

**Regulation
Comments
Supplement**

Comment #	Date	Name	Affiliation
1	11/29/2013	Douglas Barcon, Pharm.D.	n/a
2	12/1/2013	Martin Hesky, Pharm.D.	n/a
3	12/9/2013	Romic Eskandarian, Pharm.D.	Glandale Adventist Medical Center
4	12/10/2013	Dennis K. McAllister, R.Ph., D.Ph., FASHP	Express Scripts
5	12/10/2013	Elliot Kwok, Pharm.D. Muno Bholat, Goorgen Boghossian, Tawny Bui,	Abbott's Compounding Pharmacy, Inc.
6	12/12/2013	Teresa Lee-Yu, and Hiroyuki Nishi Doug O'Brien, Pharm.D. and Donald Kaplan,	Providence Health & Services Southern California
7	12/18/2013	Pharm.D.	Kaiser
8	12/27/2013	Alan Endo	Presbyterian Intercommunity Hospital
9	1/4/2014	Marie Cottman, Pharm.D.	Pacific Compounding Pharmacy and Consultation:
10	1/6/2014	Terry Lerma, Pharm.D.	St. Joseph Health
11	1/7/2014	Rita Shane, Pharm.D., FASHP, FCSHP	Cedars-Sinai Medical Center
12	1/7/2014	William J. Blair, Pharm.D., MBA	McGuff Compounding Pharmacy Services, Inc.
13	1/8/2014	Dennis Lau	Methodist Hospital
14	1/9/2014	Hank Rahe, BSIM, MSE	Containment Technology Group, Inc.
15	1/9/2014	Richard Sakai	Children's Central Cal
16	1/10/2014	BJ Bartleson, RN, MS, NEA-BC	California Hospital Association
17	1/10/2014	Timothy Lopez, Pharm.D., PIC	Community Medical Centers
18	1/12/2014	Michael Moore, R.Ph.	n/a
19	1/13/2014	Arthur C. Whitney, R.Ph.	Advantage Pharmaceuticals, Inc.
20	1/13/2014	Dawn Benton, MBA	California Society of Health-System Pharmacists
21	1/13/2014	Brian Warren	California Pharmacists Association
22	1/13/2014	Michael Moné, R.Ph., J.D., FAPhA	Cardinal Health
23	1/13/2014	Bill Jones Candace Fong, Pharm.D., and Rachelle Reyes	Central Admixture Pharmacy Services, Inc. (CAPS)
24	1/13/2014	Wenger	Dignity Health
25	1/13/2014	Vivian Matsuo, Pharm.D., PIC Dan Kardasinski, Pharm.D. (1/13/14 and	Silicon Valley Pharmacy
26	1/13/2014	1/10/14)	Loma Linda University Medical Center
27	1/13/2014	Krista Bramble	n/a

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RECEIVED BY CALIF.
BOARD OF PHARMAC.
2013 DEC -2 PM 1:38

Virginia Herold
Executive Officer
California State Board of Pharmacy
1625 N Market Blvd, N219
Sacramento, CA 95834

November 29, 2013

Re: Draft Sterile Compounding Regulations

Dear Ms. Herold,

After reviewing the draft compounding regulations in the California Code of Regulations Division 17, Title 16, Article 4.5 Compounding and the applicable sections of the United States Pharmacopeia, including General Chapters 797, 71, 1079, 1191, 85, 151, 1211, 1116, and 1208, I have found several inconsistencies and areas that should be addressed in the draft regulations before they are finalized. These will be addressed in this letter. Please note that all references to the United States Pharmacopeia in the letter are referring to USP36-NF31 through the Second Supplement, which is official as of December 1, 2013 and supersedes earlier versions. I do suggest that the Board members visit the Nevada Board of Pharmacy website and look at the sterile compounding regulations in that state. Nevada has codified USP 797 and other compounding standards into regulations that are more restrictive than California regulations.

In regulation 1735.1 Compounding Definitions, paragraph (q) on page 3 of the draft, a segregated compounding area is defined. I found no issue with the definition, which is taken from USP 797. However, the draft compounding regulation does not address the "Immediate-Use CSP" section in USP 797. Since a pharmacist-in-charge is responsible for drugs throughout the facility for which he or she is listed on the Pharmacy Permit, I believe the "Immediate-Use CSP" section in USP 797 should be addressed in the draft compounding regulations. Hospitals have used the term "segregated area" to describe an area where an immediate-use CSP is compounded. In this use of "segregated area," it does not meet the criteria for a "segregated compounding area" as described in USP 797. In order to describe the situation better regarding the preparation of immediate-use CSPs, without using the term "segregated compounding area," I describe it this way: Compounding must occur in a clean area that may not meet the definition of a segregated compounding area, in that it may have air quality worse than a controlled ISO Class 5 controlled environment. Such an area could include a specific area on a countertop that has been disinfected with 70% isopropyl alcohol in a medication room within a nursing station. A pharmacist does not directly supervise all such compounding, but a pharmacist could be present and actively involved with such compounding during a cardiopulmonary resuscitation, and the compounding could occur on a countertop or portable table. If the "Immediate-Use CSP" section of USP 797 is incorporated into the draft regulations, it should include a definition differentiating the preparation area from a segregated compounding area.

Although USP General Chapter 797 addresses facility design and environmental controls that directly impact the staff performing the sterile compounding, some parts of it may be overlooked during the dynamic operation of a cleanroom or a room housing a compounding aseptic isolator. For example, a cleanroom in one such facility was built in a section of the building that had no air conditioning and had ambient room air temperatures around 90 degrees Fahrenheit during the summer months. The temperature in the cleanroom was even warmer, making work difficult. The cleanroom was cooled with a portable air conditioner placed inside that decreased the ambient temperature to 83 degrees Fahrenheit, which was still excessive for staff garbed to compound sterile products. USP 797 includes a statement that controlled sterile compounding facilities shall provide a comfortable and well-lighted working environment, which typically includes a temperature of 20 degrees centigrade (68 degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel to perform flawlessly when attired in the required aseptic compounding garb. In my opinion, this section from USP 797 should be included in the draft compounding regulations to ensure it is not overlooked during cleanroom design and certification. A good location would be adding it as paragraph (i) to regulation 1751.4 on page 15.

Since the draft compounding regulations are inclusive of all risk levels of compounding, including the storage of bulk compounds, perhaps humidity should be added to regulation 1735.5 paragraph (c) (7) on page 8 of the draft, since it is addressed in USP 797 and USP 1079. If humidity is added to the draft regulations, it should also be added to regulation 1751.1 Sterile Compounding Recordkeeping Requirements paragraph (b) (4) on page 10.

In draft regulation 1735.3 Recordkeeping of Compounded Drug Products paragraph (c) beginning on page 6, the sentence, "Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration" was deleted. Is the board's intention with this change to require pharmacies to acquire certificates of purity and analysis for all drugs used in compounding, including those in vials, such as antibiotics and TPN electrolytes purchased from manufacturers direct or through wholesalers? If so, this could pose a problem for hospital pharmacies and compounding pharmacies if that information wasn't supplied with every package purchased from the supplier, since brands change due to changes in availability, shortages, and GPO contracts. Alternative text should be developed.

In draft regulation 1751.4 Facility and Equipment Standards for Sterile Compounding [from Non-Sterile Ingredients] beginning at the bottom of page 13, the addition of "from non-sterile ingredients" has rendered this important regulation applicable only to the preparation of non-sterile-to-sterile compounding. This section of the draft needs to address non-sterile-to-sterile and sterile-to-sterile compounding, which could be addressed in the title of the regulation and the text.

Also, in draft regulation 1751.4, paragraph (f) beginning on page 14, the regulation states "The hood shall be decontaminated when switching between cytotoxic and non-cytotoxic ingredients." Since cytotoxic products should be compounded in a compounding aseptic isolator designed for cytotoxic compounding or in a vertical airflow biological safety cabinet designed for cytotoxic agents, and both are generally in a negative pressure room relative to the surrounding ante-room, this sentence seems to conflict with paragraph (g) and with regulation 505.5.1 in the 2013 California Pharmacy Law Book. This is also repeated in regulation 1751.4, paragraph (d) (vi). I

did check with GermFree regarding their LFGI compounding aseptic isolator. Those units can be switched between cytotoxic compounding and non-cytotoxic compounding, but it requires cleaning, modification, and recertification when making the change—it cannot be done on the fly. In today’s environment, I would hope that facilities are not switching back and forth between cytotoxic compounding and non-cytotoxic compounding in the same biological safety cabinet or compounding aseptic isolator.

Also, in regulation 1751.4, there is no reference to temperature monitoring. Perhaps a paragraph (i) could be added to address monitoring cleanroom temperature to address storage of drugs on carts within the cleanroom and personnel comfort in the cleanroom.

In regulation 1751.6 Training of Sterile Compounding Staff, Patient, and Caregiver paragraph (1)(J)(2) on page 18 of the draft, it states, “Each person who handles compounded sterile drug products...” which is not clear. A delivery driver in a long term care pharmacy or delivery staff in other environments would not be expected to be trained on aseptic technique. Delivery staff, however, does need training on the proper storage of compounded sterile products in transit between the pharmacy and the final destination, and policies and procedures should address this and require documentation of training. I believe this paragraph in 1751.6 needs clarification, and perhaps delivery should be addressed somewhere in the draft regulation.

In regulation 1751.7 Sterile Compounding Quality Assurance and Process Validation paragraph (b) on page 19 of the draft mentions, “validation process on technique.” I believe the intent was to address “validation process on aseptic technique,” but it is not clear.

Also, in draft regulation 1751.7 paragraph (e) on page 20, the regulation addresses tests for sterility and presence of pyrogens per USP General Chapters 71, 85, and 151 for batch-produced sterile products. Pyrogen testing as per USP General Chapter 151 specifies the rabbit pyrogen test, which poses problems if used: It is quite expensive and would be beyond the capacity of a compounding pharmacy that is not compounding large batch quantities of non-sterile-to-sterile products where costs could be amortized over many doses. Such a batch size could fall under manufacturing and not pharmacy. Additionally, some medications cannot be tested on rabbits because they are harmful to the rabbit. Further, the rabbit pyrogen test is not 100% accurate (some pyrogens are only pyrogens in humans) and it does cause pain and suffering to the rabbits. An alternate test used for presence of pyrogens is the Bacterial Endotoxin Test, as discussed in USP General Chapter 85, even though endotoxin appears not to be categorized as a pyrogen in USP.

Bacterial Endotoxin Testing using Limulus Amebocyte Lysate (LAL) clotting is affordable and has replaced rabbit pyrogen testing in many instances, but it generally only responds to gram-negative bacteria, which is the source of endotoxin. The LAL test can also respond to fungal glucans. Non-endotoxin pyrogens, such as gram-positive organisms and fungal organisms, are a problem, and have been reported in published papers. Depending on the capabilities of the sterile compounding pharmacy and whether it is in a hospital or not, these testing procedures may need to be outsourced.

Associates of Cape Cod, Inc., a company in Massachusetts, specializes in products to test for endotoxin and glucans, using the LAL test. Their Pyros Kinetix Flex product is capable of using

LAL with and without an endotoxin blocker to test for the quantified presence of bacterial endotoxin and fungal glucans as pyrogens. Such a product could be used to track a source of pyrogens by separating fungal from bacterial. QI Medical, in Nevada City, California, is another source for sterility, pyrogen, and aseptic technique validation products.

There is also a new pyrogen test that is sensitive to all of these pyrogens. The monocyte activation test (MAT) uses whole human blood, which will be an issue. It is also an expensive test (around \$500) per test sample and uses an ELISA antibody response. It is not a standalone process and would likely require sending samples to an outside lab. Information on the MAT test can be found in the following journal article: Hasiwa N, Daneshian M, Bruegger P, et al. Evidence for the detection of non-endotoxin pyrogens by the whole blood monocyte activation test. *ALTEX*. 2013; 30(2):169-208. A kit product for the MAT test is available in the U.S., but it is expensive, as stated above, even when it does not include the lab equipment.

Depyrogenation of glassware or glass vials by heating per USP 151 is affordable, but validating such depyrogenation would be an expensive process if rabbits were used. Of course, endotoxin testing is an alternative, as discussed below. Note that USP 797 also states that sterility tests for autoclaved high-risk CSPs are not required unless they are prepared in batches of more than 25 units. The current draft regulations [1751.7 (3)(e)] on page 20 do not specify the type of sterilization or batch size, which prevents pharmacies from compounding any size batch of non-sterile to sterile products without performing sterility testing. If the Board of Pharmacy was to specify a limit to the batch size of non-sterile to sterile autoclaved CSPs where sterility testing is not required, it would allow pharmacies to do small batches affordably and more timely. The Board would have to define a small batch. If there is still concern about the safety of not doing a sterility test on a small batch, the CSP solution (not suspension) could be filtered through a 0.22 micron or smaller pyrogen-free filter into the final containers prior to autoclaving.

Further in draft regulation 1751.7 paragraph (e), on page 20, the quarantine period specifies sterility and pyrogen levels, but does not address endotoxin levels, which are specified in USP monographs and in General Chapter 85. This is confusing because the text of USP 797 intimates that pyrogens and endotoxin are considered one and the same, and in some sense, they are. As stated earlier, USP 151 addresses the pyrogen test. Levels of pyrogens themselves are not measured. It is the number of febrile responses to the product injected into rabbits that is measured to be within an acceptable level. In the section on depyrogenation by dry heat, USP 797 states, "The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECVs to verify that the cycle is capable of achieving a 3-log reduction in endotoxin (see *Sterilization and Sterility Assurance of Compendial Articles* (1211) and *Bacterial Endotoxins Test* (85))." USP 151 addresses all pyrogens regardless of the type. Any changes to this paragraph of the draft regulation should include the addition of endotoxin levels. Since filtration is another form of sterilization, perhaps adding a sentence addressing filtration of the final product through a bacterial-retentive sterile pyrogen-free 0.22 micron or smaller pore filter and validating the integrity of the filter with a bubble-point test after the transfer should be added to this regulation and other regulations addressing non-sterile-to-sterile compounding for terminal sterilization of those products. Likewise, USP 797 specifies that CSP *solutions* sterilized by autoclaving are filtered through a sterile pyrogen-free 1.2 micron or smaller pore filter prior to sterilization or during the transfer to

the final container to remove particulate matter. Filtration of the final product cannot be done on suspensions such as those produced by the New England Compounding Center. Suspensions would require alternative processes and procedures for filtration as specified in USP and the literature to ensure sterility. These processes may be beyond the capability of a compounding pharmacy. A review article discussing such methods was found with a Google.com search on November 11, 2013 entitled Parenteral Suspension: An Overview by Patel RM in the International Journal of Current Pharmaceutical Research, Vol. 2, Issue 3, 2010, 4-13. This foreign journal is not indexed through PubMed.

The Board may wish to add a list of sterilization processes as specified in USP General Chapter 797 and USP General Chapter 1211 (Sterilization and Sterility Assurance of Compendial Articles), which includes filtration, bubble point testing of filters for validation of filter integrity following filtration, autoclaving with steam, and dry heat to the draft regulations versus just stating, "sterilization" within the text. Ionizing radiation and ethylene oxide sterilization processes could also be included in the list.

In regulation 1751.8 Beyond Use Dating for Sterile Compounded Products paragraph (d) on page 22 of the draft, I believe this was adapted from USP 797 but misquoted. It could use clarification, so there is no misunderstanding. As currently written it appears to conflict with other paragraphs. If I understand the intent of this paragraph, I believe it should state, "Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood not located within an ISO Class 7 buffer room with an anteroom or is an ISO Class 5 barrier isolator not located within an ISO Class 7 buffer room with an anteroom and documentation from the manufacturer of the barrier isolator does not permit operation in an environment that exceeds ISO Class 7 in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours." If my understanding was incorrect, is this current paragraph of the draft addressing sterile-to-sterile low-risk CSPs with a 12-hour or less BUD where the placement of primary engineering controls did not meet specified criteria (ISO class 5 hood within ISO Class 7 buffer room) for a longer beyond-use date? Alternatively, if the current paragraph is meant for a *non-batched* sterilized high-risk sterile compound in USP 797, the beyond-use date of a preparation without sterility testing is 24 hours; and if it meant for a *batched* sterilized high-risk sterile compounds, the beyond-use date would generally be 12 hours, depending on storage conditions.

Designing and building sterile compounding facilities in hospitals and health-systems is an extremely expensive process that makes it difficult for many health facilities to comply in a manner that optimizes their productivity, due to the delays, costs, and requirements of the Office of Statewide Health Planning and Development (OSHPD). Facilities often opt for \$20,000 barrier isolators rather than build one or more cleanrooms that can cost upwards of \$100,000 each. Sterile compounding regulations have gotten to the point that it has become very time-consuming and expensive to do sterile compounding, when one considers all the documentation, process validations, equipment, supplies, testing, and training required. NECC, as a worst-case scenario, and several other sterile compounding pharmacies, show that we need these regulations to ensure patient safety. Outsourcing of compounding and validation testing will likely increase, due to the

costs. Unfortunately, without sufficient reimbursement, many sterile compounding pharmacies will be unable to continue to compound at previous levels and provide the level of service necessary to service their customers, and some will cut corners to remain profitable.

As was pointed out during the sterile compounding forum at CSHP Seminar 2013, problems also occur due to trainers who learned improper techniques and pass those bad skills on to others. Training is an issue, because some pharmacists and pharmacy technicians work at more than one pharmacy and have to remember the compounding procedures and processes used at each of those pharmacies and not confuse them. Perhaps if more premixed products were available from FDA regulated manufacturers, much of these problems would go away. In any case, we need the proposed sterile compounding regulations enacted for patient safety.

Please take all of this into consideration when revising the draft compounding regulations. I think the board is moving in a positive direction that will improve patient safety throughout California.

Sincerely,

A handwritten signature in cursive script that reads "Douglas Barcon, Pharm.D." The signature is written in dark ink and is positioned above the typed name.

Douglas Barcon, Pharm.D.

Damoth, Debbie@DCA

From: Martin Hesky <mhesky@aol.com>
Sent: Sunday, December 01, 2013 3:40 PM
To: Damoth, Debbie@DCA
Subject: Proposed Changes to Board of Pharmacy proposed amendments Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations

Hello Debbie,

In trying to wade through the considerable lengthy language, I have not been able to determine if the board is handling Compounding Aseptic Isolators (CAI) any differently as USP 797 does in certain areas. e.g. there is an exception for CAI having to be located in an Iso7 environment (If certain requirements are met), there is an exception for standard garbing requirements (again if certain requirements are met), and also sterile gloves are not necessarily a requirement (although the use of sterile Isopropyl alcohol use on the gloves is).

Can you point me to any specific proposed language that discusses any differences in how CAI's will be regulated?

Thank you,

Martin Hesky Pharm.D.
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Proposals for Compounding Regulations Revisions

December 9, 2013

Regulation Revision	Proposal
p.1 Line 31-33 Definition of Batch	<ul style="list-style-type: none"> • USP 797 definition is different than BOP definition • <u>Sterile to non-sterile preparations</u> • Limit to only <u>high risk purposes</u>, and do not add low and medium risk products • What is the benefit of defining a batch as a single dose.
P.2 Line 2-3 Beyond use date	<ul style="list-style-type: none"> • The terminology should not be <u>USED</u>. • Must parallel the terminology of USP 797. <ul style="list-style-type: none"> ◦ Replace <u>Used</u> with <u>Stored and transported</u>.
P.2 Line 13 Controlled <u>room</u> temperature	<ul style="list-style-type: none"> • Proposed controlled room temperature of 20-25 degrees Celsius may be too warm given garbing requirements • USP 797 recommends a temperature of 20 degrees or cooler
P.2 Line 17-20 Gloved fingertip sampling	<ul style="list-style-type: none"> • Use of sterile gloves during this process • Must be performed: <ul style="list-style-type: none"> ◦ in the beginning of compounding, immediately after garbing with CFU 0 ◦ During compounding, with CFU < 3
P. 4 Line 15 Inactive ingredients	<ul style="list-style-type: none"> • Referring to vehicle/suspending agent
P. 6 Line 11-13 Deleted lines: "Certificates of purity or analysis are not required for drug products that are approved by Food and Drug Administration"	<ul style="list-style-type: none"> • This revision is significant for those hospitals that utilize chemicals to compound certain products • Remove deletion of this sentence • The revision states that the chemicals used to compound drug products shall be obtained from reliable <u>FDA-registered suppliers</u>. (clarify FDA-registered supplier; not all places where pharmacies obtain chemicals from are FDA-registered)
P. 7 Line 7-9 The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct	<ul style="list-style-type: none"> • Adding <u>intentionally or grossly or willfully</u> • The word <u>shall</u> should be changed to <u>may</u>
P. 11 Line 5 Logs of room pressure differentials	<ul style="list-style-type: none"> • This should be done per policies and procedures of each hospital. • Addition of "use of electronic air pressure meters with alarms and alerts to be used" • Air displacement as means of air segregation
P. 13 Line 13-14 Sterility and bacterial endotoxin testing	<ul style="list-style-type: none"> • Only needs to be done for <u>high risk</u> preparations.
P. 14 Line 14-15 Cleaning shall include the periodic use of sporicidal agent	<ul style="list-style-type: none"> • Use of sporicidal agent is not recommended by USP 797
P. 20 Line 14 7 days at controlled cold temperatures BUD for low risk preparations	<ul style="list-style-type: none"> • Change <u>7</u> days to <u>9</u> days
P. 14 Line 1-8 Cleaning the surfaces	<ul style="list-style-type: none"> • According to the revisions of BOP AND USP: cleaning and disinfecting surfaces in the ISO class 5 hood shall occur frequently, including: at the beginning of each shift, before

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Proposals for Compounding Regulations Revisions

December 9, 2013

	<p>each batch, every 30 minutes during continuous compounding of individual compounded sterile drug products, after each spill, when surface contamination is known or suspected, and when switching between cytotoxic and non-cytotoxic ingredients.</p> <ul style="list-style-type: none">• Concern is: how do we interrupt compounding in order to clean surface every 30 minutes and record accordingly.
Facility design and environmental controls	<ul style="list-style-type: none">• OSHPD requirements for renovations within the IV room in accordance to Ca BOP and USP 797 requirements.• The Board of Pharmacy should allow for approximately three months for submission of a document for strategic planning to meet the requirements for facility design and environmental controls.• The Board of Pharmacy should allow for approximately six to twelve months to complete the required redesigning and renovations.

References:

Compounding. Revisions made at 10/21/13 subcommittee meeting. *California Board Of Pharmacy.*

Pharmaceutical Compounding—Sterile Preparations. USP-NF General Chapter <797>. *The United States Pharmacopeial Convention.* 2011.

Damoth, Debbie@DCA

From: Eskandarian,Romic <Romic.Eskandarian@ah.org>
Sent: Monday, December 09, 2013 9:16 AM
To: Damoth, Debbie@DCA
Subject: Compounding Regulations Revisions_Comments from Glendale Adventist Medical Center
Attachments: Compounding regulations revisions_Glendale Adventist Medical Center.doc

Please see attached for comments on latest proposed language changes in CA Board of Pharmacy Compounding Regulations.

Romic Eskandarian, Pharm.D.

Director of Pharmaceutical Services

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Damoth, Debbie@DCA

From: Herold, Virginia@DCA
Sent: Tuesday, December 10, 2013 10:13 AM
To: 'Mcallister, Dennis (WDC)'
Cc: Damoth, Debbie@DCA
Subject: RE: Comments on the compounding rules

Importance: High

Thank you. I will forward to our regulation coordinator.

From: Mcallister, Dennis (WDC) [mailto:Dennis_McAllister@express-scripts.com]
Sent: Tuesday, December 10, 2013 8:49 AM
To: Herold, Virginia@DCA
Subject: Comments on the compounding rules

Giny,
We have only to minor comments. We think it important to clearly define a "product" which is manufactured, and a "preparation" which is compounded. Then, they should be used correctly throughout the document. These definitions will align with other states and federal definitions.

Dennis K. McAllister R.Ph.,D.Ph., FASHP
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Ms Debbie Damoth
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State Board of Pharmacy,
1625 N. Market Blvd., N219
Sacramento, CA 95834

December 10, 2013

Dear Ms Damoth;

RE: Title 16

We at Abbotts Compounding Pharmacy, Inc. agree with most of the changes in Title 16 because it is a real benefit to our patients, customers and people of the State of California. It also levels the playing field for all compounding pharmacies within the State and out of State pharmacies.

However, we have a few comments that we hope the State Board of Pharmacy will consider changing:

1. Amend 16 CCR&1735.1:
"Batch" defines in Webster dictionary as a "group". A "group" is three or more. Not just more than one. It is impractical to either make two separate preparations of the same thing or have to test the "Batch".
For example: A husband and wife with eye infection want to have the same antibiotic eye medication compounded. It will take more time and cost more to prepare separate doses.
2. Amend 16 CCR&1735.3:
"Lack of supplier's expiration date cannot be used after one year." Many minerals and their salt forms are stable for a long time. For example: Potassium Chloride, Sodium Selenite etc do not expire, change or degrade in one year. The expiration dates of this kind of chemicals should be determined by either the pharmacist or the manufacturer based on actual nature of the substances, not just arbitrary for one year.
3. Amend 16CCR&1751.4:
"Cleaning and disinfecting ... every 30 minutes during continuous compounding of individual compounded sterile drug products..."

The 30 minute rule is totally unsafe and impractical. We have patients who require 20 to 40 vials of a product and it requires 45 to 60 minutes to prepare. We cannot remove these vials in the middle of compounding to do a thorough cleaning after 30 minutes. Such a practice will increase the risk of contamination, error as well as adding the cost of the product. We agree with the other provisions within this regulation.

4. Amend 16CCR1751.5:
"Gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol after contact with non-sterile objects."
Please clarify "routinely", does it mean "every time" or "as necessary"? If it means "every time", it is impractical because most exterior of vials, syringes and bottles are non-sterile. Even the exterior of the 70% isopropyl alcohol bottle is non-sterile.
5. Amend 16CCR&1751.7:
"Requires samples for sterility testing to be taken at the beginning, middle and end of the compounding process."
Please clarify at what volume of the sterile product that you require the three samples. Also, do we put all 3 samples in a single dose vial or 3 different vials for sterility testing? We need to test the end product dispensed to patients not testing the process. Testing a process is for complicated manufacturing and not necessary applicable for simple drug compounding.
6. On the Discussion Draft dated 9/2013, Page 16 of 19, line 8:
(5) Storage Limits: "24 hours at room temperature, 3 days at cold temperature and 45 days in solid frozen state".
This is again not practical in real life setting. According to the Handbook on Injectable Drugs, many sterile products are stable longer than your requirement. Furthermore, patients getting inhalation therapy or eye drops which are stable at cold temperature or room temperature, you cannot tell those patients to discard their expensive medication in a day to 3 days because there is not sterility testing done.
7. Cost Impact on Representative Private Person or Business:
There would be definite increase in cost to compounding pharmacies as more testing and separate compounding are required. These costs will be passed onto patients/consumers.

Again, most of the changes in Title 16 are beneficial to our patients. But as mention above, some of these requirements need careful discussion and or consideration before put into law. Thanks for the time to consider my comments.

Best Regards,

Elliot Kwok, Pharm.D.

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December 12, 2013

California Board of Pharmacy
Attn: Debbie Damoth
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Sacramento, CA 95834

VIA E-MAIL AND U.S. MAIL

**RE: Compounding Regulations, Notice of Proposed Action
Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations
Section 1735 et seq. and 1751 et seq.**

Dear Ms. Damoth:

On behalf of Providence Health & Services, Southern California, we appreciate the opportunity to submit comments on the proposed changes to compounding regulations for hospital pharmacies. Proposed amendments cover Articles 4.5 and 7 of Division 17 of Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq.

Providence Health & Services, Southern California, is a Catholic not-for-profit organization dedicated to providing quality and compassionate health care and reaching out to the poor and the vulnerable in the communities it serves. Providence Southern California operates five award-winning acute-care medical centers in the Los Angeles area, providing a full continuum of health care services: Providence Saint Joseph Medical Center in Burbank, Providence Holy Cross Medical Center in Mission Hills, Providence Tarzana Medical Center, and Providence Little Company of Mary Medical Centers in Torrance and San Pedro. The region also has numerous ancillary facilities including hospice care, long-term care, numerous outpatient clinics, Providence Medical Institute, and an affiliation with Facey Medical Group.

Our response has three parts: overall recommendations; a set of recommendations relating to acute care; and further detailed recommendations on the rule language. *These proposed compounding regulations are important to Providence because we operate pharmacies at each of our five medical centers and another pharmacy at the Disney Family Cancer Center in Burbank.*

Providence Southern California supports the goal of updating state compounding regulations to improve overall patient safety and consistently align with USP Chapter 797 guidelines. We offer the following comments and recommended improvements to ensure that we can collectively achieve this goal while maintaining our ability to safely compound treatment therapies for our patients in all care settings. This is especially important when our pharmacies are responding to immediate needs and working with cytotoxic agents.

Our overall recommendations:

- We strongly urge the board to adopt regulations that reflect the best quality outcomes, and to codify the measures implemented by hospital pharmacies, as documented here, that already are protecting patient safety and are aligned with USP Chapter 797 guidelines.

Compounding in the acute care environment requires speed and flexibility

Critical medications in hospitals are compounded for emergent situations and direct patient administration including code blue responses, heart attacks and strokes. Preparation inside an ISO 5 hood within an ISO 7 buffer zone with cleansing and garbing would cause significant delays to patient therapy and risk patient harm. During code blue responses, hospital pharmacists mix or “compound” sterile drug products at the patient bedside to provide life sustaining IV medication to patients requiring cardiopulmonary resuscitation.

Our recommendations:

- Add the immediate-use provision with a one-hour beyond-use date, as set out in USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration.
- Allow use of an ISO Class 5 hood within a segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom (ante-area and buffer room).
- Allow hospital pharmacies to compound hazardous drugs in non-negative pressure rooms, such as a closed-system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. Hospital pharmacies have safely prepared chemotherapy for cancer patients within this environment, which is permitted under USP 797 guidelines.

Timely access to care is essential

Without needed rule amendments to permit sterile compounding in environments other than cleanrooms, a hospital or facility without a cleanroom will not be able to prepare any sterile compounded medications for patients. Furthermore, if the board adopts the proposed regulations, hospitals would not have enough time to come into compliance and would be unable to provide timely intravenous therapy, risking harm to our patients.

