability for sterile compounds.**

In addition to being inconsistent with the extended BUD stability requirements of Section 1735.2(i)(1) and USP General Chapters <795> and <797>, the stability studies required in Section 1735.2(i)(3)(C), along with the corresponding requirements of Section 1735.2(i)(4), mimic the stability requirements of current Good Manufacturing Practice (cGMP) standards that are applicable to drug manufacturers. Unlike drug manufacturers, compounding pharmacies prepare unique medications for particular medical needs when a prescriber determines a commercially available drug is not suitable for treatment. The Food Drug & Cosmetic Act ("FDCA") requirements for manufactured drugs, including cGMPs, were not designed for these specialized medications. CGMP stability testing practices are extremely expensive and are therefore not economically practical when small amounts of customized drug product is being produced. This is one of the reasons why commercial drug manufacturers only produce large quantities of medication in standard strengths and dosage forms. Compounding pharmacies cannot, with any economic feasibility, comply with cGMP testing requirements. If compounding pharmacies are required to comply with cGMP, the increased cost will be passed on to patients or cause pharmacies to discontinue compounding activities. In either case, patients suffer due to drastically increased prices and restricted access to necessary medications. Therefore, it is essential that Section 1735.2(i)(3)(C) and Section 1735.2(i)(4) be amended to include criteria similar to Section 1735.2(i)(1)(G) in order to ensure that all patients in California have access to critical compounded sterile preparations.

Wedgewood Pharmacy appreciates the opportunity to provide these comments to the Board in support of the mutual goal of protecting and promoting the health and safety of Californians. Please find attached suggested text that would effectively address the concerns expressed above related to Section 1735.2(i). Wedgewood Pharmacy welcomes the opportunity to work with the Board in pursuing the highest quality of pharmacist's care while preserving patient access to vital compounded medications.

Sincerely,

Marcy A. Bliss
President & CEO

Attachment

Suggested Amendments to the Proposed Modifications to Title 16 CCR § 1735.2(i)

Amend section 1735.2, subdivision (i), in Article 4.5 of Division 17 of Title 16 California Code of Regulations to read as follows: 1735.2. Compounding Limitations and Requirements; Self-Assessment.

(i) Every compounded drug preparation shall be given a beyond use date representing the date or date and time beyond which the compounded drug preparation should not be used, stored, transported or administered, and determined based on the professional judgment of the pharmacist performing or supervising the compounding.

(1) For non-sterile compounded drug preparation(s), the beyond use date shall not exceed any of the following:

(A) the shortest expiration date or beyond use date of any ingredient in the compounded drug preparation,

(B) the chemical stability of any one ingredient in the compounded drug preparation; ,

(C) the chemical stability of the combination of all ingredients in the compounded drug preparation,

(D) ~~180 days~~ for non-aqueous formulations, 180 days or an extended date established by the pharmacist's research, analysis, and documentation,

(E) ~~14 days~~ for water-containing oral formulations, 14 days or an extended date established by the pharmacist's research, analysis, and documentation, and

(F) ~~30 days~~ for water-containing topical/dermal and mucosal liquid and semisolid formulations, 30 days or an extended date established by the pharmacist's research, analysis, and documentation.

(G) A pharmacist, using his or her professional judgment may establish an extended date as provided in (D), (E), and (F), if the pharmacist researches by consulting and applying drug-specific and general stability documentation and literature; analyzes such documentation and literature as well as the other factors set forth in this subdivision, and maintains documentation of the research, analysis and conclusion. The factors the pharmacist must analyze include:

(i) the nature of the drug and its degradation mechanism,

(ii) the dosage form and its components,

(iii) the potential for microbial proliferation in the preparation,

(iv) the container in which it is packaged,

(v) the expected storage conditions, and

(vi) the intended duration of therapy.

Documentation of the pharmacist's research and analysis supporting an

extension must be maintained in a readily retrievable format as part of the master formula.

(2) For sterile compounded drug preparations, the beyond use date shall not exceed any of the following:

(A) The shortest expiration date or beyond use date of any ingredient in the sterile compounded drug product preparation,

(B) The chemical stability of any one ingredient in the sterile compounded drug preparation,

(C) The chemical stability of the combination of all ingredients in the sterile compounded drug preparation, ~~and~~

(D) In the absence of sterility testing ~~T~~ the beyond use date assigned for sterility in section 1751.8.

(E) For non-aqueous formulations that undergo sterility testing, 180 days or an extended date established by the pharmacist's research, analysis, and documentation, and

(F) For water-containing formulations that undergo sterility testing, 14 days or an extended date established by the pharmacist's research, analysis, and documentation.