Our recommendations:

- This is the least preferred option. If the board adopts regulations with the current requirements, an extended timeframe will be needed to allow facility changes and construction to be completed in compliance with state building regulations and hospital licensure requirements. Without this, our patients will not receive life-saving therapy.

Further detailed recommendations and comments

For ease of reference, we have organized our detailed comments in a matrix. On the left is the location of the language as proposed in the rule and in the center column that language appears. On the right, we propose new language either by tracked deletions or by additions in red italics.

Section	Proposed language	Providence Health & Services Comments/recommendations
General comments	Multiple Occurrence of Amendment #2	Consistent with “Multiple Occurrence of Amendment #2,” Providence requests that the board change “expiration date” to “ <i>beyond-use date</i> ” in section 1735.4(c) [Labeling of Compounded Drug Products].
General comments	Sections 1735.2(d), 1735.5(a), 1751.3(a), 1751.3(b), 1751.3(c), 1751.3(d), 1751.3(d)(3)(I), 1751.6(e)(1), 1751.6(e)(2), 1751.7(a), 1751.7(a)(3)	Add <i>Multiple Occurrence of Amendment #6</i> to strike the word “written” and “in writing” from all sections within the proposed regulations. This change would allow pharmacies to be able to maintain electronic

1735(a), page 1	<p>"Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:</p>	<p>policy and procedure manuals.</p> <p><i>"Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:</i></p> <p>Providence requests the removal of the reference to activity performed by a pharmacist to clarify that the regulations do not apply outside of the licensed pharmacy. This change will allow pharmacists to continue to prepare emergency sterile compounded drugs at the bedside during a code blue, and conform to the immediate use provision under USP Chapter 797.</p>
1735.1(b), page 2	<p>"Batch" means more than one does of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.</p>	<p><i>"Batch" means multiple doses of sterile products combined or pooled to prepare a product that will be administered either to multiple patients or one patient on multiple occasions, or 25 or more units compounded from non-sterile ingredients.</i></p> <p>More than one dose is a very small quantity to apply the term "batch" to unless other specific processes apply, such as pooling/combining ingredients into multiple doses or using non-sterile ingredients to prepare multiple doses. Hospital pharmacies typically prepare patients' doses for the same drug at the same time but without pooling/combining ingredients. For instance, hospital pharmacies could prepare patient doses for the same drug for a certain timeframe, generally 12 hours (based on 12-hour beyond-use dating) or 24 hours at a time. This type of preparation is not considered batch compounding per USP or AHSP definitions.</p>
1735.1(c), page 2	<p>"Beyond use date" means the date after which a compounded drug product should not be used.</p>	<p><i>"Beyond use date" means the date or time after which a compounded drug product should not be used stored or transported. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond-use date.</i></p> <p>The current draft regulation definition implies that the administration of the drug should not take place after the beyond use date. The definition above from USP 797 seeks to avoid any confusion or misinterpretation about the duration of</p>

1735.1(d), page 2	<p>"Parenteral" means a sterile preparation of drugs for injection through one or more layers of skin.</p>	<p>administration or administration time permitted because of the beyond-use dating.</p> <p><i>"Parenteral means a sterile preparation of drugs for injection through one or more layers of skin, to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation.</i></p> <p>Providence recommends that the regulatory definition should be consistent with medical definition of "parenteral" and SB 294 [Article 7.5, Sec 3. 4127(a)].</p>
1735.3(c), page 6	<p>Chemicals, bulk drug substances, and drug products used to compound drug products shall be obtained from reliable FDA-registered suppliers.</p>	<p>Providence recommends defining "chemicals, bulk drug substances, and drug products." We also request that the board define "reliable FDA-registered supplier."</p>
1735.3(c), page 6	<p>The pharmacy shall acquire and retain certificates of purity or analysis for chemicals, bulk drug substances, and drug products used in compounding.</p>	<p><i>The pharmacy shall acquire and retain certificates of purity or analysis for chemicals, and bulk drug substances, and drug products used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.</i></p> <p>USP 797 requires certificates of analysis from suppliers only when nonofficial (non-USP or NF) ingredients are used.</p> <p>Providence requests background information or evidence that supports the requirement for pharmacies to acquire/retain certificates of purity or analysis for FDA approved drug products to help explain why the exemption was removed from the draft revisions.</p> <p>FDA approved drugs are produced according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of these drugs beyond the FDA approved standards.</p> <p>Providence urges the board to amend this section to require manufacturers to provide these certificates to pharmacies with each of their products, rather than impose the burden on hospital pharmacies to obtain these documents from the manufacturer.</p>

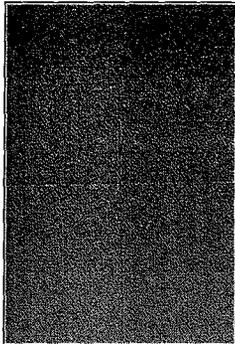
<p>1735.5(c)(7), page 8</p>	<p>The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures.</p>	<p><i>The storage of compounded sterile drug products in the pharmacy and daily routine monitoring and documentation of room, refrigerator, and freezer temperatures. If the compounding facility uses a continuous temperature recording device, compounding personnel shall verify at least once daily that the recording device itself is functioning properly.</i></p> <p>Providence recommends adding the qualifying language from USP 797 to consistently align with the national standards. Our refrigeration units provide continuous temperature monitoring and alert systems. Daily documentation would not provide an advantage to this 24/7 monitoring nor does it increase patient safety beyond the systems already in place.</p>
<p>1751.1(b)(4), page 10</p>	<p>Daily documentation of room, refrigerator, and freezer temperatures appropriate for drug preparations consistent with the temperatures listed in section 1735.1...</p>	<p><i>Add to section 1751.1(b)(4): If the compounding facility uses a continuous temperature recording device, compounding personnel shall verify at least once daily that the recording device itself is functioning properly.</i></p> <p>Providence recommends adding the qualifying language from USP 797 to consistently align with the national standards. Our refrigeration units provide continuous temperature monitoring and alert systems. Daily documentation would not provide an advantage to this 24/7 monitoring nor does it increase patient safety beyond the systems already in place.</p>
<p>1751.1(b)(6), page 10</p>	<p>Logs of room pressure differentials</p>	<p><i>Logs of room pressure differentials when applicable</i></p> <p>Providence recommends including the wording "when applicable."</p> <p>Facilities without cleanrooms or buffer areas within anterooms cannot have pressure differentials so a log would not be required.</p>
<p>1751.3(d)(3)(i), page 13</p>	<p>For sterile compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing.</p>	<p><i>For sterile compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing for non-sterile compounding or extending beyond-use dating past specifications from Section 1751.8.</i></p>

		Providence recommends amending language for sterility and bacterial endotoxin testing to be done when non-sterile ingredients are used or when extended dating beyond USP 797 storage specifications is desired (as in draft section 1751.8).
1751.3(d)(3)(I)(ii), page 13	(J) For non-sterile to sterile compounding: (i) Sterilization (ii) End-product evaluation and testing.	<i>(J) For non-sterile to sterile compounding: (i) Sterilization (ii) End-product evaluation and testing, including sterility and bacterial endotoxin testing.</i> Remove sterility and endotoxin testing verbiage from 1751.3(d)(3)(I) and add it to 1751.3(d)(3)(J) section on non-sterile to sterile compounding: <ul style="list-style-type: none"> ▪ USP797 guidelines require sterility and bacterial endotoxin testing only for high-risk level (i.e. non-sterile to sterile) compounding prepared in groups of more than 25 individual single-dose packages. ▪ Low-risk and medium-risk preparations would only require sterility testing if extended beyond-use dating was being used per USP 797.
1751.4, page 13	Facility and Equipment Standards for Sterile Compounding [from Non-Sterile Ingredients].	<i>Facility and Equipment Standards for Sterile Compounding</i> [from Non-Sterile Ingredients] . Providence recommends removing wording from the title "from non-sterile ingredients" since the contents of the section relate exclusively to non-sterile ingredients. This section pertains to all sterile compounding and the title is not clear.
1751.4(e), page 14	Cleaning shall include the periodic use of a sporicidal agent.	Cleaning shall include the periodic use of a sporicidal agent. Remove requirement of a sporicidal cleaning agent. USP 797 does not require use of a sporicidal agent. USP 797 does require careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Sporicidal agents may not be appropriate in all cases.
1751.4(g), page 15	Pharmacies preparing sterile cytotoxic agents shall use a biological safety cabinet or compounding aseptic containment isolator that provides an ISO Class 5 environment during dynamic compounding conditions which is	<i>Add to Section 1751.4(g): The use of a closed-system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable.</i>

	<p>maintained in accordance with the manufacturer's recommendations and which is certified every six months. If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area, the compounding area shall maintain negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.</p>	<p>Providence urges the board to amend this section to allow sterile compounding of cytotoxic agents in a non-negative pressure room when closed-system vial-transfer devices (CSTDs) are used within a BSC or a CACI in a non-negative pressure room as deemed acceptable per USP797 guidelines (referred to as two-tiers of containment).</p> <p>USP797 guidelines allow for facilities that prepare a low volume of hazardous drugs to utilize CSTDs within BSC/CACI's as two-tiers of containment in a non-negative pressure room.</p> <p>Closed-system vial-transfer devices are approved by NIOSH (National Institute for Occupational Safety and Health) guidelines. FDA created a product code, ONB, specific for closed antineoplastic and hazardous drug reconstitution and transfer system devices that require data to prove a system is closed for use with hazardous drugs and reduces exposure.</p>
<p>1751.6(e)(2), page 18</p>	<p>Each person who handles compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures.</p>	<p><i>Each person who handles prepares compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures.</i></p> <p>Providence recommends changing the wording from "handles" to "prepares." Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation, or dispensing should not be required to undergo aseptic technique training.</p>
<p>1751.7(a)(3), page 19</p>	<p>Written justification of the chosen beyond use dates for compounded sterile drug products.</p>	<p>Written justification Documentation justifying of the chosen beyond use dates for compounded sterile drug products.</p> <p>Providence recommends amending the language to remove the word "written" while still requiring documentation to justify appropriate beyond-use dating.</p>
<p>1751.8(a), page</p>	<p>Criteria matching USP797 Low-Risk</p>	<p>Add to Section 1751.8(a):</p>

21	<p>Level compounding and beyond use dating: Where the sterile compounded drug product was compounded... using only sterile ingredients, products, components, and devices...</p>	<p><i>Compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package of sterile products or administration container/device to prepare the drug product. Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.</i></p> <p>Providence recommends adding in all three criteria to quality compounded sterile products that should have beyond-use dating matching the USP 797 low-risk category.</p> <p>Excluding all criteria for each category allows for looser interpretation and permits some compounded sterile products to be dated in different risk level categories and with different beyond-use dating from established USP 797 guidelines.</p>
1751.8(b), page 21	<p>Where the sterile compounded drug product was compounded... using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions</p>	<p><i>Add to Section 1751.8 (b): or where the process includes complex aseptic manipulations other than the single-volume transfer, or requires unusually long duration such as that required to complete dissolution or homogenous mixing.</i></p> <p>Providence recommends adding in the other two examples of conditions which would qualify a compounded sterile product to be consistent with the beyond-use dating in this section that aligns with the USP 797 medium-risk level.</p>
1751.8(b)(2), page 21	(2) 7 days at controlled cold temperature	<p><i>(2) 7 9 days at controlled cold temperature</i></p> <p>Providence recommends changing the cold temperature beyond-use date to 9 days to match conditions that correlate with USP 797 Medium-Risk Level.</p>
1751.8(d), page 22	<p>Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood in the absence of passing a sterility test in accordance with</p>	<p><i>Add to Section 1751.8 (d): Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood that is located in a segregated</i></p>

	<p>standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours.</p>	<p><i>compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours.</i></p> <p>Providence recommends adding in criteria to qualify conditions that would meet the beyond-use dating. Without qualifiers non-sterile (high-risk level) products could be prepared in this manner which would be very unsafe.</p> <p>This section is meant to include the provision from USP 797 for Low-Risk Level CSPs with 12-hour or less beyond-use dating – when an ISO Class 5 hood cannot be located within an ISO Class 7 buffer area. Many hospitals operate under this provision safely and meet the USP 797 criteria.</p>
<p>1751.8, page 22</p>	<p>Lack of immediate-use provision, with a 1 hour beyond-use date, for compounding sterile products outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7 buffer room or cleanroom would cause delays and risk patient harm.</p>	<p><i>Add to Section 1751.8:</i> <i>(e) Where the sterile compounded drug product was compounded solely with aseptic manipulations in conditions worse than ISO Class 5, involving simple transfer using only sterile ingredients and components, the beyond use date shall be one hour. These preparations are limited to situations where there is a need for emergency or immediate patient administration of a compounded sterile product where preparation inside an ISO Class 5 environment would subject the patient to additional risk due to delays in therapy. If administration has not begun within one hour from the start of preparation, the compounded sterile product must be discarded appropriately.</i></p> <p>Providence recommends adding the immediate-use provision, with a 1-hour beyond-use date, as per USP 797 to allow for preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration. Critical medications in hospitals are</p>



compounded for emergent situations and direct patient administration including code blues, heart attacks, and strokes, and preparation inside an ISO 5 hood within an ISO 7 buffer zone with cleansing and garbing would cause significant delays to patient therapy and risk patient harm. Hospital pharmacists mix or "compound" sterile drug products at the patient bedside during code blue to provide life sustaining medication to patients.

Thank you for the opportunity to submit comments. We strongly urge the state Board of Pharmacy to give full and careful consideration to the comments and recommendations offered by Providence, as well as those comments submitted by our hospital pharmacy colleagues throughout the state.

Sincerely,

Munro Bholat
Pharmacy Director
Providence Little Company of Mary
Medical Center Torrance

Goorgen Boghossian
Pharmacy Director
Providence Tarzana Medical Center

Tawny Bui
Pharmacy Director
Providence Holy Cross Medical Center

Teresa Lee-Yu
Pharmacy Director
Providence Saint Joseph Medical Center

Hiroyuki Nishi
Pharmacy Director
Providence Little Company of Mary
Medical Center San Pedro

cc: California Board of Pharmacy, Board Members
California Society of Health-System Pharmacists
California Hospital Association

Damoth, Debbie@DCA

From: Tou, Michael P <Michael.Tou@providence.org>
Sent: Friday, December 13, 2013 2:22 PM
To: Damoth, Debbie@DCA
Subject: Compounding Drug Products - Proposed Regulations
Attachments: Providence Southern California FINAL Comment Letter - Compounding Regulations 12.12.13.pdf

Importance: High

Good afternoon Ms. Damoth,

On behalf of Providence Health & Services, Southern California, I wish to submit the attached comments to the Board of Pharmacy in response to the Notice of Proposed Action to amend Title 16 CCR, Section 1735 et seq. and 1751 et seq.

We greatly appreciate the opportunity to share our recommendations with the board. We hope the board will carefully consider our comments and adopt our recommendations so that we can move together in enacting regulations that achieve our mutual goals in providing life saving therapy to our patients, while protecting public health and safety.

Please let me know if you have any questions about our letter.

Thank you for your time and consideration. Happy Holidays to you and your colleagues.

Michael

Michael Tou, MPA
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Kaiser Permanente Pharmacy Concerns about BOP Compounding Language

Updated 12/18/13 Doug O'Brien, Pharm.D., Northern California Regional Director for Inpatient Pharmacy Services and Donald Kaplan, Pharm.D., Southern California Inpatient Pharmacy Practice Coordinator

BOP Proposed Cmpd Regs Text 112613 was used as a reference.

Introductory Comments:

Kaiser Permanente is submitting this document on behalf of our 35 hospital pharmacies, eight licensed home infusion pharmacies, and 29 ambulatory oncology pharmacies that have Calif Board of Pharmacy-issued sterile compounding licenses.

Pharmacy managers and administrative pharmacy leaders in our organization carefully reviewed the draft regulations. We prepared a grid to clearly show the language that we believe to be problematic or unclear; the rationale for our concerns, suggestions to improve the language, and a point-by-point assessment of the impact to our organization if the language is not changed.

We noticed that the draft regulations posted on the Board of Pharmacy effective 11/26/13 did not contain the Title 24 language that was present in the 10/25/13 draft regulations (Title 24, Part 2, Chapter 12,1250.4 (6)). While the deletion of the Title 24 language reduces costly obstacles to compliance with the draft regulations, we understand the Board will be pursuing the Title 24 language through other means. Therefore, we are including our concerns regarding the Title 24 language in this document.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735.1(b) Page 2 of 27	A batch means more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding	<p>Concern: There is no benefit in defining a batch for sterile to sterile transfers, whether for a single dose or multiple doses. There is already language in existing and proposed regulations that limit the risk associated with low and medium risk compounded sterile preparations (CSPs). For example: process validation is already required for personnel compounding these types of preparations (1751.7(b)). The term "batch" should only be applicable for high-risk CSPs, where <u>end-product</u> testing representative samples is specifically <u>required</u>.</p> <p>The use of this definition creates problems in other parts of the proposed regulations. For example, 1751(e) describes sterility testing to be performed. It states that "Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch." If a batch consists of two doses, it would be impossible to perform that testing without destroying all the finished product. Also, 1754(d)ii (page 14 of 23, line 3) states that cleaning and disinfecting surfaces in the ISO Class 5 hood shall occur before each batch. If a batch is defined as a single dose as</p>	Operational inefficiency

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		<p>described in 1735.1(b), pharmacy personnel would be required to perform hood cleaning up to several hundred times per day.</p> <p>Recommendation: Define batch in the context of performing high-risk compounding only (e.g. sterile compounding using non-sterile ingredients) as described in USP <797>, and in a quantity that can be tested without destroying all the finished product.</p> <p>Batch Definition: "All high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampules, bags, syringes, vials) or in multiple-dose vials (MDVs) for administration to multiple patients or that are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized shall meet the sterility test (see <i>Sterility Tests</i> <71>) before they are dispensed or administered."</p>	
1735.1 (c) Page 2 of 27	"Beyond Use Date" means the date after which a compounded drug product should not be used.	<p>Concern: The term "used" is ambiguous and unclear. It could be construed to mean "used up" or "completed", which, in the context of sterile compounding, would mean the completion of drug administration to a patient. Some drug products are administered over several minutes; others can be infused continuously for 24 hours or more.</p> <p>Recommendation: Change language to be consistent with USP <797>.</p> <p>"The date or time after which a compounded sterile preparation shall not be stored or transported."</p>	High cost due to drug waste and to prevent interruption of therapy that is being administered to patients
1735.1 (e) Page 2 of 27	"Cleanroom" means a separate room meeting an ISO Class 7 or better air quality	<p>Concern: This is a non-standard definition that appears to have been created by the Board of Pharmacy Compounding Subcommittee. According to USP <797>, a clean room for the preparation of low and medium risk level compounded products could be an ISO Class 7 buffer area where laminar flow hoods are placed, and an ISO</p>	Remodeling & construction costs: \$115 million for our organization.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		<p>Class 8 ante area for gowning, handwashing, and staging of ingredients and supplies. When preparing high risk compounded products or hazardous drugs, however, an ISO Class 7 clean room is required. The clean room definition should therefore consider the risk level(s) of the products being compounded.</p> <p>Recommendation: Change language to be consistent with USP Chapter 797: “A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface and personnel gear are not exceeded for a specified cleanliness class.”</p>	
1735.1(f), Page 2 of 27	Controlled cold temperature” means 2° to 8° C (36° to 46° F)	<p>Concern: Although this proposed definition is consistent with USP <797>, it conflicts with California H&S 70263(q)(6), which states: “Drugs shall be stored at appropriate temperatures. Refrigerator temperature shall be between 2.2° C (36° F) and 7.7° C (46° F)...”</p> <p>Recommendation: Change wording to read: “Controlled cold temperature” means 2.2° to 7.7° C (36° to 46° F)”</p>	Consistency with existing California statute
1735.1(j) Page 2 of 27	“Gloved fingertip sampling” means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated and then examined for growth of microorganisms.	<p>Concern: This language is incomplete. It is important that growth media be incubated properly. This will reduce the risk of inaccurate results.</p> <p>Recommendation: Use USP <797> language.</p> <p>“Gloved fingertip sampling” means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms.”</p>	Operational efficiency
1735.1 (q)	“Segregated compounding area” means a designated	Concern: The proposed language does not acknowledge that barrier	Unnecessarily

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
Page 3 of 27	space, either a demarcated area or room, that is restricted to preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such an area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile products and shall be void of activities and materials that are extraneous to sterile compounding	isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on "Placement of Primary Engineering Controls"). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room. Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in the "Placement of Primary Engineering Controls" subsection, USP <797>, page 22.	short beyond use dating may cause excessive drug waste. Cost impact: exceeding \$1 million/year for our organization.
1735.3 (a)(9)(c) Page 6 of 27	The pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products, and components used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. Certificates of purity or analysis are to be matched to the product received.	Concern: the existing regulation exempts FDA-approved drugs from the requirement to obtain certificates of purity or analysis. The proposed regulation would delete this exemption. Under the proposed regulation, if lidocaine 1% injection USP used as an ingredient during compounding, a certificate of purity or analysis would be required in the compounding record. The FDA-approved product labeling already attests to its identity, strength, and sterility. Recommendation: Retain this language: "Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration."	Operational inefficiency
1735.5 (a) Page 7 of 27The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.	Concern: The proposed language is overly harsh, and provides no latitude if minor deviations are found in observance of policies and procedures that pose no reasonable risk to the public. There needs to be room for judgment on the part of the inspector and/or the Board. Recommendation: "The pharmacy shall follow its policies and procedures. Intentionally (or grossly) failing to follow these policies and procedures may be deemed unprofessional conduct."	Draconian language; Suggest adopting concepts of "Just Culture"

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735.5 (c)(7) Page 7 of 27 and 1751.1 (b)(4) Page 10 of 27	The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures.	<p>Concern: This language, particularly the phrase “daily documentation” could be interpreted to mean that only paper logs would be acceptable. Continuous electronic monitoring technology is at least as good as, if not superior to, manual documentation on paper logs.</p> <p>Recommendation: Add language that supports the use of methods other than daily logs.</p> <p>“The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.</p>	Operational inefficiency
1751.1(b)(6) Page 10 of 27	Logs of pressure differentials	<p>It is appropriate to include this language when a physical separation is used between the buffer area and the ante area.</p> <p>Concern: This statement could imply that a log of pressure differentials would be required in a cleanroom that does not have a physical separation between the buffer area and the ante area, in which airflow displacement method is used as a means of separation. This would be inappropriate. There is no requirement in USP <797> to maintain a log when airflow displacement is used in this manner.</p> <p>Recommendation: Change language to be consistent with the context of USP <797>:</p> <p>“Logs of pressure differentials for rooms providing a physical separation through the use of walls, doors, and pass-throughs. A minimum differential positive pressure of 0.02- to 0.05-inch water column is required. This can be achieved by using paper logs or continuous pressure monitoring devices with appropriate alarms/alerts.”</p> <p>In addition, we propose the use of displacement airflow adopted in</p>	Remodeling & construction costs: \$115 million for our organization.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		USP Chapter 797 be added to the proposed regulations: "For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area."	
1751.3(a)(6) Page 12 of 27	A viable and nonviable sampling plan.	Concern: This language is unclear and ambiguous. Recommendation: "Viable and nonviable environmental airborne particle testing plan"	Clarity
1751.3(d)(I) Page 13 of 27	For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing.	Concern: This language appears to imply that all sterile batch compounding must have some sterility and bacterial endotoxin testing. If that is the intention, it is not reasonable or appropriate for low or medium-risk CSPs. It is not in alignment with USP <797>, which routinely requires this type of testing <u>ONLY</u> for high-risk compounded sterile preparations (e.g. non-sterile to sterile compounding), if the batch size is greater than or equal to 25 units. Recommendation: This language could be acceptable if the policy could be that sterility and endotoxin testing are only required on high risk level preparations or preparations suspected to be contaminated. Otherwise move the sterility and bacterial endotoxin testing language to 1751.3(d)(J)(ii)	High cost due to unnecessary testing; wasting finished drug product.
1751.4 Page 13 of 27	1751.4. Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients].	Concern: This title appears to state that the section below would apply when compounding from non-sterile Ingredients. The language of the section should apply to all sterile compounding activities. This looks like an error. Recommendation: Clarify whether this section would <u>ONLY</u> apply to sterile compounding from non-sterile ingredients.	Operational inefficiency

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1751.4(g) Page 15 of 27	Pharmacies preparing sterile cytotoxic agents shall use a biological safety cabinet or compounding aseptic containment isolator that provides an ISO Class 5 environment during dynamic compounding conditions which is maintained in accordance with the manufacturer's recommendations and which is certified every six months. If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area, the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.	<p>Concern: The proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on "Placement of Primary Engineering Controls). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room.</p> <p>Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.</p>	Limits the flexibility in selecting the appropriate engineering control for sterile compounding of cytotoxic agents
1751.6 (e)(1)(J)(2) Page 18 of 27	Each person who handles compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures...	<p>Concern: This language is unclear. It could mean that a person who merely delivers compounded sterile drug products to patient care areas would be required to complete specific training and testing.</p> <p>Recommendation: Use this language instead: "Each person who compounds sterile drug products must successfully complete practical skills training..."</p>	Clarification
1751.8 (b) Page 21 of 27	(b) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1,2013), hereby	Concern: This section appears to have been extracted from the medium-risk category definition in USP <797>. The bolded text appears to have been changed by the Board of Pharmacy subcommittee. The current version of USP <797> specifies a beyond use date for medium-risk level compounded sterile preparations of nine (9) days at controlled cold temperature. Nine days is more appropriate and practical, as it supports the ability of home infusion pharmacies to prepare and distribute weekly supplies of total parenteral nutrition solutions. It should be noted that the original version of USP <797> listed a beyond use date of seven days for medium-risk level CSPs, and changed the BUD to nine (9) days for that reason.	Operational inefficiency; higher costs for drug delivery to home infusion patients.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
	<p>incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following:</p> <p>(1) 30 hours at controlled room temperature (2) 7 days at controlled cold temperature (3) 45 days at controlled freezer temperature</p>	<p>Recommendation: Change to nine (9) days at controlled cold temperature.</p>	
1751.8 (d) Page 22 of 27	<p>The section addresses sterile preparations compounded in ISO Class 5 hoods not located in ISO Class 7 areas.</p>	<p>Concern: An additional statement needs to be added that if the sterile preparations are compounded in an ISO Class 5 compounding aseptic containment isolator (not located in an ISO Class 7 area), the beyond use date will be the same as if the CACI was located in an ISO Class 7 area.</p> <p>Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.</p>	<p>Unnecessarily short beyond use dating will cause drug waste.</p> <p>Cost impact: exceeding \$1 million/year for our organization.</p>
1751.8 Page 22 of 27	<p>Missing language in this section.</p>	<p>Concern: The current proposed regulations do not contain beyond use dating requirements for "immediate use" preparations</p> <p>Recommendation: To be more consistent with USP <797>, we recommend that this language be used:</p> <p>" 'Immediate use' is when administration is expected to begin no later than one hour following the start of the preparation of the compounded sterile preparation. The immediate use provision is intended only for those situations where there is a need for immediate administration of a compounded sterile preparation. Preparations that are medium-risk level, high-risk level, or hazardous drug compounded sterile preparations shall not be prepared as immediate-use compounded sterile preparations. . Immediate use preparations are exempt from the requirements of low-risk level preparations and may be compounded in a less stringent environment than ISO Class 5 conditions."</p>	<p>Operational inefficiency</p>
1751.8 (d) Page 22 of 27	<p>Where the sterile compounded drug product was compounded solely with aseptic manipulations</p>	<p>Concern: This language is inconsistent with the other parts of 1751.8.</p>	<p>Operational inefficiency</p>

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
	entirely within an ISO Class 5 hood in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1 st Supplement) (36 th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours.	<p>Recommendation: “Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date cannot exceed 12 hours.”</p>	
Title 24, Part 2, Chapter 12, 1250.4 (5.1)	Any pharmacy that compounds sterile drug products must compound the medication in one of the following environments: 5.1 An ISO Class laminar airflow hood within an ISO Class 7 cleanroom. The cleanroom must have positive air pressure differential relative to adjacent areas.	<p>Concern: We are assuming this language would apply to a pharmacy that prepares non-hazardous products only. Even then, this language is incomplete. USP <797> articulates a well thought-out description of the sterile compounding environment and engineering controls, based on the input and experience of nationally respected clean room engineers. It is inappropriate to extract a piece of this language and place it in regulations.</p> <p>Instead, we propose the use of displacement airflow described in USP Chapter 797: “For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area.”</p>	Remodeling & construction costs: exceeding \$60 million for our organization.
Title 24, Part 2, Chapter 12, 1250.4 (6)	When compounding hazardous drugs, the surrounding environment must provide at least 0.01 water column negative air pressure and 12 air changes per hour.	<p>Concern #1: There needs to be an allowance for a low volume of chemotherapy preparations in biological safety cabinets in clean rooms that also contain other types of laminar air flow hoods. Consider a hospital pharmacy in which a low volume of inpatient chemotherapy is prepared, and where the clean room was remodeled following the original 2004 USP <797> standards. It</p>	Remodeling & construction costs: \$115 million for our organization.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		<p>would likely be a single clean room, with an ante area and a buffer area. That remodel probably cost \$1 to \$2 million, depending on the size of the pharmacy. In order to meet the proposed regulation, this clean room would need to be remodeled again to provide a separate anteroom, positive pressure buffer room, and a negative pressure room for preparing hazardous drugs (chemotherapy). This would cost approx. an additional \$2 million per pharmacy. The cost is excessive when weighed against the incremental safety benefits.</p> <p>Instead, we propose the USP <797> language, with a caveat that "low volume" be defined, since the USP <797> language is subjective and not enforceable.</p> <p>"In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., Closed System Transfer Device within a BSC or CACI that is located in a non-negative pressure room) is acceptable."</p> <p>We propose this definition:" A low volume is defined as less than or equal to a mean number of twenty doses per week, averaged over a period of one month."</p> <p>Concern #2: There needs to be an allowance for ambulatory oncology pharmacies which do not currently meet this requirement, and prepare a high volume of chemotherapy (e.g. greater than twenty doses per week) for administration to patients in medical offices and clinics. These pharmacies are typically equipped with a Class II vertical flow hood in a small ISO Class 7 or ISO Class 8 clean room under positive pressure. It will be very costly and time-consuming to remodel these pharmacies.</p> <p>We propose that ambulatory oncology pharmacies be given a five-year period to come into compliance.</p>	
505.5.1	In all pharmacies preparing cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag in-bag out design. The	Concern: This language is unnecessary. 1751.4(g) already describes the requirements for use of Class II vertical laminar airflow hoods. In addition, 505.5.1 does not mention that a compounding aseptic containment isolator (CACI) can be used for this purpose. The use	Operational Inefficiency, employee safety

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
	pharmacy must ensure that contaminated air plenums that are under positive pressure are leak tight.	of a CACI for the preparation of cytotoxic agents is described in 1751.4(g). Recommendation: Delete 505.5.1.	

Damoth, Debbie@DCA

From: Doug.C.O'Brien@kp.org
Sent: Wednesday, December 18, 2013 6:48 PM
To: Damoth, Debbie@DCA
Cc: Donald.R.Kaplan@nsmtp.kp.org; Tony.H.Wang@nsmtp.kp.org
Subject: Kaiser Permanente Comments Pertaining to the Proposed Sterile Compounding Regulations
Attachments: BOP Proposed Cmpd Regs, KP Response, 12.18.13.pdf

Hello Debbie,

Attached are comments from Kaiser Permanente pertaining to the Proposed Sterile Compounding Regulations:

Please don't hesitate to contact me if further discussion, or clarification of the KP comments, are required.

Thanks Very Much,

Doug

Doug O'Brien, Pharm.D.
Kaiser Foundation Hospitals
Regional Director for Inpatient Pharmacy Services
Northern California Region
Office: (916) 486-5113
Cell: (510) 301-3990

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From: "Damoth, Debbie@DCA" <Debbie.Damoth@dca.ca.gov>
To: Tony H Wang/CA/KAIPERM@KAIPERM
Cc: Donald R Kaplan/CA/KAIPERM@KAIPERM, Doug C O'brien/CA/KAIPERM@Kaiperm
Date: 12/13/2013 09:21 AM
Subject: RE: Comments for Compounding Regulation

Hello Tony,

Thank you for your email. I am actually relieved to hear they haven't been submitted yet. I would be worried if they had been submitted and I hadn't received them. The board looks forward to receiving the comments. Thank you, Debbie

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Tony.H.Wang@kp.org [<mailto:Tony.H.Wang@kp.org>]

Sent: Thursday, December 12, 2013 5:03 PM
To: Damoth, Debbie@DCA
Cc: Donald.R.Kaplan@nsmtmp.kp.org; Doug.C.O'brien@nsmtmp.kp.org
Subject: Re: Comments for Compounding Regulation

Hi Debbie,

Thank you so much for checking! I spoke with Don Kaplan and he said that they wanted to make a few more edits based upon the newest draft of the regulations under consideration. He informed me that they hope to send along the document to you in short course. I have cc'ed Don Kaplan as well as Doug O'brien, our resident subject matter experts, on this email as well. Once again, we appreciate your follow-up.

Kind Regards,

Tony H. Wang, Pharm.D., J.D.
Director of Pharmacy Regulatory Affairs
National Pharmacy Compliance
12254 Bellflower Blvd.
Downey, CA 90242

(562) 658-3559 Office (Tie 320)
(562) 445-2612 Cell
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From: "Damoth, Debbie@DCA" <Debbie.Damoth@dca.ca.gov>
To: Tony H Wang/CA/KAIPERM@KAIPERM
Date: 12/12/2013 03:28 PM
Subject: Comments for Compounding Regulation

Hello Dr. Wang,

I checked my records and have not received the comments from Dr. Donald Kaplan. Is it possible to forward my email to him and ask him to send them to me? I want to ensure I receive all the comments. Thank you, Debbie

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

Damoth, Debbie@DCA

From: Alan Endo <Alan.Endo@pihhealth.org>
Sent: Friday, December 27, 2013 11:04 AM
To: Damoth, Debbie@DCA
Subject: Comments on Proposed Changes Sterile Compounding Regulations
Attachments: State Board Compounding Comments PIH.docx

Dear Debbie,

I would like to submit my comments to the proposed changes to the revision of the Sterile Compounding Regulation. Please consider my recommendations.

I would appreciate if you can inform me of any future meetings or Board actions that will be taken on this matter.

Sincerely,

Alan Y. Endo, Pharm.D., FCSHP (RPh 27276)
Administrative Director of Enterprise Pharmacy Services
PIH Health
562.698.0811 x 16384
Alan.Endo@PIHHealth.org

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State Board Compounding Regulations Proposed Changes – Recommendations from Presbyterian
Intercommunity Hospital, Whittier, CA (HSP 21517)*

State Board Section	Proposed Language	Comments/Recommendations
Recommendations		
1735.1 – page 1, line 31 - 33	“Batch” means more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.	Webster’s Definition of Batch: d: a quantity (as of persons or things) considered as a group. USP 797 refers to high-risk (non-sterile to sterile) preparations requiring sterility testing if number of items is more than 25 in a batch. Recommendation: Define batch as medications compounded either with high-risk methods (non-sterile to sterile) or when extended dating beyond USP 797 specifications is desired.
1735.1, page 2, line 2-3	“Beyond use date”	“The date or time after which a compounded sterile preparation shall not be stored or transported”
1735.3 – page 6, lines 8 - 11	(c) Chemicals, bulk drug substances, and drug products used to compound drug products shall be obtained from reliable FDA registered suppliers. The pharmacy shall acquire and retain certificates of purity or analysis for chemicals, bulk drug substances and drug products used in compounding.	Definition of chemicals, bulk drug substances and drug products. Recommendation: “Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”
1735.1 – page 7, line 8-9	Compounding Policy and Procedures	“The pharmacy shall follow its policies and procedures. Intentionally (or grossly) failing to follow these policies and procedures may be deemed unprofessional conduct.”
1751.1 – page 10, line 32-33	“Daily documentation of”	“The storage of compounded sterile drug products in the pharmacy and the daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices.”
1751.1- page 11, line 5	Logs of room pressure differentials	Recommendation: Pressure gauge OR air velocity meter to monitor the pressure differential or airflow between the buffer area and ante-area in cleanrooms (not segregated compounding areas).
1751.3, section 1,	Policy and procedure for	Recommendation: Endotoxin/pyrogen testing is

*Changes reflect the published document as of 10/25/13 from the 10/21/13 subcommittee meeting

State Board Compounding Regulations Proposed Changes – Recommendations from Presbyterian
Intercommunity Hospital, Whittier, CA (HSP 21517)*

State Board Section	Proposed Language	Comments/Recommendations
page 13 lines 12-14	sterility and bacterial endotoxin testing	to be done for high-risk preparations (non-sterile to sterile) or for extended dating beyond USP 797 storage specifications.
1751.4 – page 14, line 14-15	Cleaning shall include the periodic use of a sporicidal agent.	USP 797 does not require the use of a sporicidal agent. Recommendation: Eliminate reference to sporicidal agent.
1751.4- page 15, lines 1-3	Compounding of cytotoxic agents, ISO 5 and negative pressure differential	Location of BSC or isolator in ISO 7 area, with min negative pressure of 0.01-inch water column and minimum of 12 air changes per hour. Recommendation: Include timeframe (ex. 5 years) to allow facility changes to be made before enforcing. Proposed language: Location of BSC or isolator in ISO 7 area with: 1) min negative pressure of 0.01-inch water column and minimum of 12 air changes per hour; OR 2) air velocity measurement (minimum 40 feet per minute) between ante and buffer areas if the BSC or isolator isn't in a dedicated negative pressure room.
1751.8- page 20, line 14	Medium Risk beyond use date	Medium Risk beyond use date at controlled cold temperature is 7 days. Recommendation: 9 days at controlled cold temperature (USP 797).

*Changes reflect the published document as of 10/25/13 from the 10/21/13 subcommittee meeting



RECEIVED BY CALIF
BOARD OF PHARMACY
2014 JAN -6 AM 11:18

January 4, 2014

Debbie Damoth
Licensing Manager, fax 916-574-8616
California Board of Pharmacy
1625 N. Market Blvd., N219
Sacramento, CA 95834

Re: Suggested edits regarding the Board of Pharmacy Proposed Regulation to amend Sections 1735, 1735.1, 1735.2, 1735.3, 1735.5 and Sections 1751, 1751.1, 1751.2, 1751.3, 1751.4, 1751.5, 1751.6, 1751.7, 1751.8, 1751.9, 1751.10, 1751.11, 1751.12 as well as add Section 1751.9 of Division 17 of Title 16 of the California Code of Regulations Notice Published September 13, 2013

Dear Ms. Damoth,

On behalf of myself and my business, Pacific Compounding Pharmacy and Consultations (PCPC), I am pleased to submit comments in support of the California State Board of Pharmacy ("Board") adoption of its proposed amendments regarding Sterile Compounding.

I am a pharmacy owner and full-time compounding pharmacist at PCPC. I have been involved in non-sterile compounding for 15 years and high-risk sterile compounding for almost two. In addition, I have taught the Advanced Compounding Elective at the Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific for the last ten years and have been a practicing community pharmacist since graduating from UCSF in 1997.

I applaud the efforts of the Board to keep standards for pharmacy compounding at their highest levels. For many years, the Board has been a leader among State Boards of Pharmacy, setting high expectations for quality and safety among compounding pharmacies in the state of California. My desire in submitting these comments is to share the practical expertise I possess to further our mutual goals of protecting patients while maintaining viable business practices.

I would like to express our thanks to the Board and its staff for its sustained focus and ongoing efforts regarding this important aspect of compounding pharmacy regulation. If you have any questions about my comments, please feel free to contact me. I am eager to provide as much information as possible so that the Board can make educated decisions and understand how the practice of sterile compounding can be carried out at the highest quality.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Marie Cottman, Pharm.D.", is written over the typed name.

Marie Cottman, Pharm.D.
Owner/PIC

BOP Proposed Item: Multiple occurrence of Amendment #1 - The board's proposal removes "injectable" and replaces the word with "drug" when referring to sterile injectable compounding... SB 294 adds sterile compounding licensing requirements for sterile compounded drug products to include route of administration of injection as well as route of administration into the eye or inhalation.

Recommendation #1 (Cottman): *Removing the word "injectable" is prudent.*

Comment #1 (Cottman): *Please note that the definition of "sterile compounded product (CSP)" by USP <797> is still more inclusive than injection, ophthalmic, or inhalation.*

Reference USP <797>:

"For the purposes of this chapter, CSPs include any of the following: 1) Compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants."

BOP Proposed Item: Amend 16 CCR §1735.1 to add a definition of "batch" for purposes of compounding drug products. The definition clarifies and specifies "batch" as more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.

Recommendation #2 (Cottman): *Change the definition of "batch" to be a unique CSP.*

Comment #2 (Cottman): *USP <797> is not specific regarding the term "batch." It is only used four unique times in the entire document! The context however, references a unique CSP regardless of the number of doses.*

Reasoning:

USP <797> is not specific regarding the term "batch." It is only used four unique times in the entire document! The context however, references a unique CSP regardless of the number of doses.

*"Cleaning and disinfecting surfaces in the ISO Class 5 hood shall occur frequently, including: at the beginning of shift; before each **batch**; every 30 minutes during continuous compounding of individual compounded sterile drug products; after each spill;"*

I believe the original intent of "batch" in CCR 1751.1 was to differentiate CSPs that would be dispensed to more than one patient.

BOP Proposed Item: Amend 16 CCR §1735.1

The purpose of the board's proposal to add subdivision (r) is to add a definition of "smoke test" for purposes of compounding drug products. The definition clarifies and specifies "smoke test" as an analysis of the airflow in the ISO Class 5 hood using a smoke generating device.

Comment #3 (Cottman): *This definition is good, but it is never used in the proposed amendments. However, the inclusion of a smoke test criterion may be appropriate in Article 7 CCR 1751 Section 4 because USP <797> requires that:*

"Proper design and control prevents turbulence and stagnant air in the critical area. In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions."

BOP Proposed Item: Amend 16 CCR §1735.3 subdivision (c) to ...require reliable suppliers of drug products for compounders to be FDA-registered. This change is necessary to add the requirement of "FDA-registered" to ensure that the supplier of drug products are adequately regulated by the Food and Drug Administration (FDA) and addressed the problem of the integrity of the purchased drug products by compounders providing compounded drug products to California consumers. The board's proposal further clarifies by deleting "any available" and adding requirements for certificates of purity or analysis are to be matched to the product received. The requirement that all certifications of purity or analysis are to be kept and matched to the product received also includes the now required FDA-registered suppliers. This change is necessary to ensure a consolidated record for a compounded drug product that may have multiple ingredients from multiple FDA-registered suppliers. This addressed the problem of clarifying the requirements of recordkeeping for certificates of purity and analysis of drug products.

Recommendation #4 (Cottman): *This line should either a) not be removed or b) amended to include manufactured available drug products.*

Comment #4 (Cottman): *There is no explanation from the Board to relative to the removal of "Certificates of purity or analysis (C of A) are not required for drug products that are approved by the Food and Drug Administration." This is an important issue in compounding. When we compound with manufactured, FDA approved drug products (i.e. Atenolol tablets or Cefuroxime injection 750mg vials) we do not have access to a C of A and no other pharmacy is required to have a C of A to dispense these products.*

BOP Proposed Item: Add Subdivision (d) to 16 CCR §1735.3 to specify after receipt by the pharmacy, packages of ingredients that lack a supplier's expiration date cannot be used after one (1) year unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in compounded drug products. This change is necessary to identify for the board's regulated licensees the maximum time a drug product can be used without appropriate inspection or testing if the manufacturer failed to provide an expiration date. This

addressed the problem of clarity to the board's regulated licensees and in accordance to compounding pharmacy professional standards USP 36 <797>.

Comment #5 (Cottman): Section §1735.3 is relative to all compounding, not just sterile compounding. The standards included for assigning expiration dating to non-dated ingredients for non-sterile compounding differ from sterile compounding. For non-sterile compounding, you can find a three year recommendations in USP <795>.

Recommendation #5 (Cottman): CCR §1735.3 Subdivision (d) should read:

(d) After receipt by the pharmacy, packages of ingredients that lack a supplier's expiration date cannot be used after three (3) years unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in non-sterile compounded drug products.

CCR §1751.1 Sterile Compounding Recordkeeping Requirements Subdivision (c) should be added (and renumber the current Subdivision (c) to Subdivision (d)).

After receipt by the pharmacy, packages of ingredients that lack a supplier's expiration date cannot be used after one (1) year unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in non-sterile compounded drug products.

Reference USP <795>:

*"COMPONENT SELECTION, HANDLING, AND STORAGE sub section 6.
For components that do not have expiration dates assigned by the manufacturer or supplier, the compounder shall label the container with the date of receipt and assign a conservative expiration date, not to exceed three years after receipt, to the component (see the General Notices and Requirements, Preservation, Packaging, Storage, and Labeling, Labeling, Expiration Date and Beyond-Use Date) based on the nature of the component and its degradation mechanism, the container in which it is packaged, and the storage conditions."*

BOP Proposed Item: Amend 16 CCR §1735.5 to add to subdivision (a) the requirement that the pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct. This change is necessary to specifying the requirement of not only maintaining compounding policies and procedures but also a requirement to following the pharmacy's policies and procedures..

Comment #6 (Cottman): *In CCR §4037 "Pharmacy" means an area, place, or premises licensed by the board in which the profession of pharmacy is practiced and where prescriptions are compounded..." A Pharmacy is NOT capable of following a procedure nor can it be responsible for unprofessional conduct.*

Recommendations #6 (Cottman): *Please consider changing "pharmacy" to "pharmacy compounding personnel" or "pharmacy compounding staff."*

As policies and procedures should not be carried out by non-trained pharmacy staff, the use of the term 'compounding' to describe who carries out these policies and procedures is prudent.

Additionally, under Subdivision (b) of CCR §1735.5, please consider changing the annual review from being the sole responsibility of the PIC to include all compounding pharmacy staff. I would guess that in some pharmacy situations, the PIC is not involved in compounding at all, though I understand why that PIC should still be responsible for reviewing the policies and procedures, regardless.

BOP Proposed Item: Amend 16 CCR §1751 paragraph (4) of subdivision (b) to replace “be” with “The ISO environment shall be” and “annually” is replaced with “at least six months.” “Clean room” is replaced with “cleanroom.” Additionally, “and whenever the device or cleanroom is relocated, altered, or a service to the facility is performed that would impact the cleanroom or device.” is added.

Comment #7 (Cottman): *I concur with the proposed changes, but recommend that you go further for clarification. USP <797> has specific tests that need to be done in a cleanroom used to prepare CSPs. There are several ways to certify a laminar air flow hood... not all are in compliance with USP <797> and CETA.*

Recommendation #7 (Cottman): *I propose that 16 CCR §1751 Paragraph b, section 4 read: The ISO environment shall be certified at least every six months by a qualified technician familiar with the methods and procedures for certifying laminar air flow hoods and cleanroom requirements for compounded sterile products as outlined in CETA Certification Guide for Sterile Compounding Facilities. Testing will be conducted under dynamic conditions as appropriate and include at a minimum smoke studies, environmental samples for viable and non-viable particles, and total particle counts (for ISO classifications).*

BOP Proposed Item: Amend 16 CCR §1751.1
Existing regulation at 16 CCR specifies the title of §1751.1 to be “Sterile Injectable Recordkeeping Requirements.” As a result of SB 294, the name of §1751.1 will be changed to “Sterile Compounding Recordkeeping Requirements.”

Recommendation #8 (Cottman): *I propose that this be slightly modified to be consistent with CCR §1735.3 Recordkeeping of Compounded Drug Products. “Recordkeeping of Sterile Compounded Products.”*

Comment #9 (Cottman): Existing regulations at 16 CCR §1751.3 specify requirements for sterile compounding policies and procedures. Subparagraph 2 of Subdivision d. “All personnel involved must read the policies and procedures...”

Recommendation #9 (Cottman): *There should be a similar paragraph in the non-sterile compounding section of the pharmacy law, CCR §1735.5 Subdivision (b) could possibly be amended to:*

"All personnel involved in compounding must read the policies and procedures before compounding non-sterile drug products and at least annually ongoing. The Pharmacist In Charge is responsible for reviewing the policies and procedures at least annually."

BOP Proposed Item: Amend 16 CCR §1751.6 paragraph (2) of subdivision (e) to add additional information to the requirement outlining *who of the compounding personnel must complete practical skills training in aseptic technique and aseptic area practices*. Specifically, the board's proposal strikes "assigned to the controlled area" and replaces with "who handles compounded sterile drug products" so that the paragraph will read as "Each person who handles compounded sterile drug products must successfully complete practical skills training in aseptic technique and aseptic area practices..."

Comment #10 (Cottman): *"Handles" is a very broad term which may be interpreted as "touching" the product. I do not believe that it is the intent of this proposal that the retail cashier or the hospital pharmacy clerk who is "handling" the product when it is dispensed to the patient or the floor is required to be trained and tested on the methods of aseptic techniques or aseptic area practices.*

Recommendation #10 (Cottman): *Change the term "handles" to "participates in the preparation of"*

BOP Proposed Item: Add 16 CCR §1751.8 Beyond Use Dating for Sterile Compounded Drug Products.

Comment #11 (Cottman): *This is a good addition to CA BOP Regulations! It is directly from USP <797>.*

Recommendation #11(Cottman): *I recommend that you approve the addition of Section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products and reword section 1751.7 Subdivision (e) as indicated below.*

BOP Proposed Item: Amend 16 CCR §1751.7. Sterile Compounding Quality Assurance and Process Validation. Subdivision (e) (e). Batch-produced sterile drug products... shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing.

Comment #12 (Cottman): *Batch is defined in these amendments as "more than one dose..." which results in this section applying to ALL CSPs yet it is in direct conflict with the proposed CCR §1751.8 Beyond Use Dating for Sterile Compounded Drug Products.*

Recommendation #12(Cottman): *Remove the phrase "Batch-produced"*

Comment #13 (Cottman): *Not all sterile products need to be tested for pyrogens. For example, USP <797> specifically exempts ophthalmic drops and inhalations from testing for pyrogens.*

Comment #14 (Cottman): *A requirement to quarantine any product made as more than a single dose is too restrictive as some drug products are not chemically stable for 14 days (the time it takes to conduct a USP <71> sterility test). Additionally, since we compound sterile products on an as needed/ as prescribed basis, many patients are not able to wait 14 days for therapy.*

Comment #15 (Cottman): *The methodologies found in USP <71> are very difficult to attain. There are very few testing labs in the United States that is conducting true <71> testing for CSPs. It costs \$500-800 additional to perform this test. Additionally, the Board may want to consider allowing Rapid Scan RDI or other similar Sterility Tests that are not currently included in USP <71> but may be equivalent (but much faster) testing.*

Recommendation #12 (Cottman): *I recommend that you approve the addition of Section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products (as noted above) and reword section 1751.7 Subdivision (e) to the following:*

Sterile drug products compounded from one or more non-sterile ingredients in groups of more than 25 identical individual single-use packages, in MDV's for administration to multiple patients, or with beyond use dating exceeding that stated in CCR 1751.8 shall be tested for sterility in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference. For sterile drug products (except ophthalmic drops and inhalations) compounded from one or more non-sterile ingredients in groups of more than 25 identical individual single-use packages or in MDV's for administration to multiple patients shall be tested for pyrogens in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference. Whenever possible, relative to patient therapy and pharmaceutical stability, CSPs will be quarantined until the results of sterility and pyrogen testing are complete.

Reasoning:

Referenced USP <797> High Risk Sterile Compounds Sterility Testing and Bacterial Endotoxin (Pyrogen) Testing.

Damoth, Debbie@DCA

From: Terry Lerma <Terry.Lerma@stjoe.org>
Sent: Monday, January 06, 2014 8:16 PM
To: Damoth, Debbie@DCA; Klein, Carolyn@DCA
Subject: Inquiry
Attachments: ca1.pdf

Good evening Debbie and Carolyn. I have recently arrived to California state and assumed DOP and PIC at St Joseph Eureka

I am getting up to speed on the attached proposed legislative changes, implications, and timeframes

I wanted to share some feedback on this topic in order to better understand the appropriate course of action

1. Initially, I wanted to ask why California state board of Pharmacy has proposed an implementation deadline of July 1st 2014 if the new legislature is not yet law until January 16th 2014? This seems to be an unusually aggressive timeframe given the extensive capital and construction ramifications required to transition to a compliant USP 797 solution.
2. Additionally, one would anticipate a reasonable timeframe to organize construction and capital for such an endeavor.. I would expect that a one year timeframe would be minimally granted to pharmacies to accommodate these changes. For some reason, 6-7 months seems a bit short. California is a very large state with a great number of hospital pharmacies that will be affected by this new legislature. I imagine that vendors will be overwhelmed within the next 12 months to accommodate requests for product and construction.
3. I noted in the attachment above that no harm to businesses within California in not anticipated by this proposed legislature. I would disagree.. the capital cost alone will be an undue hardship to numerous facilities that are already struggling to keep doors open

I support the underpinnings of this legislature, to enhance the quality of sterile compounded pharmaceutical products prepared in California pharmacies. Many states attempted to achieve this goal with JCAHO in the early 2000's but the capital cost to rural facilities, CAH, and DSH prevented this paradigm shift from happening, which is why JCAHO modified the original patient safety goal.

I am relatively new to Eureka Ca and we are completing a gap analysis for **three** of our compounding pharmacies. With swift capital planning and a reasonable implementation timeframe I feel we can reach the "future state" detailed in the proposed legislature... I do not believe the deadline of July 1st 2014 is reasonable.

Our Oncology program is in the process of integrating a local Oncology practice (physician operated) that will potentially increase triple chemo volume in the next 90 days. I am worried that the short timeframe of 6 months to achieve compliance with proposed legislature will hinder the provision of chemotherapy to our patients in Humboldt county.

Additionally, I feel the legislature does not take into account the capital impact to organizations that are already struggling financially to keep their doors open, such as CAH and DSH hospitals. Additionally,

vendor availability (construction, IV Hoods, etc..) is also something that may impact our ability to achieve the July 1st 2014 deadline.

Because I am new to California State (Wa), I reached out to sister facilities located throughout California. Most of these facilities indicated that no action towards compliance with the proposed legislature had yet to be realized, as everyone was waiting for the legislature to become law. This again seems to reinforce my concerns regarding the timeframe and vendor availability. Prior to holding these conversations, I suspected that we were "behind" in terms of compliance....

Has California State considered offering healthcare facilities (particularly DSH and CAH) tax deductions for assuming significant capital expenses related to this proposed legislature?

Please let me know if I have missed anything in my understanding of the task at hand, timeframe, etc..

Respectfully,

Terry Lerma Pharm D
Area Director of Pharmacy
St. Joseph Hospital | 2700 Dolbeer, Eureka, CA, 95501
T: (707) 445-8121 Ext 6206 | C: (509) 607-0232

St. Joseph Health 

Notice from St. Joseph Health System:

Please note that the information contained in this message may be privileged and confidential and protected from disclosure.



January 7, 2014

Debbie Damoth
California State Board of Pharmacy
1625 N. Market Blvd., N219
Sacramento, CA 95834

RECEIVED BY CALIF.
BOARD OF PHARMACY
2014 JAN 10 PM 4:35

RE: Comments regarding Proposed Compounding Regulations

Dear Ms. Damoth:

Thank you for the opportunity to provide feedback on the proposed Compounding Regulations. Attached please find our comments and suggestions. Thank you again.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Rita Shane'.

Rita Shane, Pharm.D., FASHP, FCSHP
Chief Pharmacy Officer
Cedars-Sinai Medical Center
8700 Beverly Blvd., Room A-903
Los Angeles, CA 90048
Assistant Dean, Clinical Pharmacy
UCSF School of Pharmacy
310-423-5611
email: shane@cshs.org

Comments Regarding Proposed Compounding Regulations
Cedars-Sinai Medical Center
January 7, 2014

Proposed Regulation	Considerations	Recommendations
<p>Facility and Equipment Standards (1751.4) Page 13</p>	<p>The words “from Non-Sterile Ingredients” were added to “Facility and Equipment Standards” in the proposed language revision. It is unclear if this section only pertains to items made from non-sterile ingredients</p>	<p>Remove “from Non-Sterile Ingredients” from the title of 1751.4 OR clarify whether this section applies to sterile products</p>
<p>Facility and Equipment Standards (1751.4 (g)) Page 15</p>	<p>If a Compounding Aseptic Containment Isolator is used, the proposed regulation requires having a separate negative pressure room and 12 air changes per hour.</p> <p>If the intent is to require the same standards for Biologic Safety Cabinets as Compounding Aseptic Containment Isolators, hospitals that have not been recently renovated may not meet be able to meet these requirements by July 1, 2014 due to the need for facility changes. These changes require Office of Statewide Health Planning and Development (OSHPD) approval.</p> <p>Economic Impact: The cost of remodeling one sample facility to meet this requirement is significant (source: Facilities Management Department).</p> <ol style="list-style-type: none"> 1. Venting BSC to the outside: \$2 million 2. Wind dilution/exhaust studies: \$55,000 3. Remaining construction (not including above) cost estimate: \$3.6 million 	<ul style="list-style-type: none"> • Clarify if this section is limited to isolators. • If Biologic Safety Cabinets are to be included, hospitals may not be able to meet the July 1, 2014 deadline due to renovation required. In order to ensure that cancer patients do not have their chemotherapy treatments disrupted, consider a timeframe for meeting these new facility requirements, i.e., 3 years.
<p>Logs of room pressure differentials (1751.1 (b 6)) Page 10</p>	<p>Current draft language requires monitoring of pressure differentials. This can only be done when there is a physical barrier or separate room. USP 797 states for buffer areas not physically separated from ante-areas, displacement airflow (measured by air velocity) shall be used instead of pressure differential monitoring</p>	<p>Modify language as follows to reflect USP 797: 1751.1 Sterile Compounding Recordkeeping Requirements (b) In addition to the records required by section 1735.3 and subdivision (a) for sterile compounded drug products, the following records must be made and kept by the pharmacy: (6) Logs of room pressure differentials OR air flow velocity measurements as described in USP 797.</p>

Comments Regarding Proposed Compounding Regulations
 Cedars-Sinai Medical Center
 January 7, 2014

Proposed Regulation	Considerations	Recommendations
Controlled Room Temperature (1735.1 (f)) Page 2	Controlled room temperature as defined in the proposed regulations is 20° to 25°(68° to 77° F). USP and manufacturers allow for temperature excursions based on medication stability. USP allows temperatures between 15° and 30° (59° and 86°F) and transient spikes up to 40° C are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted based upon the manufacturer package insert.	Modify language as follows to reflect USP 797 controlled room temperature: "Controlled room temperature" indicates 20° to 25° C (68° to 77° F); excursions between 15° and 30° (59° to 86°F) or as specified in the manufacturer package insert are permitted (see page 2 of attached example).
Definition of a drug product (1735.3 (c)) Page 6	FDA-approved products do not have certificates of analysis. However, chemicals and bulk drug substances used in compounding may not always be FDA-approved.	Modify language as follows: Products used in compounding that are not FDA-approved should have a certification of analysis.
Medium Risk beyond use date (1751.8 (b)) Page 21	Current draft language states that sterile compounded drug products from multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with USP 797, storage and exposure cannot exceed 7 days stored at controlled cold temperature.	Modify language as follows to reflect USP 797 for medium risk preparations: Storage and exposure period cannot exceed more than 9 days at controlled cold temperature.
NSF Standards (1751.4 (f)) Pages 14 and 15	Current draft language references NSF International Standard/American National Standard for Biosafety Cabinetry – Biosafety Cabinetry: Design, Construction, Performance, and Field Certification [NSF/ANSI 49-2012] as revised July 7, 2012 related to certifying laminar air flow hoods and cleanrooms, as well as compounding aseptic containment isolators. This standard does not apply to laminar air flow hoods or compounding aseptic containment isolators.	Replace NSF reference with CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006-11, revised January 31, 2012.