(3) For sterile compounded drug preparations, ~~E~~ extension of a beyond use date is only allowable when supported by the following:

(A) Sterility test conducted in accordance with a Method Suitability Test, and

(B) Container Closure Integrity Test.~~, and~~

~~(C) Stability Studies~~

(4) A pharmacist, using his or her professional judgment may establish an extended date as provided in (2) and (3), if the pharmacist researches by consulting and applying drug-specific and general stability documentation and literature; analyzes such documentation and literature as well as the other factors set forth in this subdivision, and maintains documentation of the research, analysis and conclusion. The factors the pharmacist must analyze include:

(i) the nature of the drug and its degradation mechanism,

(ii) the dosage form and its components,

(iii) the potential for microbial proliferation in the preparation,

(iv) the container in which it is packaged,

(v) the expected storage conditions, and

(vi) the intended duration of therapy.

Documentation of the pharmacist's research and analysis supporting an extension must be maintained in a readily retrievable format as part of the master formula.

~~In addition to the requirements of paragraph three (3), the drugs or compounded drug preparations tested and studied shall be identical in ingredients, specific and essential compounding steps, quality reviews, and packaging as the finished drug or compounded drug preparation.~~

(5) Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.

Martinez, Lori@DCA

From: Barbara Roth <broth@calhospital.org> on behalf of BJ Bartleson <BJbartleson@calhospital.org>
Sent: Thursday, October 11, 2018 1:27 PM
To: Martinez, Lori@DCA
Subject: Compounding Drug Preparations, Notice of Modified Text, Title 16 of the California Code of Regulations, Sections 1735.1, 1735.2, 1735.6, 1751.1, 1751.4.
Attachments: CHA Letter to BoP - Compounding Drug Preparations - Modified Text commen....pdf

Good Afternoon,

Please see attached letter from the California Hospital Association with comments regarding Compounding Drug Preparations, Notice of Modified Text, Title 16 of the California Code of Regulations, Sections 1735.1, 1735.2, 1735.6, 1751.1, 1751.4.

Thank you,

BJ BARTLESON, RN, MS, NEA-BC
Vice President, Nursing & Clinical Services California Hospital Association
1215 K Street, Suite 800, Sacramento, CA 95814
916.552.7537 – Office
916.206.8714 – Mobile
916.554.2237 – Fax
bjbartleson@calhospital.org

CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

October 11, 2018

California State Board of Pharmacy
Attn: Lori Martinez
Lori.Martinez@dca.ca.gov
1625 N. Market Blvd., Suite N219
Sacramento, CA 95834

BY ELECTRONIC AND WRITTEN CORRESPONDENCE

RE: Compounding Drug Preparations, Notice of Modified Text, Title 16 of the California Code of Regulations, Sections 1735.1, 1735.2, 1735.6, 1751.1, 1751.4. Comment Period: September 26, 2018 to October 11, 2018.

Dear Ms. Martinez:

On behalf of more than 400 member hospitals and health systems, the California Hospital Association (CHA) respectfully offers the following comments for consideration to the proposed changes to compounding regulations for hospital pharmacies set forth in Title 16 California Code of Regulations Sections 1735.1, 1735.2, 1735.6, 1751.1, 1751.4.

CHA members and the CHA Medication Safety Committee are grateful for the opportunity to engage in continued refinements to the sterile compounding regulations, as we continue to strive for safe, efficient and effective delivery of pharmaceutical services across the state.

CHA attended the Board of Pharmacy Enforcement and Compounding Committee meeting on September 26th, to testify on several issues with the proposed Board of Pharmacy sterile compounding modified text. All of those concerns have been remedied, except for one area of proposed text that continues to be of concern for our members - 1751.4. Facility and Equipment Standards, relative to pharmacy room temperature.

1751.4 Facility and Equipment Standards for Sterile Compounding.

(k) The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which *typically* includes a room temperature of 20-24 degrees Celsius (68 degrees Fahrenheit or cooler) to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.

Obviously, room temperature regulations are necessary to facilitate appropriate drug storage needs, and, keep employees cool enough while garbed to prevent sweating. Since many of these issues are subjective in nature, we appreciate the board's willingness to apply a broad temperature description to accommodate normal fluctuations in personnel temperature and environmental controls. While we originally agreed that the term "typically" may be a satisfactory term to account for these fluctuations, upon further consideration and discussion, we would ask the board to reconsider the term "approximate". The term "typically" implies that normally or characteristically the temperature is 68 degrees or cooler, whereas the term "approximate" depicts a more inexact description that more closely aligns with fluctuations in hospital temperatures. This reasoning is supported by the present USP 797

language which states, "*approximately* 20 degrees Celsius, and Title § 71233. Pharmaceutical Service General Requirements, which states, "(6) Drugs shall be stored at appropriate temperatures. Refrigerator temperature shall be from 2.2°C (36°F) to 7.7°C (46°F) and *room temperature shall be between 15°C (59°F) and 30°C (86°F).*

CHA, its hospitals, health systems and Medication Safety Committee, appreciates the opportunity to comment on these proposed regulations and looks forward to the ongoing work to provide leadership, collaboration and partnership in pharmaceutical transactions to improve quality and patient safety standards across the state.