**METOPROLOL TARTRATE
INJECTION, USP**

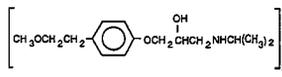
Rx Only

**METOPROLOL TARTRATE
INJECTION, USP**

Rx Only

**DESCRIPTION**

Metoprolol tartrate injection, USP is a sterile solution containing metoprolol tartrate, a selective beta₁-adrenoreceptor blocking agent, available in 5 mL vials for intravenous administration. Each vial contains a sterile solution of metoprolol tartrate USP, 5 mg and sodium chloride USP, 45 mg. Metoprolol tartrate is (-)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol L-(-)-tartrate (2:1) salt, and its structural formula is:



Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.81. Its molecular formula is (C₁₃H₂₃N₂O₃)₂·C₄H₆O₆. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

CLINICAL PHARMACOLOGY

Metoprolol tartrate is a beta-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies have shown that it has a preferential effect on beta₁ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol tartrate also inhibits beta₂ adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative beta₁ selectivity has been confirmed by the following: (1) In normal subjects, metoprolol tartrate is unable to reverse the beta₂-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective (beta₁ plus beta₂) beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol tartrate reduces FEV₁ and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta₁-receptor blocking doses.

Metoprolol tartrate has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta-blockade. Metoprolol tartrate crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that metoprolol tartrate slows the sinus rate and decreases AV nodal conduction.

In controlled clinical studies, metoprolol tartrate has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at dosages of 100 to 450 mg daily. In controlled, comparative, clinical studies, metoprolol tartrate has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, and to be equally effective in supine and standing positions.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol tartrate reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta₂-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In controlled clinical trials, metoprolol tartrate, administered two or four times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. A controlled, comparative, clinical trial showed that metoprolol tartrate was indistinguishable from propranolol in the treatment of angina pectoris.

In a large (1,395 patients randomized), double-blind, placebo-controlled clinical study, metoprolol tartrate was shown to reduce 3-month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rates as signs of congestive heart failure. Initial treatment consisted of intravenous followed by oral administration of metoprolol tartrate or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with metoprolol tartrate or placebo was then continued for 3 months. After this double-blind period, all patients were given metoprolol tartrate and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the metoprolol tartrate and placebo treatment groups. Among patients treated with metoprolol tartrate, there were comparable reductions in 3-month mortality for those treated early (≤ 8 hours) and those in whom treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial intravenous therapy were also observed with metoprolol tartrate and were independent of the interval between onset of symptoms and initiation of therapy.

The precise mechanism of action of metoprolol tartrate in patients with suspected or definite myocardial infarction is not known.

In this study, patients treated with metoprolol received the drug both very early (intravenously) and during a subsequent 3-month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early intravenous treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta-blockers.

Pharmacokinetics

In man, absorption of metoprolol tartrate is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Metoprolol is a racemic mixture of R- and S-enantiomers. Less than 5% of an oral dose of metoprolol tartrate is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. The systemic availability and half-life of metoprolol tartrate in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Metoprolol tartrate is extensively metabolized by the cytochrome P450 enzyme system in the liver. The oxidative metabolism of metoprolol tartrate is under genetic control with a major contribution of the polymorphic cytochrome P450 isozyme 2D6 (CYP2D6). There are marked ethnic differences in the prevalence of the poor metabolizers (PM) phenotype. Approximately 7% of Caucasians and less than 1% Asian are poor metabolizers.

Poor CYP2D6 metabolizers exhibit several-fold higher plasma concentrations of metoprolol tartrate than extensive metabolizers with normal CYP2D6 activity. The elimination half-life of metoprolol is about 7.5 hours in poor metabolizers and 2.8 hours in extensive metabolizers. However, the CYP2D6 dependent metabolism of metoprolol tartrate seems to have little or no effect on safety or tolerability of the drug. None of the metabolites of metoprolol tartrate contribute significantly to its beta-blocking effect.

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

Following intravenous administration of metoprolol tartrate, the urinary recovery of unchanged drug is approximately 10%. When the drug was infused over a 10-minute period, in normal volunteers, maximum beta-blockade was achieved at approximately 20 minutes. Doses of 5 mg and 15 mg yielded a maximal reduction in exercise-induced heart rate of approximately 10% and 15%, respectively. The effect on exercise heart rate decreased linearly with time at the same rate for both doses, and disappeared at approximately 5 hours and 8 hours for the 5 mg and 15 mg doses, respectively.

Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of metoprolol tartrate caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery and diastolic pressure remained unchanged.

In patients with angina pectoris, plasma concentration measured at 1 hour is linearly related to the oral dose within the range of 50 to 400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.

In elderly subjects with clinically normal renal and hepatic function, there are no significant differences in metoprolol tartrate pharmacokinetics compared to young subjects.

INDICATIONS AND USAGE**Myocardial Infarction**

Metoprolol tartrate injection is indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous metoprolol tartrate can be initiated as soon as the patient's clinical condition allows (see **DOSE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSE AND ADMINISTRATION**).

CONTRAINDICATIONS**Hypertension and Angina**

Metoprolol tartrate is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Hypersensitivity to metoprolol tartrate and related derivatives, or to any of the excipients; hypersensitivity to other beta-blockers (cross sensitivity between beta-blockers can occur).

Sick-sinus syndrome.**Severe peripheral arterial circulatory disorders.****Myocardial Infarction**

Metoprolol tartrate is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS**Hypertension and Angina**

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, metoprolol tartrate should be administered cautiously.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol tartrate should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol tartrate, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol tartrate administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol tartrate therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS, including metoprolol tartrate. Because of its relative beta₁ selectivity, however, metoprolol tartrate may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta₁ selectivity is not absolute, a beta₂-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer metoprolol tartrate in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval (see **DOSE AND ADMINISTRATION**).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy, including metoprolol tartrate, prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol tartrate, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Metoprolol tartrate should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Pheochromocytoma: If metoprolol tartrate is used in the setting of pheochromocytoma, it should be given in combination with an alpha blocker, and only after the alpha blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta-mediated vasodilatation in skeletal muscle.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta-blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with metoprolol tartrate, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, metoprolol tartrate should be discontinued.

Bradycardia: Metoprolol tartrate produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, metoprolol tartrate should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Metoprolol tartrate slows AV conduction and may produce significant first- (P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, metoprolol tartrate should be discontinued and atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, metoprolol tartrate should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

**METOPROLOL TARTRATE
INJECTION, USP**

Rx Only

**METOPROLOL TARTRATE
INJECTION, USP**

Rx Only



Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS INCLUDING METOPROLOL TARTRATE. Because of its relative beta₁ selectivity, metoprolol tartrate may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta₂-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, metoprolol tartrate should be discontinued. A theophylline derivative or a beta₂ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta₂ agonists may produce serious cardiac arrhythmias.

PRECAUTIONS

General

Metoprolol tartrate should be used with caution in patients with impaired hepatic function.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol tartrate plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Risk of Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

General Anesthetics

Some inhalation anesthetics may enhance the cardiodepressant effect of beta-blockers (see WARNINGS, Major Surgery).

CYP2D6 Inhibitors

Potent inhibitors of the CYP2D6 enzyme may increase the plasma concentration of metoprolol tartrate. Strong inhibition of CYP2D6 would mimic the pharmacokinetics of CYP2D6 poor metabolizer (see CLINICAL PHARMACOLOGY, Pharmacokinetics section). Caution should therefore be exercised when coadministering potent CYP2D6 inhibitors with metoprolol tartrate. Known clinically significant potent inhibitors of CYP2D6 are antidepressants such as fluoxetine, paroxetine or bupropion, antipsychotics such as thioridazine, antirhythmic such as quinidine or propafenone, antiretrovirals such as ritonavir, antihistamines such as diphenhydramine, antimalarials such as hydroxychloroquine or quinidine, antifungals such as terbinafine and medications for stomach ulcers such as cimetidine.

Clonidine

If a patient is treated with clonidine and metoprolol tartrate concurrently, and clonidine treatment is to be discontinued, metoprolol tartrate should be stopped several days before clonidine is withdrawn. Rebound hypertension that can follow withdrawal of clonidine may be increased in patients receiving concurrent beta-blocker treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol tartrate is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when metoprolol tartrate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical trials of metoprolol tartrate in hypertension did not include sufficient numbers of elderly patients to determine whether patients over 65 years of age differ from younger subjects in their response to metoprolol tartrate. Other reported clinical experience in elderly hypertensive patients has not identified any difference in response from the younger patients.

In worldwide clinical trials of metoprolol tartrate in myocardial infarction, where approximately 478 patients were over 65 years of age (0 over 75 years of age), no age-related differences in safety and effectiveness were found. Other reported clinical experience in myocardial infarction has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some elderly individuals taking metoprolol tartrate cannot be categorically ruled out. Therefore, in general, it is recommended that dosing proceed with caution in this population.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. Gangrene in patients with pre-existing severe peripheral circulatory disorders has also been reported very rarely. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS). Rhinitis has also been reported.

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients. Vomiting was a common occurrence. Postmarketing experience reveals very rare reports of hepatitis, jaundice and non-specific hepatic dysfunction. Isolated cases of transaminase, alkaline phosphatase, and lactic dehydrogenase elevations have also been reported.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Very rarely, photosensitivity and worsening of psoriasis has been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and linitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. There have been very rare reports of weight gain, arthritis, and retroperitoneal fibrosis (relationship to metoprolol tartrate has not been definitely established).

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol tartrate.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of metoprolol tartrate and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

	Metoprolol Tartrate	Placebo
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol tartrate.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometric tests.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Postmarketing Experience

The following adverse reactions have been reported during postapproval use of metoprolol tartrate: confusional state, an increase in blood triglycerides and a decrease in High Density Lipoprotein (HDL). Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD₅₀'s (mg/kg): mice, 1158 to 2460; rats, 3090 to 4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol tartrate are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see WARNINGS, Myocardial Infarction).

On the basis of the pharmacologic actions of metoprolol tartrate, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., norepinephrine or dopamine.

Bronchospasm: A beta₂-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Myocardial Infarction

Early Treatment: During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol tartrate each; the injections should be given at approximately 2-minute intervals. During the intravenous administration of metoprolol tartrate, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), metoprolol tartrate tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see Late Treatment below).

Patients who appear not to tolerate the full intravenous dose should be started on metoprolol tartrate tablets either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with metoprolol tartrate should be discontinued (see WARNINGS).

Late Treatment: Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least 3 months. Although the efficacy of metoprolol tartrate beyond 3 months has not been conclusively established, data from studies with other beta-blockers suggest that treatment should be continued for 1 to 3 years.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Metoprolol Tartrate Injection, USP is available as:

NDC 0517-1355-10	5 mg/5 mL Single Dose Vial	Packages of 10
NDC 0517-1355-25	5 mg/5 mL Single Dose Vial	Packages of 25

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Do not freeze.

PROTECT FROM LIGHT. Retain in carton until time of use.

Discard unused portion.

Vial stoppers do not contain natural rubber latex.

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

IN1455
Rev. 3/10
MG# 26651

**AMERICAN
REGENT, INC.
SHIRLEY, NY 11967**

Damoth, Debbie@DCA

From: Herold, Virginia@DCA
Sent: Tuesday, January 07, 2014 4:39 PM
To: 'William Blair'
Cc: Damoth, Debbie@DCA
Subject: RE: Comments to Proposed Changes to Articles 4.5 and 7 of Title 16 of the California Code of Regulation

Importance: High

Thank you.

From: William Blair [<mailto:Williamblair@mcguff.com>]
Sent: Tuesday, January 07, 2014 3:28 PM
To: Herold, Virginia@DCA
Subject: Comments to Proposed Changes to Articles 4.5 and 7 of Title 16 of the California Code of Regulation

Dear Ms. Herold,

McGuff Compounding Pharmacy Services, Inc. is submitting comments to the proposed text amending Articles 4.5 and 7 of Title 16 of the California Code of Regulations related to Compounding Drug Products.

Very Best Wishes,



William J. Blair, Pharm.D., MBA

Vice President and Director of Pharmacy Services
McGuff Compounding Pharmacy Services, Inc.
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Title 16. Board of Pharmacy

Proposed Language

To Amend § 1735 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735. Compounding in Licensed Pharmacies.

(a) "Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:

- (1) Altering the dosage form or delivery system of a drug
- (2) Altering the strength of a drug
- (3) Combining components or active ingredients
- (4) Preparing a drug product from chemicals or bulk drug substances

(b) "Compounding" does not include reconstitution of a drug pursuant to a manufacturer's direction(s) for oral, rectal, ~~typical~~, or injectable administration, nor does it include tablet splitting or the addition of flavoring agent(s) to enhance palatability.

(c) "Compounding" does not include, except in small quantities under limited circumstances as justified by a specific, documented, medical need, preparation of a compounded drug product that is commercially available in the marketplace or that is essentially a copy of a drug product that is commercially available in the marketplace.

(d) The parameters and requirements stated by this Article 4.5 (Section 1735 et seq.) apply to all compounding practices. Additional parameters and requirements applicable solely to sterile ~~injectable~~ compounding are stated by Article 7 (Section 1751 et seq.).

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

Summary of Comments on 4

Page: 1

Number: 1 Author: ron Subject: Inserted Text Date: 1/7/2014 7:55:45 AM

To Amend § 1735.1 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.1. Compounding Definitions.

(a) "Anteroom" means an ISO Class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, ~~order entry, compounded sterile product labeling, and~~ other high-particulate-generating activities are performed. It is a transition area that provides assurance that air flows from clean to dirty areas.

1
Order entry and labeling do not require Class 8 environment.

(b) "Batch" means more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.

(c) "Beyond use date" means the date after which a compounded drug product should not be used.

(d) "Buffer area" means an area where the ISO Class 5 hood is physically located.

(e) "Cleanroom" means a separate room meeting an ISO Class 7 or better air quality.

(f) "Controlled cold temperature" means 2° to 8° C (36° to 46° F)

(g) "Controlled freezer temperature" means -25° to -10° C (-13° to 14° F)

(h) "Controlled room temperature" means 20° to 25° C (68° to 77° F)

3
Once sterile gloves are pressed into growth media the gloves are contaminated and can not be used.

~~(a)~~ (i) "Equipment" means items that must be calibrated, maintained or periodically certified.

(j) "Gloved fingertip sampling" means the requirement that immediately after aseptic ~~donning of sterile gloves~~ compounding, ~~personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated and then examined for growth of~~ microorganisms.

~~(b)~~ (k) "Integrity" means retention of potency until the ~~expiration~~ ^{beyond use} date noted on the label.

(l) "Parenteral" means a sterile preparation of drugs for injection through one or more layers of skin.

8
personal protective equipment applies to sterile and non-sterile compounding

(m) "Personal protective equipment" means clothing or devices that protect the employee from exposure to drug products and minimize the contamination of compounded ~~sterile~~ products and include shoe covers, head and facial hair covers, face masks, gowns, and gloves.

10
insert new definition: "Inhalation" means via the oral route and excludes the nasal route. (compounders can not sterilize nasal containers/sprayers.)

-
- ≡ Number: 1 Author: ron Subject: Callout Date: 1/7/2014 8:02:27 AM
Order entry and labeling do not require Class 8 environment.

 - ⊠ Number: 2 Author: ron Subject: Cross-Out Date: 1/7/2014 7:56:30 AM

 - ≡ Number: 3 Author: ron Subject: Callout Date: 1/7/2014 12:52:24 PM
Once sterile gloves are pressed into growth media the gloves are contaminated and can not be used.

 - ⊠ Number: 4 Author: ron Subject: Cross-Out Date: 1/7/2014 8:00:45 AM

 - ⊠ Number: 5 Author: ron Subject: Inserted Text Date: 1/7/2014 8:00:49 AM

 - ≡ Number: 6 Author: ron Subject: Callout Date: 1/7/2014 8:04:51 AM
beyond use

 - ⊠ Number: 7 Author: ron Subject: Cross-Out Date: 1/7/2014 8:03:17 AM

 - ≡ Number: 8 Author: ron Subject: Callout Date: 1/7/2014 8:12:10 AM
personal protective equipment applies to sterile and non-sterile compounding

 - ⊠ Number: 9 Author: ron Subject: Cross-Out Date: 1/7/2014 8:10:36 AM

 - ≡ Number: 10 Author: ron Subject: Callout Date: 1/7/2014 12:52:54 PM
insert new definition: "Inhalation" means via the oral route and excludes the nasal route. (compounders can not sterilize nasal containers/sprayers.)

process validation
is too broad of a
term ¹

add: or the range
specified in the
current USP NF ²

~~(e)~~ (n) "Potency" means active ingredient strength within +/- 10% of the labeled amount.

~~(o)~~ "Process validation" means establishing by objective evidence that a process consistently produces a result or product meeting simulation of an aseptic process with growth medium processed in a manner similar to the normal order of production and with the same container or closure. ⁵

Use of rational bracketing of container sizes should be allowed similar to drug manufacturing. Reference Federal Guidances for explanation of rational bracketing

~~(e)~~ (p) "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, and absence of active ingredients other than those noted on the label.

~~(q)~~ "Segregated compounding area" means a designated space, either a demarcated area or room, that is restricted to preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile products and shall be void of activities and materials that are extraneous to sterile compounding.

~~(r)~~ "Smoke test" means an analysis of the airflow in the ISO Class 5 hood using a smoke generating device.

~~(e)~~ (s) "Strength" means amount of active ingredient per unit of a compounded drug product.

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

To Amend § 1735.2 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.2. Compounding Limitations and Requirements; Self-Assessment.

(a) Except as specified in (b) and (c), no drug product shall be compounded prior to receipt by a pharmacy of a valid prescription for an individual patient where the prescriber has approved use of a compounded drug product either orally or in writing. Where approval is given orally, that approval shall be noted on the prescription prior to compounding.

-
- Number: 1 Author: ron Subject: Callout Date: 1/7/2014 8:20:43 AM
process validation is too broad of a term
-
- Number: 2 Author: ron Subject: Callout Date: 1/7/2014 8:13:26 AM
add: or the range specified in the current USP NF
-
- Number: 3 Author: ron Subject: Inserted Text Date: 1/7/2014 8:16:18 AM
Media fill
-
- Number: 4 Author: doug Subject: Callout Date: 1/7/2014 8:36:00 AM
Use of rational bracketing of container sizes should be allowed similar to drug manufacturing. Reference Federal Guidances for explanation of rational bracketing.
-
- Number: 5 Author: doug Subject: Inserted Text Date: 1/7/2014 8:33:10 AM
The use of rational bracketing is allowed.
-
- Number: 6 Author: doug Subject: Inserted Text Date: 1/7/2014 8:44:08 AM
compounding batches for aseptic filtration operations. If the compounding activities involve the dissolution of non-sterile ingredients, the mixing process will occur in no less than a Class ISO 8 area before being aseptically filtered in Class ISO 5 environment. If the segregated compounding area is for sterile-to-sterile compounding.
-
- Number: 7 Author: doug Subject: Inserted Text Date: 1/7/2014 8:40:24 AM
This
-
- Number: 8 Author: doug Subject: Replacement Text Date: 1/7/2014 8:40:11 AM

(g) All ~~chemicals, bulk drug substances,~~ drug products, and other components used for drug compounding shall be stored and used according to compendial and other applicable requirements to maintain their integrity, potency, quality, and labeled strength.

(h) Every compounded drug product shall be given ~~an expiration date~~ beyond use date representing the date beyond which, in the professional judgment of the pharmacist performing or supervising the compounding, it should not be used. This "beyond use date" of the compounded drug product shall not exceed 180 days from preparation or the shortest expiration date of any component in the compounded drug product, unless a longer date is supported by stability studies of finished drugs or compounded drug products using the same components and packaging. Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.

(i) The pharmacist performing or supervising compounding is responsible for the proper preparation, labeling, storage, and delivery of the compounded drug product.

(j) Prior to allowing any drug product 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. 02/12.) 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 ~~injectable~~ compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of odd-numbered each year, within 30 days of the start of a new pharmacist-in-charge, 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.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code, Sections 1735, 1735.1, 1735.8, and 1751.1-1715.8 of Title 16 of the California Code of Regulations.

(d) After receipt by the pharmacy, packages of ingredients that lack a supplier's expiration date cannot be used after one (1) year unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in compounded drug products.

~~(d)~~ (e) Pharmacies shall maintain and retain all records required by this article in the pharmacy in a readily retrievable form for at least three years from the date the record was created.

Authority cited: Sections 4005, 4127, and 4169, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1735.5 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.5. Compounding Policies and Procedures.

(a) Any pharmacy engaged in compounding shall maintain a written policy and procedure manual for compounding that establishes procurement procedures, methodologies for the formula² ing, maintenance, operation² of unprofessional conduct. Pattern of such failure may² unding. The pharmacy shall follow² policies and procedures shall be deemed unprofessional conduct.

(b) The policy and procedure manual shall be reviewed on an annual basis by the pharmacist-in-charge and shall be updated whenever changes in processes are implemented.

(c) The policy and procedure manual shall include the following:

(1) Procedures for notifying staff assigned to compounding duties of any changes in processes or to the policy and procedure manual.

(2) Documentation of a plan for recall of a dispensed compounded drug product where subsequent verification demonstrates the potential for adverse effects⁶ with continued use of a compounded drug product. ⁵adverse effects is too general

(3) The procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in compounding, and for training on these procedures as part of the staff training and competency evaluation process.

-
-  Number: 1 Author: doug Subject: Inserted Text Date: 1/7/2014 8:55:00 AM
from the date of receipt,
-
-  Number: 2 Author: doug Subject: Callout Date: 1/7/2014 12:56:29 PM
Reason: Unintentional or minor failure to follow policy/procedure should not result in immediate determination of unprofessional conduct. Pattern of such failure may be considered unprofessional conduct.
-
-  Number: 3 Author: doug Subject: Cross-Out Date: 1/7/2014 8:55:19 AM
-
-  Number: 4 Author: doug Subject: Inserted Text Date: 1/7/2014 8:55:53 AM
cause for consideration of
-
-  Number: 5 Author: doug Subject: Callout Date: 1/7/2014 8:48:54 AM
adverse effects is too general
-
-  Number: 6 Author: doug Subject: Cross-Out Date: 1/7/2014 8:47:19 AM
-
-  Number: 7 Author: doug Subject: Inserted Text Date: 1/7/2014 8:47:16 AM
serious
-
-  Number: 8 Author: doug Subject: Inserted Text Date: 1/7/2014 8:47:24 AM
events

Reason: Validate is too extensive of an indication. ¹

(4) Documentation of the methodology appropriate to compounded drug products used to ~~test~~ ² ~~validate~~ ³ integrity, potency, quality, and labeled strength ~~of compounded drug products.~~

(5) Documentation of the methodology used to determine appropriate ~~expiration~~ beyond use dates for compounded drug products.

(6) Dates of annual reviews and signature or initials by the pharmacist-in-charge and dates of any revisions to the policies and procedures.

(7) The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, ~~and~~ 4127, and 4301, Business and Professions Code.

To Amend § 1751 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

Article 7. Sterile ~~Injectable~~ Compounding

1751. Sterile ~~Injectable~~ Compounding; Compounding Area; Self-Assessment.

(a) Any pharmacy engaged in compounding sterile ~~injectable~~ drug products shall conform to the parameters and requirements stated by Article 4.5 (Section 1735 et seq.), applicable to all compounding, and shall also conform to the parameters and requirements stated by this Article 7 (Section 1751 et seq.), applicable solely to sterile ~~injectable~~ compounding.

(b) Any pharmacy compounding sterile ~~injectable~~ drug products shall have a designated compounding area for the preparati⁴ Reason: We can not determine what this Section 1250 of the Title 24, Part 2, Chapter 12, of the CA Code of following standards: The environment Regulations is.

(1) ~~Clean Room~~ Cleanroom and Work Station Requirements, shall ⁵ ~~be~~ ⁶ ~~in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations.~~

(2) Walls, ceilings and floors shall be constructed in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations.

≡ Number: 1 Author: doug Subject: Callout Date: 1/7/2014 12:57:16 PM
Reason: Validate is too extensive of an indication.

⊕ Number: 2 Author: doug Subject: Cross-Out Date: 1/7/2014 8:59:24 AM

⊕ Number: 3 Author: doug Subject: Inserted Text Date: 1/7/2014 8:59:59 AM
Verify

≡ Number: 4 Author: doug Subject: Callout Date: 1/7/2014 9:07:12 AM
Reason: We can not determine what this Section 1250 of the Title 24, Part 2, Chapter 12, of the CA Code of Regulations is.

⊕ Number: 5 Author: doug Subject: Cross-Out Date: 1/7/2014 9:05:05 AM

⊕ Number: 6 Author: doug Subject: Inserted Text Date: 1/7/2014 9:04:55 AM
occur in ISO Class 8 or better.

Semi-annually allows flexibility for unforeseen occurrences.

(3) ~~Be~~ The pharmacy shall be ventilated in a manner in accordance with Section 505.12 of Title 24, Part 4, Chapter 5 of the California Code of Regulations.

(4) ~~Be~~ The ISO environment shall be certified annually ² ~~at least every six months~~ ¹ by a qualified technician who is familiar with the methods and procedures for certifying laminar air flow hoods and ~~clean room~~ cleanroom requirements, in accordance with standards adopted by the United States General Services Administration and whenever the device or cleanroom is relocated, altered, or a service to the facility is performed that would impact the cleanroom or device. Certification records must be retained for at least 3 years.

(5) The pharmacy shall be arranged in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations. Items related to the compounding of sterile ~~injectable~~ drug products within the compounding area shall be stored in such a way as to maintain the integrity of an aseptic environment.

(6) A sink shall be included in accordance in Section 1250 of Title 24, Part 2, of the California Code of Regulations. Sinks and drains shall not be present in an ISO Class 7 or better cleanroom, in buffer area, nor adjacent to an ISO Class 5 hood in a segregated compounding area. A sink may be located in an anteroom.

(7) There shall be a refrigerator and/or freezer of sufficient capacity to meet the storage requirements for all material requiring refrigeration.

(c) Any pharmacy compounding a sterile ~~injectable~~ drug product from one or more non-sterile ingredients shall comply with Business and Professions Code section 4127.7.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4127 and 4127.7, Business and Professions Code; Sections 1735, 1735.1,-1735.8., and 1751.1-1751.8. of Title 16 of the California Code of Regulations; and Section 18944, Health and Safety Code.

To Amend § 1751.1 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.1. Sterile ~~injectable~~ Compounding Recordkeeping Requirements.

≡ Number: 1 Author: doug Subject: Callout Date: 1/7/2014 12:58:20 PM
Semi-annually allows flexibility for unforeseen occurrences.

⊞ Number: 2 Author: doug Subject: Cross-Out Date: 1/7/2014 9:08:29 AM

⊞ Number: 3 Author: doug Subject: Inserted Text Date: 1/7/2014 9:08:51 AM
semi-annually

⊞ Number: 4 Author: doug Subject: Inserted Text Date: 1/7/2014 9:26:59 AM
that is ISO Class 7 or better

To Amend § 1751.2 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.2. Sterile ~~Injectable~~ Compounding Labeling Requirements.

In addition to the labeling information required under Business and Professions Code section 4076 and section 1735.4, a pharmacy which compounds sterile ~~injectable~~ drug products shall include the following information on the labels for those products:

- (a) Telephone number of the pharmacy, except for sterile ~~injectable~~ drug products dispensed for inpatients of a hospital pharmacy.
- (b) Name and concentrations of ~~ing~~ ingredients contained in the sterile ~~injectable~~ drug product.
- (c) Instructions for storage and handling.
- (d) All cytotoxic agents shall bear a special label which states "Chemotherapy - Dispose of Properly" or "Cytotoxic – Dispose of Properly."

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4076 and 4127, Business and Professions Code.

To Amend § 1751.3 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.3. Sterile ~~Injectable~~ Compounding Policies and Procedures.

- (a) Any pharmacy engaged in compounding sterile ~~injectable~~ drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following:
 - (1) Compounding, filling, and labeling of sterile ~~injectable~~ compounds.
 - (2) Labeling of the sterile ~~injectable~~ drug product based on the intended route of administration and recommended rate of administration.
 - (3) Equipment and supplies.

Number: 1 Author: doug
each active pharmaceutical

Subject: Inserted Text Date: 1/7/2014 9:20:22 AM

(4) Training of staff in the preparation of sterile ~~injectable~~ drug products.

(5) Training of staff in the cleaning and maintenance of an ISO environment and segregated compounding areas.

(6) A viable and nonviable sampling plan.

(7) For barrier isolators, documentation of the manufacturer's recommended purge time.

~~(5)~~ (8) Procedures for handling cytotoxic agents.

~~(6)~~ (9) Quality assurance program.

~~(7)~~ (10) Record keeping requirements.

(b) The ingredients and the compounding process for each preparation must be determined in writing before compounding begins and must be reviewed by a pharmacist.

(c) Pharmacies compounding sterile ~~injectable~~ drug products shall have written policies and procedures for the disposal of infectious materials and/or materials containing cytotoxic residues. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.

(d) Pharmacies compounding sterile ~~injectable~~ drug products ~~from one or more non-sterile ingredients~~ must have written policies and procedures that comply with the following:

(1) All written policies and procedures shall be immediately available to all personnel involved in these activities and board inspectors.

(2) All personnel involved must read the policies and procedures before compounding sterile ~~injectable~~ drug products, and any additions, revisions, and deletions to the written policies and procedures must be communicated to all personnel involved in sterile compounding.

(3) Policies and procedures must address at least the following:

(A) Competency evaluation.

(B) Storage and handling of products and supplies.

(C) Storage and delivery of final products.

(D) ~~Process~~ validation.

(E) Personnel access and movement of materials into and near the controlled area.

T Number: 1 Author: doug Subject: Inserted Text Date: 1/7/2014 9:23:58 AM
if cytotoxic agents are compounded.

T Number: 2 Author: ron Subject: Inserted Text Date: 1/7/2014 8:18:16 AM
Media fill

(a) No sterile ~~injectable~~ drug product shall be compounded if it is known, or reasonably should be known, that the compounding environment fails to meet criteria specified in the pharmacy's written policies and procedures for the safe compounding of sterile ~~injectable~~ drug products.

(b) During the preparation of sterile ~~injectable~~ drug products, access to the designated area or cleanroom must be limited to those individuals who are properly attired.

(c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected.

(d) Cleaning and disinfecting surfaces in the ISO Class 5 hood shall occur frequently, including:

(i) at the beginning of shift;

(ii) before each batch;

(iii) ~~Every 30 minutes during continuous compounding of individual compounded sterile drug products;~~ ⁴

(iv) after each spill;

(v) when surface contamination is known or suspected; and

(vi) when switching between cytotoxic and non-cytotoxic ingredients.

~~(d) (e) Exterior workbench surfaces and other hard surfaces in the designated area, such as walls, floors, ceilings, shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination. Counters, cleanable work surfaces and floors shall be cleaned and disinfected daily. Walls, ceiling, storage shelving, tables and stools are to be cleaned and disinfected monthly. Cleaning shall occur after any unanticipated event that could increase the risk of contamination. Cleaning shall include the periodic use of a sporicidal agent.~~

~~(e) (f) Pharmacies preparing parenteral sterile cytotoxic agents shall do so in accordance with Section 505.12.1 of Title 24, Chapter 5, of the California Administrative Code, requiring a laminar air flow hood. The hood must be certified annually ⁴ ~~every six months~~ ⁵ by a qualified technician who is familiar with the methods and procedures for certifying laminar air flow hoods and cleanroom requirements, in accordance with ~~National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, as revised May, 1983~~ NSF International Standard/American National Standard for Biosafety Cabinetry - Biosafety~~

Reason: Manually intervening an aseptic process with cleaning poses a greater risk of cross-contamination.

-
- ≡ Number: 1 Author: doug Subject: Callout Date: 1/7/2014 1:01:57 PM
Reason: Manually intervening an aseptic process with cleaning poses a greater risk of cross-contamination.

 - ⊞ Number: 2 Author: doug Subject: Cross-Out Date: 1/7/2014 9:31:44 AM

 - ⊞ Number: 3 Author: doug Subject: Inserted Text Date: 1/7/2014 9:32:09 AM
at the end of each batch.

 - ⊞ Number: 4 Author: doug Subject: Cross-Out Date: 1/7/2014 9:34:45 AM

 - ⊞ Number: 5 Author: doug Subject: Inserted Text Date: 1/7/2014 9:35:07 AM
semi-annually

Cabinetry: Design, Construction, Performance, and Field Certification [NSF/ANSI 49-2012], as revised July 7, 2012 (available from the National Sanitation Foundation, 3475 Plymouth Road, P.O. Box 1468, Ann Arbor, Michigan 48106, phone number (313) 769-8010 Chair, Joint Committee on Biosafety Cabinetry c/o NSF International, P.O. Box 130140, 789 N. Dixboro Road, Ann Arbor, MI 48105, USA, phone number (734) 769-8010) or manufacturer's specifications. Certification records must be retained for at least 3 years. The hood shall be decontaminated when switching between cytotoxic and non-cytotoxic ingredients.

(g) Pharmacies preparing sterile cytotoxic agents shall use a biological safety cabinet or compounding aseptic containment isolator that provides an ISO Class 5 environment during dynamic compounding conditions which is maintained in accordance with the manufacturer's recommendations and which is certified every six months. If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area, the compounding area shall maintain a minimum negative pressure of

0.01-inch Microbial monitoring should occur routinely on no less than a monthly basis. Reason: microbial growth can bloom quickly and become a problem ¹er hour.

(h) Viable surface and volumetric air sampling by impaction shall occur at least every six months by a qualified technician who is familiar with the methods and procedures for surface testing and air sampling. Viable air sampling is to be performed under dynamic conditions that simulate actual production. Exceeded action levels shall prompt an immediate investigation of cleaning and compounding operations and facility management.

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

To Amend § 1751.5 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.5. Sterile ~~Injectable~~ Compounding Attire.

(a) When preparing cytotoxic agents, gowns and gloves shall be worn.

☰ Number: 1 Author: doug Subject: Callout Date: 1/7/2014 9:46:21 AM

Microbial monitoring should occur routinely on no less than a monthly basis. Reason: microbial growth can bloom quickly and become a problem well within a 6-month period.

☒ Number: 2 Author: doug Subject: Cross-Out Date: 1/7/2014 9:37:08 AM

☒ Number: 3 Author: doug Subject: Inserted Text Date: 1/7/2014 9:44:20 AM
monthly

(E) Aseptic preparation procedures using media fill tests which are as complicated as the most complex manipulations performed by staff and which contain the same amount of volume transferred during the compounding process.

(F) Proper gowning and gloving technique.

(G) General conduct in the controlled area.

(H) Cleaning, sanitizing, and maintaining equipment used in the controlled area.

(I) Sterilization techniques for compounding sterile drug products from one or more non-sterile ingredients.

(J) Container, equipment, and closure system selection.

(2) Each person assigned to the controlled area who ¹ handles compounded sterile drug products, ² must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months, ³ results of these assessments must be documented and retained in the pharmacy for three years.

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

To Amend § 1751.7 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.7. Sterile ~~injectable~~ Compounding Quality Assurance and ~~Process~~ Validation.

(a) Any pharmacy engaged in compounding sterile ~~injectable~~ drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure

F Number: 1 Author: doug Subject: Cross-Out Date: 1/7/2014 9:53:31 AM

T Number: 2 Author: doug Subject: Inserted Text Date: 1/7/2014 9:54:05 AM
performs aseptic processing

F Number: 3 Author: doug Subject: Cross-Out Date: 1/7/2014 9:54:07 AM

T Number: 4 Author: doug Subject: Inserted Text Date: 1/7/2014 9:54:39 AM
annually

T Number: 5 Author: doug Subject: Inserted Text Date: 1/7/2014 9:49:55 AM
Media Fill

that it meets required specifications. The Quality Assurance Program shall include at least the following:

(1) Cleaning and sanitization of the ~~parenteral medication~~ sterile preparation area.

~~(2) The storage of compounded sterile injectable products in the pharmacy and periodic documentation of refrigerator temperature.~~

~~(3) (2) Actions to be taken in the event of a drug recall.~~

~~(4) (3) Written justification of the chosen expiration~~ beyond use dates for compounded sterile injectable drug products.

(b) Each individual involved in the ~~preparation of sterile injectable~~ drug products must first successfully complete a ²validation ³process on technique before being allowed to prepare sterile injectable drug products. The ⁴validation ⁵process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. ~~The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare.~~ The ⁶validation ⁷process shall be as complicated as the most complex manipulations performed by staff and which contain the same amount of volume transferred during the compounding process. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated in a manner consistent with the manufacturer's recommendations and demonstrated to promote growth. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the ⁹validation ¹¹process repeated. Personnel competency must be ¹⁰revalidated ¹²at least ⁸every twelve months ¹⁴sterile to sterile compounding and at least ¹³every six months ¹⁵individuals compounding sterile products from non-sterile ingredients, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile ~~injectable~~ drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. ¹⁶Revalidation ¹⁷must be documented.

(c) All compounding personnel must successfully complete an initial competency evaluation. In addition, immediately following the hand hygiene and garbing procedure, all compounding

<input checked="" type="checkbox"/>	Number: 1 Author: doug aseptic	Subject: Inserted Text	Date: 1/7/2014 9:56:28 AM
<input type="checkbox"/>	Number: 2 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:50:26 AM
<input checked="" type="checkbox"/>	Number: 3 Author: doug qualification	Subject: Inserted Text	Date: 1/7/2014 9:50:45 AM
<input type="checkbox"/>	Number: 4 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:50:49 AM
<input checked="" type="checkbox"/>	Number: 5 Author: doug qualification	Subject: Inserted Text	Date: 1/7/2014 9:51:02 AM
<input type="checkbox"/>	Number: 6 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:51:07 AM
<input checked="" type="checkbox"/>	Number: 7 Author: doug qualification	Subject: Inserted Text	Date: 1/7/2014 9:52:26 AM
<input type="checkbox"/>	Number: 8 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:56:53 AM
<input type="checkbox"/>	Number: 9 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:56:31 AM
<input type="checkbox"/>	Number: 10 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:57:55 AM
<input checked="" type="checkbox"/>	Number: 11 Author: doug qualification	Subject: Inserted Text	Date: 1/7/2014 9:56:48 AM
<input checked="" type="checkbox"/>	Number: 12 Author: doug requalified	Subject: Inserted Text	Date: 1/7/2014 9:59:10 AM
<input type="checkbox"/>	Number: 13 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:57:08 AM
<input checked="" type="checkbox"/>	Number: 14 Author: doug annually	Subject: Inserted Text	Date: 1/7/2014 9:57:06 AM
<input checked="" type="checkbox"/>	Number: 15 Author: doug semi-annually	Subject: Inserted Text	Date: 1/7/2014 9:57:32 AM
<input type="checkbox"/>	Number: 16 Author: doug	Subject: Cross-Out	Date: 1/7/2014 9:57:35 AM
<input checked="" type="checkbox"/>	Number: 17 Author: doug Requalification	Subject: Inserted Text	Date: 1/7/2014 9:57:49 AM

personnel must successfully
forming units) at least three
products.

(d) Re-evaluation of garbin
compounding products mac
personnel compounding pro

(e) (e) Batch-produced steri

sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States

Pharmaceutics (USP Ch <151> is the pyrogens testing in rabbits. This test is not practical and effective August 1, 2013), and pyrogens accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st

Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and

shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens or to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile.

(d) (f) Batch-produced sterile to sterile transfers shall be subject to periodic testing through process validation for sterility as determined by the pharmacist-in-charge and described in the written policies and procedures.

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

To Amend § 1751.8 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.8. Beyond Use Dating for Sterile Compounded Drug Products.

There should be concessions made for test method validation of each compounded preparation. For Ch <71>, concession should be to use maximum rinse indicated in USP <71> for membrane filtration sterility testing method.

There should be concessions made for test method validation of each compounded preparation. For Ch <85>, concession should be to test for inhibition only and allow to use 4 lamda positive product control and eliminate full scope of individual inhibition/enhancement testing.

-
- ≡ Number: 1 Author: doug Subject: Callout Date: 1/7/2014 1:03:33 PM
There should be concessions made for test method validation of each compounded preparation. For Ch <71>, concession should be to use maximum rinse indicated in USP <71> for membrane filtration sterility testing method.

 - ≡ Number: 2 Author: doug Subject: Callout Date: 1/7/2014 1:03:02 PM
There should be concessions made for test method validation of each compounded preparation. For Ch <85>, concession should be to test for inhibition only and allow to use 4 lamda positive product control and eliminate full scope of individual inhibition/enhancement testing.

 - ⊞ Number: 3 Author: doug Subject: Cross-Out Date: 1/7/2014 10:01:20 AM

 - ⊞ Number: 4 Author: doug Subject: Inserted Text Date: 1/7/2014 10:04:01 AM
semi-annually

 - ≡ Number: 5 Author: doug Subject: Callout Date: 1/7/2014 1:03:43 PM
USP Ch <151> is the pyrogens testing in rabbits. This test is not practical and should be removed.

 - ⊞ Number: 6 Author: doug Subject: Cross-Out Date: 1/7/2014 10:07:54 AM

 - ⊞ Number: 7 Author: doug Subject: Cross-Out Date: 1/7/2014 10:17:13 AM

 - ⊞ Number: 8 Author: doug Subject: Inserted Text Date: 1/7/2014 10:17:25 AM
endotoxins

 - ⊞ Number: 9 Author: doug Subject: Cross-Out Date: 1/7/2014 10:17:31 AM

 - ⊞ Number: 10 Author: doug Subject: Inserted Text Date: 1/7/2014 10:17:36 AM
endotoxins

 - ⊞ Number: 11 Author: doug Subject: Cross-Out Date: 1/7/2014 10:17:52 AM

 - ⊞ Number: 12 Author: doug Subject: Inserted Text Date: 1/7/2014 10:17:55 AM
endotoxins

 - ⊞ Number: 13 Author: ron Subject: Inserted Text Date: 1/7/2014 8:20:23 AM
media fill

Damoth, Debbie@DCA

From: Lau, Dennis <Dennis.Lau@methodisthospital.org>
Sent: Wednesday, January 08, 2014 8:03 AM
To: Damoth, Debbie@DCA
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Oh yes Debbie please do, that will be helpful. I am pursuing this specific issue on behalf of the many women in the pharmacy profession and the unpredictability of staffing levels inherent in hospital work.

Thank you again,
Dennis

From: Damoth, Debbie@DCA [mailto:Debbie.Damoth@dca.ca.gov]
Sent: January 07, 2014 11:04
To: Lau, Dennis
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Hello Dr. Lau,
Would you like this to be added to your comments too? Happy New Year!
Thank you, Debbie

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Lau, Dennis [mailto:Dennis.Lau@methodisthospital.org]
Sent: Friday, January 03, 2014 8:24 AM
To: Damoth, Debbie@DCA
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Thank you Debbie and Happy New Year!

I am also looking into cosmetic "sealers" used by professional makeup artists as a possible way to prevent shedding of "flakes and particles". Reason being, at any given time, any pharmacist or pharmacy technician on staff in a hospital pharmacy may be called upon to compound a sterile IV, such as in an emergency or unexpected staffing shortage.

Thanks again!
Dennis

From: Damoth, Debbie@DCA [mailto:Debbie.Damoth@dca.ca.gov]
Sent: January 02, 2014 16:44
To: Lau, Dennis
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Hello again Dr. Lau,
I will add this to your comments.
Thank you, Debbie

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Lau, Dennis [<mailto:Dennis.Lau@methodisthospital.org>]
Sent: Friday, December 27, 2013 1:55 PM
To: Damoth, Debbie@DCA
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Hello Again Debbie,
Can you dovetail my request with the following?

Would the Board consider surgery face shields with cosmetics in the ISO Class 5 and 7 compounding areas?

Thanks again,
Dennis Lau
Pharmacist

From: Damoth, Debbie@DCA [<mailto:Debbie.Damoth@dca.ca.gov>]
Sent: December 24, 2013 11:40
To: Lau, Dennis
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

You are most welcome ☺ It is my pleasure to serve.

From now until 1/2/14, the board is open Monday through Friday 8-5 but closed on 12/25 and 1/1.

Have a great Christmas Eve and Christmas ☺

Debbie

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Lau, Dennis [<mailto:Dennis.Lau@methodisthospital.org>]
Sent: Tuesday, December 24, 2013 11:11 AM
To: Damoth, Debbie@DCA
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Wow Debbie, I didn't expect to get a response until after the Holidays. Thank you for staffing the Board, even on Christmas Eve! I thought government offices would be closed until after the New Year.
Grateful,

Dennis

From: Damoth, Debbie@DCA [<mailto:Debbie.Damoth@dca.ca.gov>]
Sent: December 24, 2013 10:49
To: Lau, Dennis
Subject: RE: New Sterile Compounding Law--Comment Period 45 days

Thank you Dr. Lau. This will be considered in the comments.

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Lau, Dennis [<mailto:Dennis.Lau@methodisthospital.org>]
Sent: Tuesday, December 24, 2013 9:54 AM
To: Damoth, Debbie@DCA
Subject: New Sterile Compounding Law--Comment Period 45 days

Dear Debbie,

The new Section 1751.5(6) states:

(6) Individuals experiencing rashes, sunburn, weeping sores, conjunctivitis, active respiratory infections, or those wearing cosmetics shall be excluded from working in ISO Class 5 and ISO Class 7 compounding areas until their conditions are remedied.

Would it be possible for the Board to consider specifying the cosmetic types or formulations not allowed (shedding of flakes and particles) in ISO Class 5 and ISO Class 7 compounding areas similar to the FDA cosmetic product categories?

FDA Product category code = 03 [Eye Makeup Preparations]

- a. Eyebrow Pencil
- b. Eyeliner
- c. Eye Shadow
- d. Eye Lotion
- e. Eye Makeup Remover
- f. Mascara
- g. Other Eye Makeup Preparations

FDA Product category code = 07 [Makeup Preparations (not eye)]

- a. Blushers (all types)
- b. Face Powders
- c. Foundations
- d. Leg and Body Paints
- e. Lipstick
- f. Makeup Bases
- g. Rouges
- h. Makeup Fixatives
- i. Other Makeup Preparations

Thank you very much for your consideration.

Dennis Lau
Pharmacist

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Containment Technologies Group, Inc.

January 9, 2014

Debbie Damoth
1625 N. Market Blvd., N219
Sacramento, CA 95834

RE: Recommended Revisions for Amendment of 1735 in Article 4.5 of Division 17 of Title 16 California Code of Regulations

Please accept my comments and suggested changes to the proposed revisions:

1. In a number of places in the proposed changes the term "laminar air flow" is used (i.e. 1751 section 4; 1751.4 proposed section f; plus additional places). The more consistent term used by both USP 36 revision effective August 1, 2013 of General Chapter <797> and the US Food and Drug Administration in their Guidance For Industry, Sterile Drug Products Produced by Aseptic Processing – Good Manufacturing Practice, September 2004 is "unidirectional flow". References to laminar airflow should be replaced with unidirectional airflow as laminar airflow has specific velocity requirements not consistent with the engineering controls used in pharmacy.

The following definition should also be included:

Unidirectional flow- An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

2. Existing regulations at 16 CCR §1751.4 (f last sentence) the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.

Comment: Placing an aseptic compounding isolator in a negative pressure room does not protect the compounded preparation (patient safety) or the worker in the negative pressure room. It does have a significant negative economic impact on health care cost in the State of California and should be removed from the proposed regulations.



Creating a negative pressure environment will increase the bio burden of the area by drawing in contamination from unsealed and contaminated environments such as behind walls through electrical outlets, switches and other penetrations in the walls and ceilings. Contamination could include mold and spores which are common in these areas and the root cause of the many deaths reported from compounded preparations. The contamination will settle on surfaces and could transfer to components placed into the ISO class 5 compounding environment.

The worker in the area is not protected from either potential dermal or inhalation exposure. They would be in the area of highest concentration of the hazardous drug. The proposed change does not protect worker safety and would place the worker in a work environment of higher bioburden and potential exposure to the compounded hazardous drug.

As an alternative for added protection during transport use secondary containment with a simple zip lock bag or carrier if the vial is dropped and broken the spill is contained. If a spill does occur the spill is a liquid and not vapor or aerosol and can be cleaned up with appropriate emergency spill kit containing proper PPE. This will result in minimal worker exposure.

The proposed change fails to meet the criteria of a real benefit to the people of the State of California particularly where the protection of public health and safety and worker safety are involved. The proposed change does not protect the public health and has the opposite effect of increasing the potential for contaminated preparations. The proposal does add to healthcare cost because it would require construction and maintenance of a negative pressure room. Estimated cost range from \$20,000 upwards per facility.

The requirement for a negative pressure room does appear in USP <797> but was added without the benefit of a comment period. USP unlike the State of California has no consideration for the cost of compliance.

3. The proposed changes do not include the low volume exemption of a non-negative pressure room per USP 35 General Chapter <797>. This should be added to the revisions. For consistency with USP 35 General Chapter <797> the following should be included in the revisions. "In facilities that prepare a low volume of hazardous drugs, use of two tier of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable.



Containment Technologies Group, Inc.

4. 1751.5 (3) Add the word "sterile" after percent and before isopropyl in the last sentence.
5. 1751.5 (5) Add the word "sterile" after with and before isopropyl.
6. 1751.7 (b) The word "medium" is used in several places in the section. I think the correct word is "media". This should be corrected.

Sincerely

Hank Rahe BSIM, MSE
Director Technology
Containment Technology Group, Inc.
5460 Victory Drive, Suite 300
Indianapolis, Indiana
hrahe@mic4.com

Damoth, Debbie@DCA

From: Hank Rahe <hrahe@mic4.com>
Sent: Thursday, January 09, 2014 9:02 AM
To: Damoth, Debbie@DCA
Cc: Hank Rahe
Subject: PROPSOED REVISIONS
Attachments: img-140109162042-0001 California 1-14.pdf

Hello Hello

Please find attached my comments and suggestions for the proposed Revisions to the pharmacy board proposed revisions.

If you be so kind please send me a reply to this e-mail indicating you received it.

Hank Rahe

Damoth, Debbie@DCA

From: Richard Sakai <rsakai@CHILDRENSCENTRALCAL.ORG>
Sent: Thursday, January 09, 2014 7:37 PM
To: Damoth, Debbie@DCA
Cc: Klein, Carolyn@DCA
Subject: RE: Comments on the Pharmacy Compounding Regulation
Attachments: BOP Proposed Cmpd Regs Response D3 122013.doc; Richard Sakai.vcf

Here is my comments for the Board to consider. This document was put together with input from multiple pharmacists from the San Joaquin Valley area. I plan to be at the meeting and plan to highlight those issues which I consider will significantly adversely effect the organization and the care of the patients we serve.

Thank you
Rich

>>> "Damoth, Debbie@DCA" <Debbie.Damoth@dca.ca.gov> 1/8/2014 2:39 PM >>>

Hello Rich,

As discussed, please see my answers below:

1. Yes.
2. Yes.
3. Yes, the public can make comments. Registration is not necessary prior to the regulation hearing. Please be sure to sign in at the sign in sheet the day of the hearing.

Thank you,

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Richard Sakai [<mailto:RSakai@CHILDRENSCENTRALCAL.ORG>]
Sent: Wednesday, January 08, 2014 2:12 PM
To: Klein, Carolyn@DCA; Damoth, Debbie@DCA
Subject: Comments on the Pharmacy Compounding Regulation

1. Can comments on the Pharmacy Compounding Regulation be submitted electronically?
2. Should it be sent to you via your email?
3. At the January 16th meeting, can the public make comments? If we desire, do we have to register and/or request through yourself?

Thank you

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Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735 Line 12 Page 1 of 23	"direction(s) for oral, rectal topical or injectable..."	Comment: Missing comma between the words rectal and topical. Recommendation: Add a comma between rectal and topical	Minor edit
1735 Line 12 Page 1 of 23	"...nor does it include tablet splitting or the addition of flavoring agent(s) to enhance palatability"	Comment: In order to administer medications to pediatric patients, tablets are crushed and/or capsules opened and placed in vehicles such as cherry syrup or pudding as appropriate. Recommendation: add "tablet crushing" and "capsule opening".	
1735 Line 17 Page 1 of 23	"that is commercially available in the marketplace."	Comments: There may be organizations who elect to make an IV solution with an additive that is commercially available such as D5-NS with KCl 20mEq/L from a manufacturer, but elects to have staff make these products from a D5-NS IV bag and a vial of KCl, because the organization does not have a contract with that particular manufacturer. Infrequency of use, or even fiscally, it does not justify purchase of the commercially available product. Recommendation: It would be the professional judgment of the Pharmacist-in-Charge to make that determination.	
1735.1 Line 26 Page 1 of 23	"Anteroom" means an ISO Class 8	Comment: to be consistent with USP<797> definitions and eliminate confusion. Outlined in the chapter section "Facility Design and Environmental Controls", are allowances for a buffered areas not physically separated from the ante area employing the principle of displacement airflow. Recommendation: Change the term "Anteroom" to Ante-Area"	
1735.1(b) Line 31 Page 1 of 23	"Batch" means more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding	Comment: The definition of batch goes beyond this proposed definition in the pharmacy setting and in particular the hospital setting. A batch is a grouping of products usually defined by a time period for when they are due to be administered. This "batch" is then prepared during a single production period. A "batch" may contain either patient specific products or non-patient specific products. A "batch" may contain similar or dissimilar products. For the hospital setting the definition would include "non-patient	Operational inefficiency

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735.1 (c) Line 2 Page 2 of 23	"Beyond Use Date" means the date after which a compounded drug product should not be used.	<p>specific" and "prepared in anticipation of a physician's order".</p> <p>Comment: The Beyond Use Date (BUD) term deals with the compounding to ensure sterility and not stability of a product. If the Board's intent is to incorporate both sterility and stability in the definition of (BUD), there is a significant potential for confusion. 1735.2 (d)(3) would have to be addressed. Currently software limitations of providing (BUD) versus expiration date may result in non-compliance until the software can be updated. An estimate to update software is between \$30-\$50K</p> <p>Recommendation: Change language to be consistent with USP <797>.</p>	High cost due to drug waste as well as an anticipated \$30-50K software upgrade
1735.1 (d) Line 5 Page 2 of 23	"buffer areas" means an area where the ISO Class 5 hood is physically located.	<p>Comment: The air environment could be within a physical device such as a hood or containment isolator but also a room in operations that are more sophisticated than the typical hospital clean room (compounding procedures occur over an uncontained work surface in an ISO Class 5 air environment).</p> <p>Recommendation: Change the word "hood" to "air environment to be consistent with USP<797> definition.</p>	
1735.1 (e) Line 7 Page 2 of 23	"Cleanroom" means a separate room meeting an ISO Class 7 or better air quality	<p>Comment: This is a non-standard definition that appears to have been created by the Board of Pharmacy Compounding Subcommittee. An existing, standardized definition should be used .</p> <p>Recommendation: Change language to be consistent with USP Chapter 797: "A room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface and personnel gear are not exceeded for a specified cleanliness class." Add: Compounding Barrier Isolator – a device designed to maintain an aseptic compounding environment within the isolator throughout the compounding material transfers process (Some organizations have a barrier isolator)</p>	

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735.1(h) Line 13 Page 2 of 23	"controlled room temperature" means 20° to 25° C (68° to 77° F)	<p>Comment: The USP General Notice 27 allows for temporary excursions between 15 degrees C and 30 degrees for between 59 degrees and 86 degrees F which are experienced in pharmacies, hospitals and warehouses.</p> <p>Recommendations: Allow temporary excursions as per USP General Notice 27.</p>	
1735.1 (j) Line 17 Page 2 of 23	"Gloved fingertip sampling" means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated and then examined for growth of microorganisms.	<p>Comment: It is important that growth media be incubated properly. This will reduce the risk of inaccurate results.</p> <p>Recommendation: Use USP <797> language.</p> <p>"Gloved fingertip sampling" means the requirement that immediately after aseptic donning of sterile gloves, compounding personnel will lightly press each fingertip and thumb onto appropriate growth media which will be incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms."</p>	
1735.1 (q) Line 9 Page 3 of 23	"Segregated compounding area" means a designated space, either a demarcated area or room that is restricted to preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such an area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile products and shall be void of activities and materials that are extraneous to sterile compounding	<p>Comment: The proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on "Placement of Primary Engineering Controls). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room.</p> <p>This definition also allows for the potential of "medium risk" compounding in the segregated compounding area where USP<797> limits the compounding to "low risk" in this environment.</p> <p>Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary</p>	<p>Unnecessarily short beyond use dating will cause drug waste.</p> <p>Cost impact: difficult to estimate but the would require significant construction and/or remodel</p>

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		<p>engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.</p> <p>Recommendation to Addcompounded “low risk” sterile products with a 12-hours or less.....</p>	
1735.2 Line 24 Page 3 of 23	(a) “Except as specified in (b) and (c), no drug product shall be compounded prior to receipt...”	<p>Comment: This could result in delay for service which could result in patient care issues.</p> <p>Recommendation: Add an option (d) which should be, “the medical staff governance body of an organization on behalf of individual prescribers may authorize the compounding of drug products in the institution for patients.”</p>	
1735.2 Line 14 Page 4 of 23	(3) “Beyond use dating requirements”	<p>Comment: Expiration date and BUD are not the same. Should the Board desire both recorded, this will require additional support by staff to support this as some organizations which utilize an electronic method to record this information do not have a place to record both expiration date and beyond use date. This will require a software update. Updates often cost between \$10-20K</p> <p>Recommendation: Add: “Keep Expiration Dating Requirements” ADD “ and beyond use date”.</p> <p>Comment: BUD is not the same as expiration date. The Board should consider separating into two and clearly defining each to avoid confusion.</p> <p>Recommendation: ADD Expiration date means the date after which a compounded drug product should not be used. BUD is not the same as expiration date</p>	Potential software costs ranging from \$10-20K
1735.2 Line 19 Page 4 of 23	(e) “Where a pharmacy does not routinely compound a particular drug product, the master formula record for that product may be recorded in the prescription document itself.”	Comment: Allow the pharmacist to utilize their cognitive skills to evaluate the literature to determine the required information necessary to safely compound drug products.	