Sincerely,

BJ Bartleson, RN, MS, NEA-BC
Vice President, Nursing and Clinical Services

Martinez, Lori@DCA

From: Palmer, Katherine, Pharm.D. <Katherine.Palmer@cshs.org>
Sent: Thursday, October 11, 2018 4:22 PM
To: Martinez, Lori@DCA
Cc: Shane, Rita Pharm.D.; Vinson, Bruce, Pharm.D.
Subject: Comments: Proposed Compounding Regulation Modifications
Attachments: Board of Pharmacy - Notice of Modified.docx

Dear California State Board of Pharmacy:

Please find below comments related to the text of the proposed modifications of the Compounded Drug Preparations regulations: Title 16 CCR §§ 1735.1, 1735.2, 1735.6, 1751.1, 1751.4.

	Proposed text	Comments
1735.1. (f) Compounding Definitions	Where hazardous drugs are prepared, the exhaust air from the biological safety cabinet shall be appropriately removed by properly designed external building ~~ventilation~~ exhausting. This external ~~venting~~ exhaust should be dedicated to one BSC or CACI.	USP 800 does not require each BSC be separately exhausted. This would be prohibitive in both cost and physical feasibility since it would be very challenging to have multiple vents.
1751.4. Facility and Equipment Standards for Sterile Compounding	(k) The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which includes a room temperature of 20~~-24~~ degrees Celsius (68~~-75~~ degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.	Recommend changing language to "approximately 20 degrees Celsius" to be consistent with USP 797 which states a comfortable temperature such as 68 degrees
1735.6. Compounding Facilities and Equipment	(2) Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors);	Measuring negative pressure differential above the ceiling is not required by USP 800 and would be difficult to measure since above the ceiling in pharmacy compounding areas is inaccessible as ceilings and walls are required to be smooth, impervious, and free from cracks and crevices.

Sincerely,

Katherine Palmer, Pharm.D.
Sterile Compounding Manager

Rita Shane, Pharm.D., FASHP, FCSHP
Chief Pharmacy Officer

CEDARS-SINAI
8700 Beverly Blvd., A903: Los Angeles, CA 90048
Direct: 310-967-0664 : cedars-sinai.edu

CEDARS-SINAI

October 11, 2018

Attention: Lori Martinez
California State Board of Pharmacy
1625 North Market Blvd., Suite N-219
Sacramento, CA 95834

Dear California State Board of Pharmacy:

Please find below comments related to the text of the proposed modifications of the Compounded Drug Preparations regulations: Title 16 CCR §§ 1735.1, 1735.2, 1735.6, 1751.1, 1751.4.

	Proposed text	Comments
1735.1. (f) Compounding Definitions	Where hazardous drugs are prepared, the exhaust air from the biological safety cabinet shall be appropriately removed by properly designed external building ~~ventilation~~ exhausting. This external ~~venting~~ exhaust should be dedicated to one BSC or CACI.	USP 800 does not require each BSC be separately exhausted. This would be prohibitive in both cost and physical feasibility since it would be very challenging to have multiple vents.
1751.4. Facility and Equipment Standards for Sterile Compounding	(k) The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which includes a room temperature of 20~~-24~~ degrees Celsius (68~~-75~~ degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.	Recommend changing language to "approximately 20 degrees Celsius" to be consistent with USP 797 which states a comfortable temperature such as 68 degrees
1735.6. Compounding Facilities and Equipment	(2) Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors);	Measuring negative pressure differential above the ceiling is not required by USP 800 and would be difficult to measure since above the ceiling in pharmacy compounding areas is inaccessible as ceilings and walls are required to be smooth, impervious, and free from cracks and crevices.