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		Recommendation: Add In the professional judgment of the pharmacist the care of the patient would be compromised, the written master formula may be prepared within 72 hours.	
1735.3 Line 28 Page 5 of 23	“the requirements in this paragraph are sterile products compounded on a one-time basis for administration within seventy-two (72) hours and stored in accordance with standards for “Redispensed CSPS” found in Chapter 797 of the United States Pharmacopeia	Comment: if the interpretation in this section is that a dose is not a patient specific dose as defined by a particular patient’s dose at a defined date and time, it will cost some organizations over \$144,230 annually based upon 300,000 doses taking an additional one minute to capture and record the information resulting in a need for 2.4 FTEs annually not including replacement costs nor benefits for these employees. Recommendation: Add “patient specific” before the part”...sterile products compounded...”	Estimated \$144,230 annually.
1735.3 Line 9 Page 6 of 23	“...drug products shall be obtained from reliable FDA-registered suppliers.”	Comment: Drugs approved by the Food and Drug Administration (FDA) have already passed requirements for purity as required by the FDA as well as being monitored. Pharmaceutical companies do not currently provide a certificate of purity when a healthcare facility purchases these products. Should this be part of the regulation, it is estimated that it will result in an increase of one full time equivalent (FTE) or approximately \$60K annually per organization to hire a pharmacy technician in a moderate sized hospital (350 bed facility). Recommendation: Add “...or USP quality grade products...” after the part “...FDA registered suppliers...”	
1735.3 (9)(c) Line 9 Page 6 of 23	The pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products, and components used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. Certificates of purity or analysis are to be matched to the product received.	Comment: The goal is to ensure quality products are used. USP quality grade ensures this. Products which fulfill USP standards ensure this safety. Currently organizations that utilize USP approved drugs do not acquire or maintain this information being requested. To obtain, maintain and update this information will easily require one FTE (technician) or about \$60K including benefits per organization Recommendation: Retain this language: “Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.”	Operational inefficiency; addition of one FTE of pharmacy technician or about \$60K including benefits.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735.3 Line 28 Page 6 of 23	"container or on the receipt provided to the patient..."	<p>Concern: Inpatients and outpatients being cared for in a healthcare facility currently do not receive receipts of the drugs that are prescribed during their stay. This part of the regulation appears to be of benefit for those patients receiving an actual prescription in the outpatient setting. The value for a patient receiving care from an acute care healthcare facility such as a hospital remains questionable.</p> <p>Recommendation: Add "...sterile injectable compounded products provided to patients in a healthcare facility are excluded." At the end of the sentence on line 28</p>	
1735.5 (a) Line 7 Page 7 of 23The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.	<p>Concern: The proposed language is overly harsh, and provides no latitude if minor deviations are found in observance of policies and procedures that pose no reasonable risk to the public. There needs to be room for judgment on the part of the inspector and/or the Board.</p> <p>Recommendation: "The pharmacy shall follow its policies and procedures. Intentionally (or grossly) failing to follow these policies and procedures shall be deemed unprofessional conduct."</p> <p>Recommendation: REMOVE the sentence "the pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct."</p> <p>This doesn't appear elsewhere in the regulations. The Board of Pharmacy already has the authority</p>	Draconian language; use "Just Culture".
1735.5 (c)(5) Lines 23 Page 7 of 23	Documentation of the methodology used to determine appropriate <u>expiration beyond use</u> dates for compounded drug products.	<p>Comment: Addition of the proposed language allows the pharmacist to utilize their professional training and judgement. Also separates the expiration date of a product versus beyond use date as defined by USP<797>.</p> <p>Recommendation: maintain "Expiration Date" add at the end of the sentence. drug products <u>based upon the information in the literature or supplied by the manufacturer.</u></p>	Unclear creating confusion.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
1735.5 Line 26 Page 7 of 23	Any revisions to the policies and procedures	<p>Comment: The intent of the document revisions is to ensure staff is utilizing the most current policies and procedures. The current verbiage indicates that ALL revisions would be listed. The current method most organizations utilize is that old policies and procedures are archived and not available for staff to see to prevent the utilization of an old policy and procedure. The date of the most current revision is documented on the document alerting staff of the date the policy and procedure was reviewed and approved.</p> <p>Recommendation: Remove “and” Add: “the most recent”</p>	
1735.5 (c)(7) Line 27 Page 7 of 23 and 1751.1 (b)(4) Line 26 Page 10 of 23	The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures.	<p>Comment: This language, particularly the phrase “daily documentation” could be interpreted to mean that only paper logs would be acceptable. Continuous electronic monitoring technology is at least as good as, if not superior to, manual documentation on paper logs.</p> <p>Recommendation: Add language that supports the use of methods other than daily logs.</p> <p>“The storage of compounded sterile drug products in the pharmacy and daily documentation of room, refrigerator, and freezer temperatures, through the use of paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.</p>	Operational inefficiency
1751 (b)(6) Lines 8 Pages 10 of 23	A sink shall be included..... <u>A sink may be located in an anteroom.</u>	<p>Comment: Utilize USP<797> definition as referenced previously</p> <p>Recommendation: Change from “anteroom” to “ante area”</p>	
1751.1(b)(6) Line 5 Page 11 of 23	Logs of pressure differentials	<p>Comment: This statement could imply that a log of pressure differentials would be required in a cleanroom that does not have a physical separation between the buffer area and the ante area, in which airflow displacement method is used as a means of separation. This would be inappropriate. There is no requirement in USP <797> to maintain a log when airflow displacement is used in this manner.</p>	Operational inefficiency

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		<p>Recommendation: Change language to be consistent with the context of USP <797>:</p> <p>“Logs of pressure differentials for rooms providing a physical separation through the use of walls, doors, and pass-throughs. A minimum differential positive pressure of 0.02- to 0.05-inch water column is required. This can be achieved by using paper logs or continuous temperature monitoring devices with appropriate alarms/alerts.”</p>	
1751.3 (a)(5) Lines 9 Page 12 of 23	<u>Training of staff in the cleaning and maintenance of an ISO environment and segregated compounding areas.</u>	<p>Comment: correction of this technical term</p> <p>Recommendation: Add “classified air” in between the words ISO and ENVIRONMENT.</p>	
1751.3 (a)(7) Line 12 Page 12 of 23	<u>For barrier isolators, documentation of the manufacturer’s recommended purge time.</u>	<p>Comments: The use of a barrier isolator and the purge time is just one element of the proper use of the device and in some cases the purge time is incorporated into the mechanism and use is prevented until the process is completed. Thus documentation of the purge time is not helpful</p> <p>Recommendation: For barrier isolator use, manufacturer standards shall comply with USP<797> guidelines.</p>	
1751.3 Line 4 Page 13 of 23	Class 100 cleanrooms, and barrier isolator workstations	<p>Comment: Old terminology. Not a cleanroom so this is not applicable.</p> <p>Recommendation: Remove “Class 100 cleanroom”</p>	
1751.3(d)(I) Line 12 Page 13 of 23	For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing.	<p>Concern: purpose is to ensure products are being compounded safely. The greatest risk is for non-sterile to sterile product compounding.</p> <p>Recommendation: Add “for non-sterile to sterile compounding.” After “endotoxin testing”</p>	High cost due to unnecessary testing; wasting finished drug product.
1751.4 Line 25 Page 13 of 23	1751.4. Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients].	Comment: This title appears to state that the section below would apply when compounding from non-sterile Ingredients. The language of the section should apply to all sterile compounding activities. This looks like an error.	Operational inefficiency

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		Recommendation: Clarify whether this section would ONLY apply to sterile compounding from non-sterile ingredients.	
1751.4 Line 14 Page 14 of 23	“Cleaning shall include the periodic use of sporicidal agent”	Comment: USP 797 does not use this. Recommendation: Remove the sentence	
1751.4(g) Line 33 Page 14 of 23 Line 1 Page 15 of 23If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area; the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.	Comment: The proposed language does not acknowledge that barrier isolators can provide ISO Class 5 air quality, even when located in a room that does not meet ISO 7 Class 7 conditions. USP <797> describes testing requirements to ensure barrier isolators function reliably in this manner (see USP <797> Section on “Placement of Primary Engineering Controls). This could be an important strategy for preparing CSPs with beyond use dates exceeding 12 hours in medication satellites or in inpatient pharmacies that do not have a dedicated clean room. Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.	Remodeling & construction costs – exceeding \$10 million
1751.5(a)(1) Line 17 Page 15 of 23	Cleanroom garb consisting of a non-shedding gown, head cover, face mask, and shoe covers must be worn inside the designated area at all times.	Comment: This section describes sterile compounding (not compounding hazardous drugs). Face masks are not necessary for non-hazardous sterile compounding. Recommendation: Use this language instead: “Cleanroom garb consisting of a non-shedding gown, head cover, and shoe covers must be worn inside the designated area at all times.”	Operational inefficiency; unnecessary costs of supplies.
1751.5 Line 5 Page 16 of 23	“(6) Individuals experiencing rashes, sunburn, weeping sores, conjunctivitis, active respiratory infections...”	Comment: The goal is to prevent the flaking of skin which could result in contamination of the compounded product. Covering a mild sunburn (which often does not flake) as it heals will prevent the sloughing of skin to the ambient air minimizing the risk of contamination. Inclusion of this section would result in the need to bring in additional staff to replace those employees with mild sunburns.	

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		Recommendation: Add the word “exposed” before sunburn	
1751.6 (E) Line 4 Page 17 of 23	Aseptic preparation procedures <u>using media fill tests which are as complicated as the most complex manipulations performed by staff and which contain the same amount of volume transferred during the compounding process.</u>	Comment: The volume transfers may vary in amount depending upon the final amount to be produced. If the Board wants to mimic every variation in volume possible during the compounding process, the number can be infinite and is not practical. Recommendation: Period after staff and eliminate the rest.	
1751.6 (2) Line 13 Page 17 of 23	Each person assigned to the controlled area <u>who handles compounded sterile drug products</u> must successfully complete.....	Comment: The term “handles” is too broad of a term in that other individuals “handle” the drug products such as nurses, couriers, respiratory care practitioners, physicians, nurse practitioners, Physician Assistants. Most if not all are not involved in the preparations of these products Recommendation: leave verbiage as is.	Training of everyone who “handles” these compounded medications would be an astronomical expense.
1751.7 Line 24 Page 18 of 23	“addition, immediately following the hand hygiene and garbing procedure, all compounding...”	Repeated exposures yield a 3 colony count versus USP797. Initial per USP797 is zero. Recommendation: Add the word “initial” before hand hygiene	
1751.8 (b) Line 3 Page 20 of 23	(b) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1,2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the	Comment: This section appears to have been extracted from the medium-risk category definition in USP <797>. The bolded text appears to have been changed by the Board of Pharmacy subcommittee. The current version of USP <797> specifies a beyond use date for medium-risk level compounded sterile preparations of nine (9) days at controlled cold temperature. Nine days is more appropriate and practical, as it supports the ability of home infusion pharmacies to prepare and distribute weekly supplies of total parenteral nutrition solutions. It should be noted that the original version of USP <797> listed a beyond use date of seven days for medium-risk level CSPs, and changed the BUD to nine days for that reason. Recommendation: Change to nine (9) days at controlled cold temperature.	Operational inefficiency; higher costs for drug delivery to home infusion patients.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
	sterile compounded drug product cannot exceed the following: (1) 30 hours at controlled room temperature (2) 7 days at controlled cold temperature (3) 45 days at controlled freezer temperature		
1751.8 (b) Line 14 Page 20 of 23	“(2) 7 days at controlled cold temperature”	<p>Comment: USP797 utilizes 9 days. Home Care rationale: USP797 BUD of 9 days allows for once weekly deliveries enabling CHC to serve a widespread geographic area and fulfill a need for an underserved population.</p> <p>-TPN set up of BAXA Compounder \$60.00 -Technician 1 hour \$20.00 -Pharmacist 30 minutes \$35.00 -Distribution/Driver \$60.00 -Gas/Vehicle \$25.00 Total \$200.00 per patient Average of 8 patients \$1600.00 per week or \$83,200.00 per year</p> <p>The reduction of Beyond Use Data could also result in Home Care restricting its service area or declining referrals in order to continue to provide service for the existing patients</p> <p>Recommendation: use “9” days at controlled cold temperature</p>	Approximately \$83,200 annually.
1751.8 (c) Line 17 Page 20 of 23	(c) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using nonsterile ingredients, including manufactured products not intended for sterile routes of administration, or nonsterile devices, before terminal sterilization, or where the sterile compounded drug product lacks effective antimicrobial preservatives , in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the	<p>Comment: This section appears to have been extracted from the high-risk category definition in USP <797>. The bolded text appears to have been added by the Board of Pharmacy subcommittee. It appears to say that if sterile ingredients without preservatives are used or if a preservative is not added during aseptic manipulations within an ISO Class 5 hood located in an ISO Class 7 buffer area, then these short beyond use dates would apply. This scenario occurs commonly in hospital pharmacies, and is normally associated with low and medium risk level compounded sterile preparations. It is inappropriate to place this language in a high-risk section.</p>	Unnecessarily short beyond use dating will cause drug waste. Cost impact: exceeding \$1 million/year.

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
	United States Pharmacopeia – National Formulary - (USP36-NF31 through 1st Supplement) (36 th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following: (1) 24 hours at controlled room temperature (2) 3 days at controlled cold temperature (3) 45 days at controlled freezer temperature	The issue of anteroom versus ante area has been previously discussed. Recommendation: Delete the bolded text. Change “anteroom” to “ante area”	
1751.8 (c) Line 19 Page 20 of 23	“anteroom, using non-sterile...”	Comment: The anteroom versus ante area was previously discussed. Recommendation: Change “anteroom” to “ante area”	
1751.8 (d) Line 32 Page 20 of 23	The section addresses sterile preparations compounded in ISO Class 5 hoods not located in ISO Class 7 areas.	Comment: An additional statement needs to be added that if the sterile preparations are compounded in an ISO Class 5 compounding aseptic containment isolator (not located in an ISO Class 7 area), the beyond use date will be the same as if the CACI was located in an ISO Class 7 area. Recommendation: Change language to support longer beyond use dating with the use of barrier isolators, provided that these primary engineering controls maintain ISO Class 5 air quality, and are tested as described in USP <797>.	Unnecessarily short beyond use dating will cause drug waste. Cost impact: potentially significant for facilities with a barrier isolator.
1751.8 Page 20 of 23	Missing language in this section.	Comment: The current proposed regulations do not contain beyond use dating requirements for “immediate use” preparations Recommendation: Add language to be consistent with USP Chapter 797: “The immediate use provision is intended only for those situations where there is a need for immediate administration of a compounded sterile preparation. Preparations that are medium-risk level, high-risk level, or hazardous drug compounded sterile preparations shall not be prepared as immediate-use compounded	Operational inefficiency

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
		sterile preparations. Administration begins not later than 1 hour following the start of the preparation of the compounded sterile preparation. Immediate use preparations are exempt from the requirements of low-risk level preparations and may be compounded in worse than ISO Class 5 conditions.”	
1751.8 (d) Line 3 Page 21 of 23	“...hereby incorporated by reference, the beyond use date shall be 12 hours”	Concern: Current verbiage indicates all products will be 12 hours regardless of the data. Recommendation: Replace “shall be” to “shall not exceed”	
Title 24, Part 2, Chapter 12, 1250.4 (5.1) Line 19 Page 22 of 23	Storage of items not related to the compounding of parenteral solutions	Comment: The term “solution” may be too narrow of a term. The term “sterile products” will encompass a broader variety of dosage forms that may be compounded such as ophthalmics, bronchial and nasal inhalation solutions. Recommendation: change from “solutions” to “sterile products”	
Title 24, Part 2, Chapter 12, 1250.4 (5.1) Line 28 Page 22 of 23	Any pharmacy that compounds sterile drug products must compound the medication in one of the following environments: 5.1 An ISO Class laminar airflow hood within an ISO Class 7 cleanroom. The cleanroom must have positive air pressure differential relative to adjacent areas.	Comment: This language is incomplete. USP <797> articulates a well thought-out description of the sterile compounding environment and engineering controls, based on the input and experience of nationally respected clean room engineers. It is inappropriate to extract a piece of this language and place it in regulations. Recommendation Use of displacement airflow described in USP Chapter 797: “For rooms providing a physical separation through the use of walls, doors, and pass-thrus, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. For buffer areas not physically separated from the ante-areas, the principle of displacement airflow shall be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 ft per minute or more from the buffer area across the line of demarcation into the ante-area.”	Remodeling & construction costs: exceeding \$25 million for our organization.
Title 24, Part 2, Chapter	When compounding hazardous drugs, the surrounding environment must provide at least 0.01	Comment: There needs to be an allowance for a low volume of chemotherapy preparations in biological safety cabinets in clean	Remodeling & construction

Proposed Language Citation # & Page #	Proposed Board of Pharmacy Regulations	Concern and Proposed Text Wording in quotes is proposed language from Kaiser Permanente	Impact
12, 1250.4 (6) Line 8 Page 23 of 23	water column negative air pressure and 12 air changes per hour.	<p>rooms that also contain other types of laminar air flow hoods.</p> <p>Recommendation: Consider a hospital pharmacy in which a low volume of inpatient chemotherapy is prepared, and where the clean room was remodeled following the original 2004 USP <797> standards. It would likely be a single clean room, with an ante area and a buffer area. That remodel probably cost \$1 to \$2 million, depending on the size of the pharmacy. In order to meet the proposed regulation, this clean room would need to be remodeled again to provide a separate anteroom, positive pressure buffer room, and a negative pressure room for preparing hazardous drugs (chemotherapy). This would cost another \$1 to \$2 million. The cost is excessive when weighed against the incremental safety benefits.</p> <p>Instead, we propose the USP <797> language, with a caveat that “low volume” be defined, since that terminology is subjective and not enforceable.</p> <p>“In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable.”</p> <p>We propose this definition: A low volume is defined as less than or equal to a mean number of twenty doses per week, averaged over a period of one month.”</p>	costs: exceeding \$40 million for our organization.
505.5.1 Line 18 Page 23 of 23	In all pharmacies preparing cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag in-bag out design. The pharmacy must ensure that contaminated air plenums that are under positive pressure are leak tight.	<p>Comment: This language is unnecessary. 1751.4(g) already describes the requirements for use of Class II vertical laminar airflow hoods. In addition, 505.5.1 does not mention that a compounding aseptic containment isolator (CACI) can be used for this purpose. The use of a CACI for the preparation of cytotoxic agents is described in 1751.4(g).</p> <p>Recommendation: Delete 505.5.1.</p>	Operational Inefficiency, employee safety

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*Providing Leadership in
Health Policy and Advocacy*

January 10, 2014

California State Board of Pharmacy
Attn: Debbie Damoth, Regulation Manager
1625 N. Market Blvd., Suite N219
Sacramento, CA 95834

VIA ELECTRONIC MAIL AND U.S. MAIL

**RE: Compounding Regulations, Notice of Proposed Action, Articles 4.5 and 7 of
Division 17 of Title 16 of the California Code of Regulations Section 1735 et seq.
and 1751 et seq.**

Dear Ms. Damoth:

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 Articles 4.5 and 7 of Division 17 of Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq. While not part of this regulatory package and review, CHA recommends making amendments to Title 24, Part 2, Chapter 12, 1250.4(5) to be consistent with changes requested in Title 16.

CHA and its member hospitals agree that, in light of the recent national events with sterile compounding pharmacies, public protection along with efficient, effective delivery of pharmaceutical care is of utmost importance. We agree that updating the state compounding regulations to improve overall patient safety is paramount. With most hospitals following USP Chapter 797 guidelines, we urge the board to adopt and codify regulations that are fully aligned with USP Chapter 797 guidelines, including key provisions such as the immediate use provision and hazardous drug compounding which is not present in the draft regulations.

We offer overall and detailed comments to the regulatory changes in support of these overarching principles while balancing protection of the public with efficient and effective interventions to enable all hospitals within the state, large and small, to collectively achieve them. Striving for a balance between public protection and appropriate regulatory changes so as to ensure continued hospital solvency is essential. California hospitals are under extreme financial constraints in a heavily regulated market. Unnecessary facility remodels and upgrades are in many cases cost prohibitive and ASHP reports the least expensive changes required by USP 797 tend to be the most effective in reducing compounding sterile pharmacy contamination and inaccuracy.

Out-of-state compounding pharmacies play a vital role in providing California hospitals with necessary pharmaceuticals. Now, more than ever, they are providing solutions to the ongoing drug shortage dilemma. While recent national events revealed unsafe and hazardous national sterile compounding pharmacy examples, there are many high quality sterile compounding organizations that are fully compliant with USP 797 standards. To raise the bar above USP 797 standards with unique California requirements, may force some to no longer be interested in the California market. This could have unintended consequences for California hospitals who are unable to access critical medications essential for timely patient care.

CHA applauds the board's urgency in putting forth this rulemaking through a six-month emergency formal regulation and rulemaking adoption process. We appreciate the opportunity to participate in regulatory reform that is fair, consistent and balanced with the hospitals' ability to understand the new requirements, perform their gap analysis and successfully be inspected for licensure. At the time of this writing, hospitals are aware they must submit their compounding pharmacy license application as soon as possible. We understand that while the timing of the adoption of the amendments to the articles may reflect new requirements a hospital will need for licensure, there has been no identified process established for hospitals to achieve recommended changes in a timely manner if modified regulatory language is not adopted in time for the July 1, 2014 date. Inability to meet regulatory requirements on yet unknown changes to obtain a sterile compounding license could result in hospital pharmacies being unable to provide essential patient care and risk unnecessary and harmful delays to patient care.

Our recommendations and comments are listed in three sections: I. **Overall Recommendations**, II. **Summary of Detailed Recommendations**, and III. **Comment Grid** with a detailed matrix that defines the regulation section proposed board of Pharmacy language and CHA proposed recommendations.

I. **Overall Recommendations**

A. **Lack of consistency with USP Chapter 797**

1. **Add Additional USP 797 Immediate-Use Provision**

CHA is supportive of the need for changes to Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq. Most hospitals with sterile compounding pharmacies have been operating under USP 797 guidelines and while much of the regulatory language proposed by the board reflects USP 797, essential provisions are not reflected in the draft language. The proposed changes are lacking several key provisions of USP 797 that will assist hospitals in making affordable, safe patient care changes. First, and most importantly, is the **immediate-use provision** that can eliminate unnecessary physical plant facility upgrade costs and prevent untimely patient care in fast-paced treatment areas where construction of a cleanroom (implied without the immediate-use provision) is not feasible, such as emergency departments, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. Compounding in acute care hospitals requires speed and flexibility. Critical

lifesaving medications in acute care hospitals are compounded in environments outside of pharmacies and cleanrooms; for instance, at the patient's bedside.

Without the immediate-use exemption provision, hospitals would be unable to provide IV therapy or life-sustaining medication during a code blue response or other essential patient care therapies requiring compounding within a one-hour or twelve-hour time period.

- a. CHA recommends adding the immediate-use provision with a one-hour beyond use date, as stated in USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood for emergency or immediate patient administration.
 - b. CHA recommends use of an ISO Class 5 hood within a segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom (ante-area and buffer room).
2. **CHA hospitals have successfully compounded cytotoxic or other hazardous agents in non-negative pressure rooms with closed system vial transfer devices. According to USP 797 guidelines, hazardous drug compounding can occur in a non-negative pressure room if using a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or barrier isolator. The ability for hospitals to use this has provided essential patient care to more patients who may otherwise be unable to receive these lifesaving treatments from hospitals due to facility plant space restrictions.**
- a. CHA recommends allowing hospital pharmacies to compound hazardous drugs in non-negative pressure room, such as a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. These recommendations are in full alignment with USP 797 guidelines.
3. **Include USP 797 definitions of "Batch," "Beyond Use Date" and utilize USP 797 definitions within the code sections describing, "certificates of analysis," "accuracy assessment," "documentation requirements," "disinfecting practices," "sterility testing requirements," "continuous temperature recording device" and "cytotoxic agents."**
- a. CHA recommends using USP 797 definitions where applicable and specific detailed recommendations are listed corresponding to each section in the Comment Grid.

B. The sterile compounding pharmacy licensure process should be fair, consistent and achievable for hospitals while leveraging the need for public safety and quality patient care.

1. CHA recommends a clear, detailed process on how the board will license and inspect hospitals to meet the July 1, 2014 deadline. Hospitals understand the need to apply for their compounding license but, absent the new regulatory amendments, they may be held to changes they cannot make in a timely manner. Guidance from the board will be necessary to assure there is no gap in delivery of care to patients receiving compounded medications across the state.
2. CHA recommends that since a compounding self-assessment form must be completed prior to becoming licensed, it is essential that the self-assessment form reflect the approved regulatory amendments. If the projections for this are unlikely to be met, guidance and direction from the board on what self-assessment form to utilize is necessary.

C. Title 24, Part 2, Chapter 12, 1250.4(5) does not include emergency settings or include settings with an ISO Class 5 hood in a segregated sterile compounding area as environments permissible for compounding sterile drug products. This would prevent pharmacists from preparing lifesaving sterile compounding medications. We understand the proposed mechanical code regulations in Title 24 have not yet been released for public comment because they are under the jurisdiction of the California Building Standards Commission and not the office of Administrative Law.

- a. CHA recommends that Title 24, Part 2, Chapter 12, 1250.4(5) be changed to reflect inclusion of the environment that will allow hospitals to perform sterile compounding for emergently needed sterile drug preparations both at the bedside or in settings with an ISO Class 5 hood in a segregated sterile compounding area.
- b. CHA recommends that prior to releasing the proposed mechanical code components for public comment, that the Board of Pharmacy meet with the Office of Statewide Health Planning and Development staff to ensure that there is no conflict between existing 2013 mechanical code requirements and those proposed for this regulatory package.

II. Summary of Detailed Recommendations – A summary of detailed recommendations listed within section III. Comment Grid.

1. **1735(a) Compounding in Licensed Pharmacies; Compounding** (page 1, line 5-6) – *Remove* “by or under the supervision of a licensed pharmacist” to imply that regulations do not apply outside of the licensed pharmacy. This section needs to be amended to allow preparation of emergency sterile compounding drugs outside of the pharmacy itself. This is fully permissible under USP 797 immediate use provision.

2. **1735.1(b) Compounding Definitions; Batch** (page 1, lines 31-33) – *Remove* “means more than one dose of a specific quantity of the drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding”- *replace* with “multiple doses of sterile products combined or pooled to prepare a product that will be administered either to multiple patients or one patient on multiple occasions, or 25 or more units compounded from nonsterile ingredients.” This definition needs to match USP 797 language so that hospital pharmacies can continue to prepare patient doses for the same drug (same drug order) for a certain time frame generally 12 hours or 24 hours at a time. This type of preparation is not considered batch compounding per USP or ASHP definitions
3. **1735.1(c) Compounding Definitions; Beyond Use Date** (page 2, lines 2-3) – *Remove* “means the date after which a compounded drug product should be used.” Replace with “the date or time after which a compounded drug product should not be stored or transported. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond-use date.” The current draft regulation implies that the administration of the drug should not take place after the beyond use date. This definition needs to align with USP 797 to avoid confusion about the duration of the administration or the administration time permitted because of beyond-use dating.
4. **1735.1(i) Compounding Definitions; Parenteral** (page 2, lines 24-25) – *Remove* “means a sterile preparation of drugs for injection through one or more layers of skin “ *replace* with, means a preparation of drugs to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation.” The regulatory definitions should be consistent with the medical definition of “parenteral” and SB294 language, Article 7.5, section 3. 4127(a).
5. **1735.2(d) Compounding Limitations and Requirements; Self-Assessment** (page 4, lines 10-11) – *Remove* the word “written” along with all other references to the word written throughout the regulations.

Multiple occurrence of the word “written” throughout the regulations – *Remove all occurrence of word “written” or “in writing” from all sections within the proposed regulations. This will allow pharmacies to be able to maintain electronic policy and procedures.*

Annotate all sections where “written” occurs:

Sections

1735.2(d),1735.5(a),1751.3(a),1751.3(b),1751.3(c),1751.3(d),1751.3(d)3(1),1751.6(e)(1),1751.6(e)(2),1751.7(a)(3).

6. **1735.2(j) Compounding Limitations and Requirements; Self-Assessment** (page 5, lines 3-6) – No language changes recommended to the amendments, however CHA recommends that the compounding pharmacy self-assessment form be revised simultaneously with the draft regulatory amendments as licensure will depend on meeting the regulations prescribed in the self-assessment form.
7. **1735.3(c) Recordkeeping of Compounded Drug Products** (page 6, lines 8-9) – CHA recommends no language change and requests definitions for chemicals, bulk drug substances and drug products, and, a definition for “reliable” FDA-registered supplier.
8. **1735.3(c) Recordkeeping of Compounded Drug Products** (page 6, lines 9-13) – *Remove* “the pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products. And components used in compounding” – *replace* with “The pharmacy shall acquire and retain certificates of purity or analysis for chemicals and bulk drug substances used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration”. This language aligns with USP 797. FDA approved drugs are produced according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of the drugs beyond FDA approved standards.
9. **1735.4(c) Labeling of Compounded Drug Products** (page 6, lines 29-32) – *Remove* “expiration date” and replace with “beyond use date.” There are multiple occurrences of this throughout the draft regulations. All areas that state “expiration date” need replacement with “beyond use dating”.
10. **1751.3(d)(3)(I) Sterile Compounding Policies and Procedures** (page 13, lines 12-18) – *Remove* “For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing, (j) Sterilization. For non-sterile to sterile compounding, (i) Sterilization, (k) end-product evaluation and testing. (ii) End-product evaluation and testing”, *replace*, “For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and compounding or extending beyond-use dating past specifications from Section 1751.8, (j) for non-sterile to sterile compounding: (i) Sterilization, (ii) End-product evaluation and testing including sterility and bacterial endotoxin testing.” Language needs to be amended for sterility and bacterial endotoxin testing to be done when non-sterile ingredients are used or when extended dating beyond USP 797 storage specifications is desire, and align with USP 797 guidelines for high-risk level and low-risk, medium risk preparations.
11. **1751.4 Facility and Equipment Standards** (page 13 lines 25-26) – *Remove* “from Non-sterile ingredients.” Remove this since the contents do not only pertain to non-sterile ingredients. The title is unclear since it pertains to all sterile compounding.

12. **1751.4(e) Facility and Equipment Standards** (page 14, lines 14-15) – *Remove* “cleaning shall include the periodic use of sporicidal agent.” USP 797 does not require use of a sporicidal cleaning agent but does require careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Sporicidal agents may not be appropriate in all cases.
13. **1751.4(g) Facility and Equipment Standards** (page 14-15, lines 30-33 through page 15, lines 1-3) – *Add to this section 1751.4(g):* “the use of a closed system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable.” Need to align this section with USP 797 guidelines to allow facilities to prepare a low volume of hazardous drugs to utilize CSTD’s within BSC/CACI’s as two-tiers of containment in a non-negative pressure room.
14. **1751.6(e)(2) Training of Sterile Compounding Staff, Patient, and Caregiver** (page 17, lines 13-15) – *Remove* “handles” and replace with “prepares.” Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation or dispensing should not be required to undergo aseptic technique training.
15. **1751.7(e), Sterile Compounding Quality Assurance and Process Validation** (page 18, lines 31-32 through page 19, line 4-6) – *Remove* “Batch-produced sterile drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing...and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing” and replace with “batch-produced sterile drug products compounded from one or more non-sterile ingredients that are exposed longer than 12 hours at 2 to 8 degrees and longer than 6 hours at warmer than 8 degrees before they are sterilized shall meet the sterility test in accordance with methodologies and processes... and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing.” This wording aligns with USP 797 language for end product testing.
16. **1751.8(a) Beyond Use Dating for Sterile Compounded Drug Products** (page 19, lines 22-32 through page 20, line 1) – *Add to 1751.8(a):* “Compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package of sterile products or administration container/device to prepare the drug product. Manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.” Only one of three criteria are included in these regulations. All three criteria need to be added to prevent misinterpretation and the ability for some compounded sterile products to be dated different risk categories and with different beyond-use dating from established USP guidelines.

17. **1751.8(b) Beyond Use Dating for Sterile Compounded Drug Products** (page 20, lines 3-15) – *Add to 1751.8 (b):* “or where the process includes complex aseptic manipulations other than the single-volume transfer, or requires unusually long duration such as that required to complete dissolution or homogenous mixing. This language provides consistency with USP 797 by providing examples of conditions that would qualify a compounded sterile product.
18. **1751.8(b)(3) Beyond Use Dating for Sterile Compounded Drug Products** (page 20, line 14) – *Remove 7 and replace with 9 days at controlled cold temperatures. Change to 9 days to match conditions that correlate with USP 797 Medium-Risk Level.*
19. **1751.8(d) Beyond Use Dating for Sterile Compounded Drug Products** (page 20, lines 32-33 through page 21, lines 1-4) – *Add in:* “that is located in a segregated compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed.” Criteria need to be added to qualify conditions that would meet this beyond-use dating. Without the qualifiers, non-sterile (high-risk level) products could be prepared in an unsafe manner. Regulations need to match USP 797 so that hospitals without the means to construct costly cleanrooms can operate safe operations under ISO Class 5 conditions.
20. **1751.8(e) Beyond Use Dating for Sterile Compounded Drug Products** (page 19, lines 17-32 through page 21, lines 1-4) – *Add (e):* “Where the sterile compounded drug product was compounded solely with aseptic manipulations in conditions worse than ISO Class 5, involving simple transfer using only sterile ingredients and components, the beyond use date shall be one hour. These preparations are limited to situations where there is a need for emergency or immediate patient administration of a compounded sterile product where preparation inside an ISO Class 5 environment would subject the patient to additional risk due to delays in therapy. If administration has not begun within one hour from the start of preparation, the compounded sterile product must be discarded appropriately. The addition of the immediate-use provision, with a one-hour beyond-use date, as per USP Chapter 797 must be incorporated to allow for preparation of sterile compounded products to be prepared outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7.

III. Comment Grid

See the following section for Title 16 board of Pharmacy proposed language and recommendations/comments grid.

Title 16	Proposed Language	Recommendations/Comments
<p>1735 (a) Compounding in Licensed Pharmacies. Page 1, lines 5-6</p>	<p>"Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:...</p>	<p>Remove the reference to activity performed by a pharmacist to clarify that the regulations do not apply outside of the licensed pharmacy. <i>1735 (a) "Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:..."</i></p> <p>We request that 1735(a) be reworded to remove the reference to activity "by or under the supervision of a licensed pharmacist" to be defined as compounding. Stating that compounding includes activity not only occurring within a pharmacy but also performed by a licensed pharmacist would then apply these compounding regulations from 1735 and 1751 to any such activity outside of the pharmacy if done by a pharmacist.</p> <ul style="list-style-type: none"> • 1751(a) requires that any pharmacy engaging in sterile compounding also conform to 1735 et seq. Therefore mixing of IV drips at the patient bedside by a licensed pharmacist during a code blue resuscitation would count as sterile compounding and fall under all requirements from 1735 et seq. and 1751 et seq. • USP Chapter 797 allows for this emergency preparation of sterile compounded drugs under their provision for Immediate-Use. Preparation under stricter conditions (such as within an ISO Class5 hood within a cleanroom) would subject patients to the risk of harm due to delays in therapy. Simple transfer of sterile products is allowed for immediate use in environments worse than Class 5 provided the drug product is administered immediately to a patient, not to begin more than 1 hour following the start of preparation. Emergency drug preparations meet these USP 797 Immediate-Use criteria.
<p>1735.1 (b) Compounding Definitions. Page1, lines 31-33</p>	<p>(b) "Batch" means more than one dose of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.</p>	<p><i>1735.1(b) "Batch" means multiple doses of sterile products combined or pooled to prepare a product that will be administered either to multiple patients or one patient on multiple occasions, or 25 or more units compounded from nonsterile ingredients.</i></p> <ul style="list-style-type: none"> • Batch does not match the USP797 or ASHP use of "batch" in reference to: <ul style="list-style-type: none"> ○ Medium risk compounding: multiple doses of sterile products are combined or pooled to prepare a product that will be administered either to multiple patients (i.e. <i>batching</i> of syringes or large volumes), or one patient on multiple occasions (e.g. preparation for use over several days). ○ High risk compounding: only batches with more than 25 units require additional testing for sterility and endotoxins. • More than one dose is a very small quantity to apply the term "batch" to unless other specific processes apply such as pooling/combining ingredients into multiple doses or using nonsterile ingredients to prepare multiple doses. Hospital pharmacies typically prepare patients' doses for the same drug (same order) at the same time but without pooling/combining ingredients. • Hospital pharmacies typically prepare patient doses for the same drug (same order) for a certain timeframe generally 12 hours (based on 12 hour beyond-use dating) or 24 hours at a time. (e.g. a patient may receive 4-6 doses of a sterile compounded drug in a 24 hour period such as an antibiotic.) This is type of preparation is not considered batch compounding per USP or ASHP definitions.
<p>1735.1 (c) Compounding Definitions. Page 2, lines 2-3</p>	<p>(c) "Beyond use date" means the date after which a compounded drug product should not be used.</p>	<p><i>1735.1 (c) "Beyond use date" means the date or time after which a compounded drug product should not be used stored or transported. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond-use date.</i></p> <ul style="list-style-type: none"> • Does not match USP797 definition of beyond use date: <i>the date or time after which a CSP (compounded sterile product) shall not be stored or</i>

Title 16	Proposed Language	Recommendations/Comments
		<p><i>transported. The date is determined from the date or time the preparation is compounded.</i></p> <ul style="list-style-type: none"> • The current draft regulation definition implies that the administration of the drug should not take place after the beyond use date and within the USP 797 guidelines it states that administration is to begin prior to the beyond-use date. USP797 is concerned only with preparation and storage time prior to administration. USP 797 further states that it does not include limits on times or duration of clinical administration of CSPs although it does note that these properly remain professional concerns of health care personnel for the safety of patients. <p>➤ Recommend amending the definition to adopt the USP797 definition to avoid any confusion or misinterpretation about the duration of administration or administration time permitted because of the beyond use dating.</p>
<p>1735.1(l) Compounding Definitions. Page 2, lines 24-25</p>	<p>(l) "Parenteral" means a sterile preparation of drugs for injection through one or more layers of skin.</p>	<p><i>1735.1(l) "Parenteral" means a sterile preparation of drugs to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation.</i></p> <ul style="list-style-type: none"> • From SB294: Article 7.5, Sec 3. 4127(a) <i>A pharmacy that compounds sterile drug products for injection, administration into the eye, or inhalation shall possess a sterile compounding pharmacy license as provided in this article.</i> • Definition of parenteral is outside of the alimentary canal or taken into the body or administered in a manner other than through the digestive tract, as by intravenous or intramuscular administration. (American Heritage Medical Dictionary) • Parenteral does not mean "sterile" by any definition although sterile preparations are preferred for parenteral administration • Limiting the definition of parenteral to injections through the skin only seems inconsistent with the sterile compounding regulations from 4127(a) that include sterile compounded drugs administered into the eye and by inhalation. Sterile compounded drugs could be given by other parenteral routes, besides injections only (e.g. intravitreal, ophthalmic, inhalation, irrigation) <p>➤ Recommend amending the language to broaden the definition and include other parenteral routes other than injections only.</p>
<p>1735.2(d) Compounding Limitations and Requirements; Self- Assessment. Page 4, lines 10-11</p>	<p>(d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements:</p>	<p><i>1735.2(d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements:</i></p> <ul style="list-style-type: none"> ➤ Remove the word "written" from the master formula record requirement. ➤ Remove multiple occurrence of the word "written" or "in writing" from the following sections: 1735.2(d), 1735.5(a), 1751.3(a), 1751.3(b), 1751.3(c), 1751.3(d), 1751.3(d)3(1), 1751.6(e)(1), 1751.6(e)(2), 1751.7(a)(3) • Many pharmacies prepare and maintain documents in electronic form. • Electronic documents are easily searchable and retrievable.
<p>1735.2 (j) Compounding Limitations and Requirements; Self- Assessment. Page 5, lines 3-6</p>	<p>(j) Prior to allowing any drug product 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 &</p>	<p>1735.2 (j) states that the compounding self-assessment must be completed prior to performing any compounding including sterile compounding (changed from sterile injectable compounding). Also from SB 294 Article 7.5 Sec 5. 4127.1(d)(2) the board must review the completed self-assessment form prior to issuing a sterile compounding license.</p> <p>➤ Recommend that the compounding pharmacy self-assessment form be revised simultaneously with these draft changes in the compounding</p>

Title 16	Proposed Language	Recommendations/Comments
	Hospital Outpatient Pharmacy Compounding Self-Assessment" Form 17M-39 Rev. 02/12.) That form contains a first section applicable to all compounding, and a second section applicable to sterile injectable compounding.	<p>and sterile compounding regulations to reflect the amended laws.</p> <ul style="list-style-type: none"> Licensure will depend on meeting the regulations including providing the board with the completed compounding pharmacy self-assessment. Optimally the self-assessment should match current regulations at the time of review for licensure.
1735.3 (c) Records Recordkeeping of Compounded Drug Products. Page 6, lines 8-9	(c) Chemicals, bulk drug substances, and drug products, and components used to compound drug products shall be obtained from reliable FDA-registered suppliers.	<ul style="list-style-type: none"> Define chemicals, bulk drug substances, and drug products. Define "reliable" FDA-registered supplier.
1735.3 (c) Records Recordkeeping of Compounded Drug Products. Page 6, lines 9-13	(c) ... The pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products, and components used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.	<p><i>1735.3 (c) The pharmacy shall acquire and retain certificates of purity or analysis for chemicals, and bulk drug substances, and drug products used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.</i></p> <ul style="list-style-type: none"> USP797 requires certificates of analysis from suppliers only when nonofficial (nonUSP or NF) ingredients are used. Request background information or evidence that supports the requirement for pharmacies to acquire/retain certificates of purity or analysis for FDA approved drug products. (To explain why the exemption was removed from the regulation) FDA approved sterile drug products used in sterile drug compounding per the manufacturer's approved instructions should not require certificate of analysis acquisition/retention. FDA approved drugs are produced according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of these drugs beyond the FDA approved standards.
1735.4 (c) Labeling of Compounded Drug Products. Page 6, lines 29-32	(c) Drug products compounded into unit-dose containers that are too small or otherwise impractical for full compliance with subdivisions (a) and (b) shall be labeled with at least the name(s) of the active ingredient(s), concentration or strength, volume or weight, pharmacy reference or lot number, and expiration date.	<p><i>1735.4 (c) Drug products compounded into unit-dose containers that are too small or otherwise impractical for full compliance.... shall be labeled with... expiration date beyond-use date.</i></p> <p>Recommend to change "expiration date" to "beyond-use date" to be consistent with other changes utilizing "beyond-use date."</p>
1751.3 Sterile Injectable Compounding Policies and Procedures. Page 13, lines 12-18	(I) For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, and for appropriate documentation, and for sterility and bacterial endotoxin testing. (J) Sterilization. For non-sterile to sterile compounding: (i) Sterilization (K) End-product evaluation and testing. (ii) End-product evaluation and testing.	<p><i>1751.3 (d)(3)(I) For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing for non-sterile to sterile compounding or extending beyond-use dating past specifications from Section 1751.8.</i></p> <p><i>(J) For non-sterile to sterile compounding:</i></p> <p><i>(i) Sterilization</i></p> <p><i>(ii) End-product evaluation and testing including sterility and bacterial endotoxin testing.</i></p> <ul style="list-style-type: none"> Request amending language for sterility and bacterial endotoxin testing to be done when non-sterile ingredients are used or when extended dating beyond USP 797 storage specifications is desired (as in draft section 1751.8). Remove sterility and endotoxin testing verbiage from 1751.3(d)(3)(I) and add it to 1751.3(d)(3)(J) section on non-sterile to sterile compounding: USP797 guidelines require sterility and bacterial endotoxin testing only for high-risk level (i.e. non-sterile to sterile) compounding prepared in groups of more than 25 individual single-dose packages.

Title 16	Proposed Language	Recommendations/Comments
		<ul style="list-style-type: none"> Low-risk and medium-risk preparations would only require sterility testing if extended beyond-use dating was being used per USP 797.
<p>1751.4 Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients]. Page 13, lines 25-26</p>	<p>1751.4. Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients].</p>	<p><i>1751.4 Facility and Equipment Standards for Sterile Compounding [from Non-Sterile Ingredients]</i></p> <p>Request to remove wording from the title "from non-sterile ingredients" since the contents of the section do not pertain to only non-sterile ingredients. This section pertains to all sterile compounding and the title is not clear.</p>
<p>1751.4(e) Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients]. Page 14, line 14-15</p>	<p>...Cleaning shall include the periodic use of a sporicidal agent.</p>	<p><i>1751.4 (e) ...Cleaning shall include the periodic use of a sporicidal agent.</i></p> <ul style="list-style-type: none"> ➤ Recommend removing requirement of a sporicidal cleaning agent. USP797 does not require use of a sporicidal agent. ➤ USP797 does require careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Sporicidal agents may not be appropriate in all cases.
<p>1751.4(g) Facility and Equipment Standards for Sterile Injectable Compounding [from Non-Sterile Ingredients]. Page 14, lines 30-33 through page 15, lines 1-3</p>	<p>(g) Pharmacies preparing sterile cytotoxic agents shall use a biological safety cabinet or compounding aseptic containment isolator that provides an ISO Class 5 environment during dynamic compounding conditions which is maintained in accordance with the manufacturer's recommendations and which is certified every six months. If a compounding aseptic containment isolator meeting the above criteria is located outside of an ISO Class 7 area, the compounding area shall maintain a minimum negative pressure of 0.01-inch water column and have a minimum of 12 air changes per hour.</p>	<p><i>Add to Section 1751.4(g): The use of a closed-system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable.</i></p> <ul style="list-style-type: none"> ➤ Request that this section be further amended to allow sterile compounding of cytotoxic agents in a non-negative pressure room when closed-system vial-transfer devices (CSTDs) are used within a BSC or a CACI in a non-negative pressure room as deemed acceptable per USP797 guidelines (referred to as two-tiers of containment). • USP797 guidelines allow for facilities that prepare a low volume of hazardous drugs to utilize CSTDs within BSC/CACI's as two-tiers of containment in a non-negative pressure room. • Closed-system vial-transfer devices are approved by NIOSH (National Institute for Occupational Safety and Health) guidelines. • FDA created a product code, ONB, specific for closed antineoplastic and hazardous drug reconstitution and transfer system devices that requires data to prove a system is closed for use with hazardous drugs and reduces exposure
<p>1751.6 (e)(2) Training of Sterile Injectable Compounding Staff, Patient, and Caregiver. Page 17, lines 13-15</p>	<p>Each person who handles compounded sterile drug products must successfully complete practical skills training in aseptic technique...</p>	<p><i>1751.6 (e)(2) Each person who handles prepares compounded sterile drug products must successfully complete practical skills training in aseptic technique...</i></p> <ul style="list-style-type: none"> • Recommend changing the wording from "handles" to "prepares" to be more specific • Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation, or dispensing should not be required to undergo aseptic technique training.
<p>1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation. Page 18 Lines 31-32 through Page 19 Lines 4-6</p>	<p>Batch-produced sterile drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing.....and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing.</p>	<p><i>1751.7 (e) Batch-produced sterile drug products compounded from one or more non-sterile ingredients that are exposed longer than 12 hours at 2°-8° and longer than 6 hours at warmer than 8° before they are sterilized shall meet the sterility test in accordance with methodologies and processes.....and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing.</i></p> <ul style="list-style-type: none"> ➤ Recommend using USP 797 language for end product testing of high risk compounded sterile products: ➤ "All high risk level CSP's that are prepared in groups of more than 25 identical individual single -dose packages (eg., ampuls, bags, syringes, vials) or in multiple-dose vials (MDV's) for administration to multiple patients or that are exposed longer than 12 hours at 2°-8° and longer than 6 hours at warmer than 8° before they are sterilized shall meet the sterility test (see Sterility Tests <71> before they are dispensed or

Title 16	Proposed Language	Recommendations/Comments
		<p>administered.....</p> <ul style="list-style-type: none"> ➤ "When high risk level compounded sterile products are dispensed before receiving the results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSP's when there is any evidence of microbial growth in the test specimens."
<p>1751.8(a) Beyond Use Dating for Sterile Compounded Drug Products. Page 19, lines 22-32 through Page 20, line 1</p>	<p>(a) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using only sterile ingredients, products, components, and devices, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following: (1) 48 hours at controlled room temperature (2) 14 days at controlled cold temperature (3) 45 days at controlled freezer temperature</p>	<p><i>Add to 1751.8(a): Compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package of sterile products or administration container/device to prepare the drug product. Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.</i></p> <p><u>General comment on Section 1751.8:</u> This section has adopted the low, medium, and high risk level compounding beyond-use dating and some of the criteria for categorizing the risk level as listed in USP797.</p> <ul style="list-style-type: none"> • Not including all criteria for each category allows for looser interpretation and permits some compounded sterile products to be dated in different risk level categories and with different beyond-use dating from established USP797 guidelines. ➤ Request adding in all 3 criteria (only 1 of 3 is currently in proposed draft language) to qualify compounded sterile products that should have beyond use dating matching USP797 low-risk category. • Without limiting the number and types of transfers during preparation, complex products like TPN with multiple ingredients can be prepared under the board regulations and meet this lower level of beyond use dating wherein under USP797 it would be medium risk (which should align with 1751.8(b)). • USP 797 states: "CSPs compounded under <u>all</u> the following conditions are at a low risk of contamination. Low Risk Conditions 1. The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 or better air quality using only sterile ingredients, products, components, and devices. 2. <i>The compounding involved only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package (e.g. bag, vial) of sterile product or administration container/device to prepare the CSP.</i> 3. <i>Manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing.</i>" (Then the 4th condition is included verbatim in 1751.8(a)(1-3))
<p>1751.8(b)</p>	<p>Criteria matching USP797 Medium-</p>	<p><i>Add to 1751.8 (b):</i></p>

Title 16	Proposed Language	Recommendations/Comments
<p>Beyond Use Dating for Sterile Compounded Drug Products. Page 20, line 3-15</p>	<p>Risk Level compounding and beyond-use dating: Where the sterile compounded drug product was compounded... using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions</p>	<p>, or where the process includes complex aseptic manipulations other than the single-volume transfer, or requires unusually long duration such as that required to complete dissolution or homogenous mixing.</p> <ul style="list-style-type: none"> ➤ Recommend adding in the other two examples of conditions which would qualify a compounded sterile product to be consistent with the beyond-use dating in this section that matches USP797 medium-risk level. <p>USP797 states:</p> <p>“When CSPs are compounded aseptically under low-risk conditions and one or more of the following conditions exists, such CSPs are at a medium risk of contamination.</p> <ol style="list-style-type: none"> 1. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions. 2. The compounding process includes complex aseptic manipulations other than the single-volume transfer. 3. The compounding process requires unusually long duration, such as that required to complete dissolution or homogenous mixing.” <p>(Then the 4th condition is included verbatim in 1751.8(b)(1-3))</p>
<p>1751.8(b)(3) Beyond Use Dating for Sterile Compounded Drug Products. Page 20, line 14</p>	<p>7 days at controlled cold temperatures</p>	<p>1751.8 (b)(3) 7 9 days at controlled cold temperatures.</p> <p>Request changing cold temperature beyond-use date to 9 days to match conditions that correlate with USP797 Medium-Risk Level.</p>
<p>1751.8 (d) Beyond Use Dating for Sterile Compounded Drug Products. Page 20, lines 32-33 through page 21, lines 1-4</p>	<p>Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours.</p>	<p>Add to 1751.8 (d): <i>Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood that is located in a segregated compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013) hereby incorporated by reference, the beyond use date shall be 12 hours</i></p> <ul style="list-style-type: none"> ➤ Recommend adding in criteria to qualify conditions that would meet this beyond-use dating. Without qualifiers non-sterile (high-risk level) products could be prepared in this manner which would be very unsafe. - This section is meant to include the provision from USP797 for Low-Risk Level CSPs with 12-Hour or Less BUD – when an ISO Class 5 hood cannot be located within an ISO Class 7 buffer area. - It does not include the 4 criteria listed in USP797 that need to be met to qualify a sterile compound for this exception to preparation within a cleanroom environment. - Many hospitals without the means to construct costly cleanrooms operate under this provision and meet the USP797 criteria. - Without the criteria, if left as stated above, any compound can be prepared under this regulation and be given a 12-hour beyond use date. It does not stipulate sterile to sterile compounding only nor the requirement of a segregated sterile compounding area. <ul style="list-style-type: none"> ○ Segregated sterile compounding area is defined and discussed in other sections: 1735.1(q), 1751.5(a)(2) • USP797 states that all of the following four criteria must be met in order for compounded sterile products to be prepared inside an ISO Class 5 hood that cannot be located in an ISO 7 buffer room:

Title 16	Proposed Language	Recommendations/Comments
		<ol style="list-style-type: none"> 1. PEC's (Primary engineering controls = LAFW, BSC, CACI, CAI) shall be certified and maintain ISO Class 5 and shall be in a segregated compounding area restricted to sterile compounding activities that minimize the risk of CSP contamination. 2. The segregated compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors or high traffic flow, or that is adjacent to construction sites, warehouses, or food preparation. Note that this list is not intended to be all inclusive. 3. Personnel shall follow the procedures described in <i>Personnel Cleansing and Garbing and Additional Personnel Requirements</i> prior to compounding. Sinks should not be located adjacent to the ISO Class 5 PEC. Sinks should be separated from the immediate area of the ISO Class 5 PEC device. 4. The specifications in <i>Cleaning and Disinfecting the Sterile Compounding Areas, Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures, and Nonviable Environmental Sampling Testing</i> shall be followed as described in the chapter.
<p>1751.8(e) Beyond Use Dating for Sterile Compounded Drug Products. Page 19, lines 17-32 through Page 21, lines 1-4</p>	<p>Lack of immediate-use provision, with a 1 hour beyond-use date, for compounding sterile products outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7 buffer room or cleanroom would cause delays and risk patient harm.</p>	<p><i>Add to 1751.8:</i></p> <p><i>(e) Where the sterile compounded drug product was compounded solely with aseptic manipulations in conditions worse than ISO Class 5, involving simple transfer using only sterile ingredients and components, the beyond use date shall be one hour. These preparations are limited to situations where there is a need for emergency or immediate patient administration of a compounded sterile product where preparation inside an ISO Class 5 environment would subject the patient to additional risk due to delays in therapy. If administration has not begun within one hour from the start of preparation, the compounded sterile product must be discarded appropriately.</i></p> <ul style="list-style-type: none"> ➤ Request addition of immediate-use provision, with a 1 hour beyond-use date, as per USP Chapter 797 to allow for preparation of sterile compounded products to be prepared outside of an ISO Class 5 hood for emergency or immediate patient administration where preparation inside an ISO 5 hood within an ISO 7 buffer room or cleanroom would cause delays and risk patient harm. • Critical medications in hospitals are compounded for emergent situations and direct patient administration including code blues, heart attacks, and strokes, and preparation inside an ISO 5 hood within an ISO 7 buffer room with cleansing and garbing would cause significant delays to patient therapy. • Also at our facilities pharmacists mix or "compound" sterile drug products at the patient bedside during code blues to provide life sustaining intravenous (IV) medication to patients requiring cardiopulmonary resuscitation. <ul style="list-style-type: none"> • Pursuant to section 1751, compounding sterile drug products must conform to section 1735 et seq. Section 1735 (a) defines "compounding" as "occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist". • The practice of pharmacists mixing sterile compounded drugs, at the bedside or outside of ISO Class 5 environments, during emergencies or for direct patient administration, is preferred to drug preparation or mixing performed by nursing or other healthcare staff less familiar with drugs, drug properties, and sterile compounding techniques and guidelines.

Title 16	Proposed Language	Recommendations/Comments
		<p>➤ Without amending the regulations to include immediate-use beyond-use dating, hospital pharmacies would not be able to prepare critical emergency drugs outside of a cleanroom environment and delays in preparation of therapy could cause patient harm.</p> <p>USP797 includes 6 criteria for compounded sterile products to meet in order for the Immediate-Use provision to apply:</p> <ol style="list-style-type: none"> 1. The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers' original containers and not more than two entries into any one container or package (e.g. bag, vial) of sterile infusion solution of administration container/device. For example, antineoplastics shall not be prepared as immediate-use CSPs because they are hazardous drugs. 2. Unless required for the preparation, the compounding procedure is a continuous process not to exceed 1 hour. 3. During preparation, aseptic technique is followed and, if not immediately administered, the finished CSP is under continuous supervision to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other CSPs, and direct contact of outside surfaces. 4. Administration begins not later than 1 hour following the start of the preparation of the CSP. 5. Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the CSP shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour beyond use date and time. 6. If administration has not begun within 1 hour following the start of preparing the CSP, the CSP shall be promptly, properly, and safety discarded.

CHA appreciates the opportunity to respond to these proposed regulations and looks forward to aligning regulations that improve public safety.

Sincerely,

/s/

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



California State Board of Pharmacy
1625 N. Market BLVD N219
Sacramento, CA 95834

Date: January 10th, 2014
To: California State Board of Pharmacy
From: Timothy Lopez, Pharm.D. Pharmacist in Charge, Community Regional Medical Centers
RE: Proposed Board of Pharmacy (BOP) Compounding Regulation Update

Ladies and Gentlemen,

We are pleased to hear that the California State Board of Pharmacy is emphasizing patient safety in sterile compounding; however, we have a few concerns with the proposed regulation change. We have written a summary of our concerns regarding the new proposed regulation and also made sure to attach what we believe would be an appropriate solution to the concern.

Issue #1: 1751.8 (b) (2) Beyond Use Dating for Sterile Compounded Drug Products (page 20, line 14)
"7 days at controlled cold temperatures"

Reason for concern: The proposed dating described above is not consistent with the dating for medium risk products described in USP <797> (USP-36, NF-31). This section in USP <797> states that medium risk products are sterile for 9 days at controlled room temperature and this is how many institutions, including ours, currently practice.

Solution: Change the proposed regulation to "9 days at controlled cold temperatures" to be consistent with USP <797> and current practice.

Issue #2: 1250.4 (5) Sterile Compounding Area (page 22, lines 30-31)
Missing language about principle of displacement airflow

Reason for concern: The current regulation and proposed changes do not allow for buffer zones and ante rooms that are separated by a line of demarcation to follow the principle of displacement airflow described in USP <797> (USP-36, NF-31). This section in USP <797> states that buffer areas not physically separated from ante rooms must have 40 feet per minute or more air velocity from the buffer area across the line of demarcation into the ante area.

Solution: Add to line 31: *or displacement airflow of 40 feet per minute from the buffer area to the ante area.*

Issue #3: 1735.3 (c) Recordkeeping of Compounded Drug Products (page 6, lines 11-13)
"The pharmacy shall acquire and retain certificates of purity or analysis for chemical, bulk drug substances, and drug products used in compounding."

Reason for concern: Certificates of analysis and purity are not readily available for RX legend drugs. They are available for bulk chemicals and drug products and should only be required for these products. This requirement could take up valuable time that our staff would otherwise be using to process recall notices and check for outdates.

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Solution: Restore the following language to the regulation on lines : *Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration.*

Issue #4: 1735.5 (a) Compounding Policies and Procedures (page 7, lines 7-9)

"The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct."

Reason for concern: The pharmacy law usually does not include disciplinary actions within regulations. Those are reserved for disciplinary sections only and this should remain the practice.

Solution: Delete the following language from the regulation on lines 7-9: *The pharmacy shall follow its policies and procedures and failure to follow these policies and procedures shall be deemed unprofessional conduct.*

Issue #5: 1751.3 (I) Sterile Compounding Policies and Procedures (page 13, lines 13-14)

"For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, appropriate documentation, and for sterility and bacterial endotoxin testing."

Reason for concern: USP <797> does not require sterility or bacterial endotoxin testing for products that adhere to the expiration dates in the chapter. These requirements are only for high-risk, non-sterile to sterile compounding or if the facility is using a beyond use date greater than risk level standard. Section 1751.8 describes these two instances and specifies the required sterility testing.

Solution: Delete the following from the regulation on lines 13-14: *and for sterility and bacterial endotoxin testing.*
Add to line 15: For non-sterile to sterile *and extended beyond use dating* compounding:

If there is anything that is not clear on this letter, please reach out to us so we can clarify for you. We look forward to hearing from you.

Sincerely,

Tim Lopez, Pharm.D.
Manager, Department of Pharmacy Services
Community Regional Medical Center
P.O. Box 1232
Fresno, California 93715
(559-459-3828) office
(559-459-6260) fax
(559-488-0592) pager

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Damoth, Debbie@DCA

From: Stephanie Holcomb <SHolcomb@communitymedical.org>
Sent: Monday, January 13, 2014 11:14 AM
To: Damoth, Debbie@DCA
Cc: Timothy Lopez
Subject: Compounding Law Changes - Comments from CRMC Fresno
Attachments: BOP Comment Letter CRMC Fresno - Compounding Law Changes.pdf

Good Morning Debbie,

Attached are comments from our Inpatient Pharmacy Manager. Please let me know if you have any questions.

Have a good week!

Stephanie

Stephanie Holcomb, Pharm.D.
IV Compounding Specialist, Inpatient Pharmacy
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Damoth, Debbie@DCA

From: Michael Moore <graymatter@bak.rr.com>
Sent: Sunday, January 12, 2014 1:05 PM
To: Damoth, Debbie@DCA
Subject: Comments to be reviewed by the board related to sterile product compounding

Ms. Damoth,

I am a pharmacist with nearly two decades of sterile intravenous compounding experience. In my years of practice I have worked directly in compounding these life-saving medications as well as supervising technicians and other pharmacists. Currently, a significant part of my business is focused on consulting other pharmacies in regulatory and safety compliance.

For five years I worked as a pharmacy manager for a national home infusion company that has been on the cutting edge of USP 797 compliance. This company currently, as far as I can determine, already employs ALL of the new, proposed regulatory requirements outlined in sections 1735 and 1751.

With my background established, I would like to make a few comments about the language in the proposed regulations (specifically 1751.8 and 1751.9):

- 1) 1751.8 (a), (b), and (d) all state that the maximum beyond use date respective to their manner of preparation when they are prepared "...in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797..."

What about "WITH" sterility testing? Is there going to be a maximum, or will that be left up to the individual pharmacies with the expectation that they would be able to provide justification for that dating? Should there be a requirement that EVERY batch prepared be tested? If sterility samples are submitted in an attempt to extend the dating, will a pharmacy be able to use product while waiting for the results?

- 2) 1751.8 (b) – describes the environment present at most home infusion pharmacy providers that compound TPN products. It spells out that the maximum BUD for these products without sterility testing will be 30 hours at controlled room temperature, **7 days at controlled cold temperature**, and 45 days at controlled freezer temperature.

A 7 day expiration date for this class of medications is not practical and will result in massive expense associated with provision of care to this patient population. Most medications in home infusion are prepared a week at a time. The maximum expiration dating we can even get for a certain formula of TPN is 9 days. Many patients are not within a practical delivery distance of a pharmacy. Their medications require overnight shipment via UPS or Fed-Ex. With a 7 day BUD, pharmacies will be forced to ship these patients twice weekly without sterility testing; and I do not believe sterility testing would be practical in this situation either. There would be a significant financial impact of carrying out this regulation.

Currently, I believe providers of this category of medications (TPN) are using a 9 day expiration dating. Eric Kastango, an expert in this field, has argued that the BUD for "Medium Risk" medications (including TPN) should be 9 days. The January 15th 2014 *AJHP* (ASHP Guidelines on Compounding Sterile Preparations) also reiterates this 9 day BUD.