Sincerely,

Katherine Palmer, Pharm.D.
Sterile Compounding Manager

Rita Shane, Pharm.D., FASHP, FCSHP
Chief Pharmacy Officer

Cedars-Sinai Medical Center
Department of Pharmacy Services
8700 Beverly Boulevard A903
Los Angeles, CA 90048
office 310.423.5611
fax 310.423.0412
cedars-sinai.edu

Compilation document of the comments received during the 15-day comment period with staff recommendations

Regulatory Proposal Regarding Compounded Drug Preparations
Staff Analysis of, and Recommended Responses to, Comments Received
During 15-Day Comment Period

Summarized 15-day Comments regarding Compounded Drug Preparations with board staff recommendations

Board staff notes that The United States Pharmacopeia - National Formulary (USP) is the professional industry standards used across the nation. USP contains standards developed by a committee of experts that among other things, help ensure the quality of compounded medications. USP's General Chapters for compounding establish procedures, methods and practices that are utilized by practitioners to help ensure the quality of compounded preparations. The General Chapters for compounding include Chapter 795 (Pharmaceutical Compounding – Nonsterile Compounding), Chapter 797 (Pharmaceutical Compounding – Sterile Preparations) and Chapter 800 (Hazardous Drugs – Handling in Healthcare Settings). Further, the U.S. Federal Food, Drug, and Cosmetics Act designates the USP as the official compendia for drugs marketed in the United States. All drug products within the U.S. market must conform to the standards in USP to avoid possible charges of adulteration and misbranding.

15-Day Public Comment Period

During the 15-day public comment period from September 26, 2018 to October 11, 2018, the board received eight written comments. Each comment is included in its entirety within the meeting materials.

#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 additionally 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 Staff Response to Comment #1: The board staff recommend that this comment be rejected as it is outside the scope of this comment period. Additionally, board staff notes that smoke studies are a requirement for biannual certification of ISO class areas within USP <797>. Further, CETA (Controlled Environment Testing Association) guidelines requires that a smoke pattern test be completed at every certification (13.2.4) and that certifications be completed consistent with USP <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 is the and externally exhausted BSC be used to exhaust room air.

Response to Comment #2: The board staff recommend that this comment be rejected. Board staff notes that Mr. Yakubi's comments are questions and not recommendations to the proposed text. Staff believes that Mr. Yakubi's questions are answered within the regulation text. Specifically, sections 1735.1(f) and section 1735.6(e)(3)(B) address Mr. Yakubi's questions.

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

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

Response to Comment #3: The board staff recommend that this comment be rejected as the change is consistent with the temperature recommendations within USP <797>, and the insertion of the word "typically" alleviates any potential conflict. Further, board compounding experts note that because of the garbing requirements for staff engaging in compounding, individuals may perspire at the higher temperatures requested by the Mr. O'Rourke. Perspiration contains bacteria which can ultimately compromise the sterility of the environment and of the compounded drug preparations. 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 employers need to adhere to a temperature and the word "typically" would allow them to not adhere to a temperature range.

Response to Comment #4: The board staff recommend that this comment be rejected as the change and the use of the term "typically" is consistent with the language and temperature recommendations within USP <797>. It is critical that the comfort of the individual compounding be ensured to avoid possible contamination and ensure patient safety. Individuals may perspire at the higher temperatures requested by Dr. Del Buono. Perspiration contains bacteria which can ultimately compromise the sterility of the environment and of the compounded drug preparations.

#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*.

Response to Comment #5: The board staff recommend that this comment be rejected as it is not recommending or requesting a modification to the text. Board staff notes that this in a training issue for staff and will be handled internally.

#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.

Response to Comment #6: The board staff recommend that this comment be rejected as it is outside the scope of this comment period. The board's current regulations relating to the establishment of a BUD for sterile preparations are consistent with USP <797> provisions relating to sterile preparations. The primary focus of this regulation proposal relating to BUDs is on nonsterile compounded preparations. Additionally, board staff notes that the specific beyond use date requirements for sterile compounded drug preparations are defined in section 1751.8, which has not been modified 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.

Response to Comment #7: The board staff recommend that this comment be rejected as the term "typically" is the exact term used within USP <797> for facility design and environmental controls. Additionally, the use of the term "typically" would allow for some flexibility with respect to the temperature while maintaining a comfortable work environment for staff and provide some flexibility within the negative pressure room for the storage of specific hazard drugs. It is critical that the comfort of the individual compounding be ensured to avoid possible contamination and 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 <800> does not require that each BSC be separately exhausted.

Response to Comment #8.A: The board staff recommend that this comment be rejected 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.

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 <797>.

Response to Comment #8.B: The board staff recommend that this comment be rejected as the term "typically" is the exact term used within USP <797> for facility design and environmental controls. Additionally, the use of the term "typically" would allow for some flexibility with respect to the temperature while maintaining a comfortable work environment for staff and provide some flexibility within the negative pressure room for the storage of specific hazard drugs. It is critical that the comfort of the individual compounding be ensured to avoid possible contamination 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 <800>.

Response to Comment #8.C: The board staff recommend that this comment be rejected as it is outside the scope of this proposal. The primary focus of this regulation proposal is the BUDs for nonsterile compounded drug preparations and to correct the inadvertent exclusion or CACIs and other types of containment devices with section 1735.6(e)(3). Board staff notes 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 issue with compliance.