- 3) 1751.8 (d) – describes the environment where a medication is prepared in a class 5 hood, but without a class 7 room environment. It assigns a BUD of 12 hours to everything regardless of storage.

I am aware of at least one rural district facility that still does not have a compounding room or a barrier-isolator; they compound low-risk products in a class 5 hood. I am not sure why medication BUDs are restricted to 12 hours regardless of storage conditions. If they follow all the proper aseptic technique and they prepare a single, patient-specific dose of an IV preparation from sterile components, why is there a huge chasm between the BUDs? A product compounded from non-sterile components gets 24 hours at room temperature? In a hospital setting with limited pharmacy services, a 24 hour expiration dating would be more practical, and I do not believe that patient safety would be compromised with the additional 12 hours. Perhaps a second BUD of 24 hours could be included in the regulations for storage under refrigeration.

- 4) 1751.9 – I can appreciate that the idea of a single-dose medication contains no preservative. I would draw your attention to the recent emergent shortage of many injectable products often packaged as single-dose such as the electrolytes like potassium and calcium used for preparation of TPN. If facilities had been forced to comply with the proposed regulations I am CERTAIN that the shortage would have been considerably more severe and patient lives put at significant risk. Pharmacists became very creative in extending the dates of expiration after entering single-dose medication vials. There was fear among pharmacists that they were pushing the envelope of what was safe by using vials beyond a “single-dose”, but there was an even greater fear that their patients could die without them. By mandating something like 1 to 6 hours, we will have no choice. I urge you to consider that this shortage was not a one-time event and is likely to be seen again in some form at some point in the future.

As a general comment, I would say that the dates and times for BUD seem to be fairly arbitrary – 24 hours, 7 days, 14 days, 45 days. I am curious what literature exists that supports these timeframes with hard data. I am reminded of a recent education event I attended where the idea that antibiotics are all prescribed for 7 to 10 days; not 4 or 13 days. As human beings we often desire to have things packaged in ways that make sense to us. Seven days seems normal because we are used to a 7 day week. But that alone should not dictate BUDs. I urge the board to require and publish rationale for the proposed BUDs in order for all clinicians and administrators to understand the reasons for the respective BUD dating.

The literature related to this topic explains that personnel technique is the source for most contamination risks. Those with good technique and a conscientious manner will be far less likely to jeopardize patient care than a careless individual that follows a seemingly arbitrary BUD timeline.

I am happy to answer any questions or address any concerns that might arise from my comments.

Thank you for the board’s consideration of my comments.

Sincerely,

Michael Moore, R.Ph.
10604 Hinderhill Dr.
Bakersfield, CA 93312

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January 13, 2014

Ms. Debbie Damoth
California State Board of Pharmacy
debbie.damoth@dca.ca.gov
Fax (916) 574-8618

Dear Ms. Damoth:

Thank you for the opportunity to comment upon the proposed amendments to the California Code of Regulations as they relate to sterile compounding. I commend the California State Board of Pharmacy for strengthening the sterile compounding regulations in light of the NECC tragedy, but would like clarification on several amendments as well as changes in other amendments. Following are my comments:

§ 1735.1 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations:

1735.1. Compounding Definitions.

Under (m) "Personal protective equipment" clothing and devices are delineated and while head and facial covers and face masks are included, there is no mention of head masks and helmets. Are head masks and helmets to be included under this definition?

Under (q) "Segregated compounding area" the proposed regulations state that this means a designated space, either demarcated area or room, that is restricted to preparing sterile-to-sterile compounded sterile products with a 12-hour or less beyond use date. Such area shall contain a device that provides unidirectional airflow of ISO Class 5 air quality for preparation of compounded sterile products and shall be void of activities and materials that are extraneous to sterile compounding. Does this definition also apply to physician owned infusion centers? (cf. SB 294)

Under (r) "Smoke test" means an analysis of the airflow in the ISO Class 5 hood using a generating device. Please delineate what infusion centers use under this definition.

§ 1735.2 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations:

1735.2. Compounding Limitations and Requirements; Self-Assessment.

Under (c) current regulations cite the Business and Professions Code section 4052(a) (1) when describing a "reasonable quantity" of a compounded drug product. (c)(4) Reads, **does not exceed an amount the pharmacy can reasonably and safely compound.** While a reasonable quantity is defined under the aforementioned B&P Code; the amount a pharmacy can "safely compound" is not. Please define what constitutes the amount of a safely compounded drug product.



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Further, under (g) the proposed amendments delete the words **chemicals and bulk substances** while maintaining the words **drug products and other components used for drug compounding...** Please explain why, in 1735.3 (b) and (c), there appears to be an inconsistency because the deleted terms in 1735.2 (g) are not deleted from 1735.3 (b) and (c), but in the latter **components** is deleted.

§ 1735.3 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations:

1735.3. Recordkeeping of Compounded Drug Products.

Under (c) Certificates of purity or analysis are required and must be matched to the product received. Is there a preference from whom the certificate of purity or analysis should be provided; and how are the sterile compounding pharmacies to authenticate that the certificate is from a valid lab?

§ 1751 in Article 7 of Division 17 of Title 16 of the California Code of Regulations:

Article 7. Sterile ~~Injectable~~ Compounding

1751. Sterile ~~Injectable~~ Compounding; Compounding Area; Self-Assessment.

Under (b) (6) the regulations add Sinks and drains shall not be present in an ISO Class 7 or better cleanroom, in buffer area, nor adjacent to an ISO Class 5 hood in a segregated compounding area. A sink may be located in an anteroom. In my opinion, a sink should be located outside of the anteroom and never located in an anteroom because of the strong potential for mold connected. In addition, in order to reduce the potential for contamination the countertops should be cleaned with acid every evening.

§ 1751.1 in Article 7 of Division 17 of Title 16 of the California Code of Regulations:

1751.1 Sterile ~~Injectable~~ Compounding Recordkeeping Requirements.

Under (b) In addition to the records required by section 1735.3 and subdivision (a), for sterile compounded drug products ~~compounded from one or more non-sterile ingredients~~, the following records must be made and kept by the pharmacy: I assume that this applies now to sterile to sterile compounding? Please clarify.

§ 1751.3 in Article 7 of Division 17 of Title 16 of the California Code of Regulations:

1751.3. Sterile ~~Injectable~~ Compounding Policies and Procedures.

Under (d)(2)(G) I recommend that the instead of Regular Daily cleaning and disinfection schedule for the controlled area and any equipment... that it reads, Regular Clean Daily cleaning and disinfect daily when in use or anticipation of use and disinfection schedule for of the controlled area and any equipment...

§ 1751.7 in Article 7 of Division 17 of Title 16 of the California Code of Regulations:



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1751.7. Sterile ~~Injectable~~ Compounding Quality Assurance and Process Validation

Under (b) where personnel competency validation is amended from at least every twelve months **for sterile to sterile compounding and at least every six months for individuals compounding sterile products from non-sterile ingredients**, please consider consistency by simply amending to at least months for sterile to sterile compounding and the same for non-sterile to sterile compounding. The standard of practice in sterile compounding is six months. Similarly, I suggest that the amended verbiage in 1751.1 (d) is consistent with the above recommendation. That is, that the re-evaluation of garbing and gloving competency occurs at least every six months for personnel compounding sterile to sterile products and for personnel compounding non-sterile to sterile products.

And finally, in (e) there is proposed amended language that requires **[p]roducts submitted for sterility testing are to include preparations from the beginning, middle and end of batch...** This is impractical and inconsistent and should not be amended into the proposed language.

Thank you, again, for the opportunity to comment upon the proposed amendments.

Sincerely,

Arthur C. Whitney, R.Ph.
President and CEO
Advantage Pharmaceuticals
(916) 632-9311



January 13, 2014

Debbie Damoth
California Board of Pharmacy
1625 N. Market Blvd., Suite N219
Sacramento, CA 95834

Dear Mrs. Damoth:

On behalf of our nearly 5,000 pharmacy professional members practicing in a variety of clinical settings across the State, the California Society of Health-System Pharmacists (CSHP) is pleased to comment on the Board's proposed regulatory rulemaking package set forth in Articles 4.5 and 7 of Division 17 of Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq.

In accordance with our mission to "promote wellness, patient safety and optimal use of medications," CSHP has long supported the Board's efforts to ensure the integrity of compounding pharmacy. CSHP supported the Board's 2012 sterile compounding legislation, Senate Bill 294 (Emmerson) as a sensible approach to improving patient safety without becoming onerous to the point where it could inhibit the ability of hospitals to provide care services to patients.

It is with this spirit – ensuring the integrity of compounding pharmacy while also ensuring hospitals can continue to serve their critical public health role - that we approach the proposed compounding regulatory rulemaking package. CSHP supports the work of the California Hospital Association, Kaiser Permanente, Dignity Health, Cedars Sinai, Providence Health and other institutions which have worked hard to craft meaningful recommendations.

In addition, **CSHP strongly urges the Board to separate the regulatory provisions into two domains – outpatient and acute hospitals.** This can be accomplished by either having separately numbered subsections or by placing language in key regulations that explicitly applies to acute hospitals. We believe this is absolutely critical for the following reasons:

1. The treatment of patients in acute care hospitals with compounded sterile products is substantially different from treatment of patients in outpatient (non-acute hospital settings). Patients are usually more acutely ill and less stable. This increases the need for more timely therapy administration with more frequent changes.

2. Because the new regulations will cause many remodeling and structural changes for many hospitals that cannot be accomplished by the date regulations should be adopted. The time to implantation of such changes can be substantially slower for outpatient compounding pharmacies. Separation will allow different effective dates.

CSHP also urges the Board to consider the following recommendations pertaining to Articles 4.5 and 7 of Division 17 of Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq.

A. Lack of consistency with USP Chapter 797

1. Add Additional USP 797 Immediate-Use Provision

CSHP is supportive of the need for changes to Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq. Most hospitals with CSP have been operating under USP 797 guidelines and while much of the regulatory language proposed by the Board reflects USP 797, essential provisions are not reflected in the draft language. The proposed changes are lacking several key provisions of USP 797 that will assist hospitals in making affordable, safe patient care changes. First, and most importantly, is the **immediate-use provision** that can eliminate unnecessary physical plant facility upgrade costs and prevent untimely patient care in fast-paced treatment areas where construction of a cleanroom (implied without the immediate-use provision) is not feasible, such as emergency departments, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. Compounding in acute care hospitals requires speed and flexibility. Critical lifesaving medications in acute care hospitals are compounded in environments outside of pharmacies and cleanrooms; for instance, at the patient's bedside.

Without the immediate-use exemption provision, hospitals would be unable to provide IV therapy or life-sustaining medication during a code blue response or other essential patient care therapies requiring compounding within a one-hour or twelve-hour time period.

- a. CSHP recommends adding the immediate-use provision with a one-hour beyond use date, as stated in USP 797 to allow preparation of sterile compounded products outside of an ISO Class 5 hood and segregated compounding area for emergency or immediate patient administration.
 - b. CSHP recommends use of only an ISO Class 5 hood within a specified, non-segregated compounding area with a 12-hour beyond-use date for any hospital or facility currently compounding drugs safely without a cleanroom, ante-area or buffer room.
- 2. California hospitals have successfully compounded cytotoxic or other hazardous agents in non-negative pressure rooms with closed system vial transfer devices. According to USP 797 guidelines, hazardous drug compounding can occur in a non-negative pressure room if using a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or barrier isolator. The ability for hospitals to use this has provided essential patient care to**

more patients who may otherwise be unable to receive these lifesaving treatments from hospitals due to facility plant space restrictions.

- a. CSHP recommends allowing hospital pharmacies to compound hazardous drugs in non-negative pressure room, such as a closed system vial-transfer device within an ISO Class 5 biological safety cabinet or containment isolator. These recommendations are in full alignment with USP 797 guidelines.

3. Regarding definitions of "Batch," "Beyond Use Date" and utilization of USP 797 definitions within the code sections describing, "certificates of analysis," "accuracy assessment," "documentation requirements," "disinfecting practices," "sterility testing requirements," "continuous temperature recording device" and "cytotoxic agents."

- a. CSHP recommends only using USP 797 "batch" definition for non-sterile to sterile compounded sterile products where there is enough time between compounding and administration for receiving test results. For other definitions, CSHP recommends utilizing USP 797 definitions as well.

B. The CSP Licensure process should be fair, consistent and achievable for hospitals while leveraging the need for public safety and quality patient care.

1. CSHP recommends a clear, detailed process on how the Board will license and inspect hospitals to meet the July 1, 2014 deadline. Hospitals understand the need to apply for their compounding license but, absent the new regulatory amendments, they may be held to changes they cannot make in a timely manner. Guidance from the Board will be necessary to assure there is no gap in delivery of care to patients receiving compounded medications across the state.
2. CSHP recommends that since a compounding self-assessment form must be completed prior to becoming licensed, it is essential that the self-assessment form reflect the approved regulatory amendments. If production of a compounded sterile products self-assessment form will not be ready by July 1, 2014, guidance and direction from the Board on what self-assessment form to utilize is necessary.

C. Title 24, Part 2, Chapter 12, 1250.4(5) does not include emergency settings or include settings with an ISO Class 5 hood in a segregated sterile compounding area as environments permissible for compounding sterile drug products. This would prevent pharmacists from preparing lifesaving sterile compounding medications. We understand the Title 24 section will be handled through the Building Standards Commission. We are adding our comments here to reinforce the need to amend these regulations.

- a. CSHP recommends that Title 24, Part 2, Chapter 12, 1250.4(5) be changed to reflect inclusion of the environment that will allow hospitals to perform sterile compounding for emergently needed sterile drug preparations both at the bedside or in settings with an ISO Class 5 hood in a specified sterile compounding area.

Other Recommendations:

1. **1735(a) Compounding in Licensed Pharmacies, (Page 1, line 5-6), "Compounding"** - *remove* " by or under the supervision of a licensed pharmacist" as the regulations should not apply outside of the licensed pharmacy. This section needs to be amended to allow preparation of emergency sterile compounding drugs outside of the pharmacy itself. This is fully permissible under USP 797 immediate use provision.

2. **1735.1(c) Compounding Definitions, Page 2, lines 2-3,"Beyond Use Date"** - *remove* " means the date after which a compounded drug product should not be used" - *replace with* " the date or time after which administration of the compounded drug product should not be initiated. The date is determined from the date or time the preparation is compounded. Administration of the drug product must be initiated prior to the beyond-use date." The current draft regulation implies that the administration of the drug should not continue after the beyond use date. This definition needs to align with USP 797 to avoid confusion about the duration of the administration or the administration time permitted because of beyond-use dating.

3. **1735.1(l) Compounding Definitions, page 2, lines 24-25,"Parenteral"**- *remove* " means a sterile preparation of drugs for injection through one or more layers of skin" *replace with,* means a preparation of drugs to be administered in a manner other than through the digestive tract. This includes, but is not limited to, injection through one or more layers of skin, administration into the eye and by inhalation". The regulatory definitions should be consistent with the medical definition of "parenteral" and SB294 language, Article 7.5, section 3. 4127(a). Otherwise the proposed definition is in conflict with B&P statutory language.

4. **1735.2 Compounding Limitations and Requirements; Page 4, lines 10-11, "Self-Assessment"**- *remove* the word "written" along with all other references to the word written throughout the regulations.

Multiple occurrence of the word "written" throughout the regulations – remove all occurrence of word "written" or "in writing" from all sections within the proposed regulations. This will allow pharmacies to be able to maintain electronic policy and procedures.

Annotate all sections where "written" occurs:

Sections:

1735.2(d),1735.5(a),1751.3(a),1751.3(b),1751.3(c),1751.3(d),1751.3(d)3(1),1751.6(e)(1),1751.6(e)(2),1751.7(a)(3)

5. **1735.2(j) Compounding Limitations and Requirements; Page 5, lines 3-6, "Self-Assessment"**- no language changes recommended to the amendments, however CSHP recommends that the compounding pharmacy self-assessment form be revised simultaneously with the regulatory

amendments as licensure will depend on meeting the regulations prescribed in the self-assessment form.

6. **1735.3(c), page 6 lines 8-9- "Record Keeping"** - CSHP recommends a language change using chemicals, bulk drug substances and drug products; "reliable" suppliers, not FDA-registered supplies. Some compounding components are not supplied by FDA "registered" suppliers – eg, sugar.
7. **1735.3(c) page 6, lines 9-13- "Record Keeping"** - *remove*, "the pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products. And components used in compounding" - *replace* with, "The pharmacy shall acquire and retain certificates of purity or analysis for chemicals and bulk drug substances used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration". This language aligns with USP 797. FDA approved drugs are produced according to established GMP good manufacturing practices and USP/NF guidelines. Requiring pharmacies to obtain these certificates of purity or analysis does not enhance the safety of the drugs beyond FDA approved standards.
8. **1735.4(c) –page 6, lines 29-32, "Labeling of Compounded Drug Products"** - *remove* "expiration date" –replace with "beyond use date" - multiple occurrences of this throughout the draft regulations. All areas that state "expiration date" need replacement with "beyond use dating".
9. **1751.4, page 14-15, lines 30-33 and lines 1-3, Facility and Equipment Standards.** Add to this section 1751.4(g), "the use of a closed system vial-transfer device within the ISO Class 5 barrier isolator or compounding aseptic containment isolator located in a non-negative pressure room is acceptable". Need to align this section with USP 797 guidelines to allow facilities to prepare a low volume of hazardous drugs to utilize CSTD's within BSC/CACI's as two-tiers of containment in a non-negative pressure room.
10. **1751.69e)(2), page 17, lines 13-15, "Training"**- *remove* "handles"- *replace* with "prepares" Personnel who do not perform compounding but transport or handle compounded sterile drug products for restocking, transportation or dispensing should not be required to undergo aseptic technique training.

Founded in 1962, CSHP represents nearly 5,000 pharmacists, student pharmacists, pharmacy technicians and associates who serve patients and the public through the promotion of wellness, patient safety and optimal use of medications. CSHP members practice in a variety of organized healthcare settings – including, but not limited to, hospitals, integrated healthcare systems, medication therapy management clinics, home healthcare and ambulatory care settings.

Sincerely,

A handwritten signature in black ink, appearing to read "Dawn Benton". The signature is fluid and cursive, with the first letter "D" being particularly large and stylized.

Dawn Benton, MBA
Executive Vice President & CEO

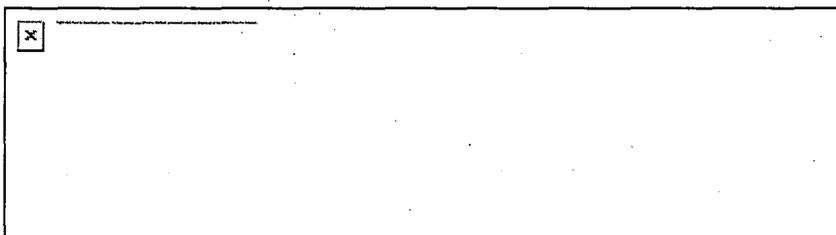
Damoth, Debbie@DCA

From: Jonathan Nelson <jonathan@cshp.org>
Sent: Monday, January 13, 2014 3:37 PM
To: Damoth, Debbie@DCA
Subject: Board of Pharmacy Rulemaking - Compounding Regulations - Comments Letter Attached
Attachments: CSHP Comments - BOP Compounding Regulatory Package - Final.pdf

Good Afternoon:

Please find the attached letter. Please let me know if you have any questions.

Best,





californiapharmacistsassociation

January 13, 2014

California State Board of Pharmacy
Attn: Debbie Damoth
1625 N. Market Blvd., N-219
Sacramento, CA 95834

VIA EMAIL to Debbie.Damoth@dca.ca.gov

Re: Written Comments on Proposed Regulations Relating to Sterile Compounding

Dear Ms. Damoth:

Thank you for the opportunity to submit written comments to the Board of Pharmacy's (Board) proposed regulations to amend Sections 1735, 1735.1, 1735.2, 1735.3, 1735.5, 1751, 1751.1, 1751.2, 1751.3, 1751.4, 1751.5, 1751.6, 1751.7, 1751.8, 1751.9, 1751.10, 1751.11, and 1751.12 of, and add Section 1751.9 to, Division 17 of Title 16 of the California Code of Regulations.

The California Pharmacists Association (CPhA) supports standards to ensure the safety of compounded drug products. As we all learned from the tragedy with the New England Compounding Center and other out-of-state facilities, sterile compounding requires specific safety regulations above and beyond what is required of non-sterile compounding. These standards should apply to all sterile compounders, including those located within California as well as compounding facilities that ship into California.

The attached comments are consistent with the intent of the proposed regulations released by the Board. We share the goal of providing the safest possible products to our patients. Overall, we thank the Board for the progress made towards greater consistency with Chapter 797 of the United States Pharmacopeia. Our comments generally call for greater consistency with this national standard.

Thank you again for the opportunity to provide written comments on this important rulemaking package. If you have any questions, please do not hesitate to contact me at (916) 779-4517.

Sincerely,

A handwritten signature in black ink, appearing to read 'Brian Warren'.

Brian Warren
Vice President, Center for Advocacy

**California Pharmacists Association
Written Comments**

Note: where specific modifications are recommended in the below written comments, the Board's proposed changes are indicated in underline for inserted text and ~~strikeout~~ for deleted text. Our proposed modifications to the Board's proposed changes are indicated in **bold double underline** for inserted text and ~~**bold double underline**~~ for deleted text.

Comment 1: Section 1735.1 (b), Definition of "Batch"

The proposed definition of "batch" in Section 1735.1 (b) should be changed to make it consistent with Chapter 797 of the United States Pharmacopeia (USP). As currently written, the definition is overly restrictive and will harm patient access to compounded drugs because requiring sterility testing for every batch, as proposed, will cause enormous increases in drug costs without a known benefit to safety.

CPhA appreciates the efforts that the Board took in drafting these proposed regulations for consistency with Chapter 797 of the United States Pharmacopeia (USP). We recognize that the Board should not abandon its authority or responsibility for regulating the pharmacy profession by automatically deferring to an external standard or convention. However, USP represents a national professional standard. Where possible, the Board should strive for consistency with USP so as to allow for continuity in professional standards. The Board acknowledges the importance of consistency with USP throughout the Notice of Proposed Action and Initial Statement of Reasons for this rulemaking package.

USP <797> does not require sterility testing of preparations of 25 or fewer doses. Defining "batch" as more than one dose unnecessarily places stricter sterility testing requirements on smaller preparations of compounded drugs. These requirements will increase the cost of preparing smaller preparations, making them less affordable for consumers. The stricter sterility testing requirements of batches of 25 or more doses are not necessary for smaller preparations because relying on end-product testing of randomized samples from a batch is an inferior method of ensuring quality, as compared to focusing on process validation. If the goal is to ensure the highest standards of quality and safety of sterile compounded drug products, then those promulgated regulations tailored to achieve this goal should directly promote those activities that best directly ensure attainment of the same.

As such, we recommend the following modification to Section 1735.1 (b):

(b) "Batch" means more than **25 doses** ~~one dose~~ of a specific quantity of drug or other material that is intended to have uniform character and quality and is produced during the same continuous cycle of compounding.

Comment 2: Section 1735.1 (n), Definition of "Potency"

The definition of "potency" in Section 1735.1 (n) should be updated for better consistency with USP. Although the Board's proposed regulations do not currently amend this existing definition, we believe this change is consistent with the overall intent of the rulemaking.

There are times where USP may define potency for a product as an active ingredient strength of greater or less than 10% of the labeled amount. Because a USP monograph represents the official standard for drug substances and is a known, citable source, deference to USP monographs should be given in regulation.

As such, we recommend the following modification to Section 1735.1 (n):

(n) "Potency" means active ingredient strength within +/- 10% of the labeled amount, or as otherwise indicated by a USP monograph.

Comment 3: Section 1735.3 (c), Certificates of Purity

The proposed changes to Section 1735.3, relating to recordkeeping, among other things, require suppliers of chemicals, bulk drug substances, and drug products to be FDA-registered, and strike an existing provision in subsection (c) that states "certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration." We believe that this sentence should not be stricken from subsection (c).

The Board states that this change is necessary to "ensure that the supplier of drug products are adequately regulated by the Food and Drug Administration (FDA) and addressed the problem of the integrity of the purchased drug products by compounders providing compounded drug products to California consumers," and to "ensure a consolidated record for a compounded drug product that may have multiple ingredients from multiple FDA-registered suppliers."

For drug products approved by the FDA, the FDA is the regulator of those products and responsible for ensuring that manufacturers ensure their products meet specification.

As such, we recommend the following modification to Section 1735.3 (c):

(c) Chemicals, bulk drug substances, and drug products, and components used to compound drug products shall be obtained from reliable FDA-registered suppliers. The pharmacy shall acquire and retain any available certificates of purity or analysis for chemicals, bulk drug substances, and drug products, and components used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. Certificates of purity or analysis are to be matched to the product received.

Comment 4: Section 1735.3 (d), Beyond Use Dates for Products with No Supplier's Expiration Date

The proposed regulations add a new subsection (d) to Section 1735.3, which would mandate a beyond use date of one year for all packages of ingredients that lack a supplier's expiration date. We believe this requirement is insufficient in that it groups active and inactive ingredients together. We propose different standards for active and non-active ingredients. When no supplier's expiration date exists, active ingredients should not be used beyond one year from receipt and inactive ingredients should not be used beyond three years from receipt.

As such, we recommend the following modification to Section 1735.3 (d):

(d) After receipt by the pharmacy, packages of ingredients that lack a supplier's expiration date cannot be used after one (1) year for active ingredients or three (3) years for inactive ingredients, unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in compounded drug products.

Comment 5: Section 1735.5 (c)(7) and Section 1751.1 (a)(4), Documentation of Temperature Readings

The proposed regulations add a new required area to the policies and procedures that compounding pharmacies must maintain. The proposed Section 1735.5 (c)(7) would require compounding pharmacies to have policies and procedures on the storage of compounded sterile drug products and daily documentation of room, refrigerator, and freezer temperatures. Additionally, the proposed regulations add to the specific recordkeeping requirements imposed on sterile compounding pharmacies. The proposed Section 1751.1(a)(4) would require daily documentation of room, refrigerator, and freezer temperatures. We suggest some modifications to the changes proposed in these two sections.

First, we suggest modifying Section 1735.5 (c)(7) by striking the word "daily" from the documentation schedule. The requirement in this paragraph is intended to require policies and procedures for recordkeeping be in place, not to impose a specific recordkeeping requirement. The specific recordkeeping requirements are included in proposed Section 1751.1(a)(4), which is the appropriate location.

As such, we recommend the following modification to Section 1735.5 (c)(7):

(7) The storage of compounded sterile drug products in the pharmacy and ~~daily~~ documentation of room, refrigerator, and freezer temperatures.

Second, we suggest a slight modification to the specific recordkeeping requirement in Section 1751.1(a)(4) to reflect the fact that some compounding pharmacies are not open daily (i.e., every calendar day). Our recommended modification would clarify that documentation is only required to be recorded on days that the pharmacy is operating. This clarification is consistent with the spirit of the proposed regulation.

As such, we recommend the following modification to Section 1751.1(a)(4):

(2) (4) ~~Daily~~ Documentation of room, R-refrigerator, and freezer temperatures appropriate for drug preparations consistent with the temperatures listed in section 1735.1, **performed on a daily basis for each day the pharmacy is operating**, for:-

- (A) Controlled room temperature.
- (B) Controlled cold temperature.
- (C) Controlled freezer temperature.

Comment 6: Section 1751.1 (a)(6), Logs of Pressure Differentials

The proposed regulations add to recordkeeping requirements imposed on sterile compounding pharmacies. Proposed Section 1751.1 (a)(6) would require sterile compounding pharmacies to have logs of room pressure differentials. To provide clarity to this requirement, we suggest modifying this paragraph by naming the areas that the pressure differentials must apply to (i.e., "buffer to anteroom or cleanroom to anteroom," and "anteroom to general").

Additionally, we recommend that the Board adopt a standard for the pressure differentials via regulation. For consistency with USP <797>, we recommend a minimum differential positive pressure of 0.02 inAq.

As such, we recommend the following modification to Section 1751.1 (a)(6):

(6) Logs of room pressure differentials between the buffer area and the anteroom or the cleanroom and the anteroom, and between the anteroom and general pharmacy area. A minimum differential positive pressure of 0.02 inch water column (inAq) shall be maintained.

Comment 7: Section 1751.4 (e), Sterile Compounding Facility Cleaning Requirements

The proposed regulations amend the cleaning and disinfection requirements applicable to sterile compounding facilities. The requirements specify that cleaning shall be done at certain intervals (e.g., daily). We suggest modifying section 1751.4 (e) to clarify that these requirements are minimum standards and that cleaning can occur more frequently.

As such, we recommend the following modification to Section 1751.4 (e):

~~(d)-(e) Exterior workbench surfaces and other hard surfaces in the designated area, such as walls, floors, ceilings, shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination. Counters, cleanable work surfaces and floors shall be cleaned and disinfected daily. Walls, ceiling, storage shelving, tables and stools are to be cleaned and disinfected monthly. Cleaning shall occur after any unanticipated event that could increase the risk of contamination. Cleaning shall include the periodic use of a sporicidal agent. The cleaning requirements specified in this subsection are intended to establish minimum standards and shall not be interpreted to prevent cleaning at more frequent intervals.~~

Comment 8: Section 1751.5 (a)(3), Use of Alcohol Antiseptic

The proposed regulations amend existing standards for cleanroom garb, cleansing, and personal protective equipment in Section 1751.5. We suggest a slight modification to paragraph (3) of subsection (a). That paragraph contains a standard that "cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves must occur within the buffer area, not prior to entering." We suggest adding the word "waterless" to the term "alcohol-based product." The word "cleansing" could be interpreted to mean cleansing using water, and addition of the word "waterless" will help avoid any confusion regarding the cleansing process.

As such, we recommend the following modification to Section 1751.5 (a) (3):

(3) Personnel shall don personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water and then the donning of a non-shedding gown. Cleansing with a persistently active waterless alcohol-based product followed by the donning of sterile gloves must occur within the buffer area, not prior to entering. Gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol after contact with non-sterile objects.

Comment 9: Barrier Isolator Hoods

Barrier isolator hoods are considered to be a self-contained cleanroom and as such usually do not have preparation and anterooms consistent with cleanrooms. Given the unique nature and prolific use in hospital pharmacies of barrier isolator hoods, we believe the regulations should clarify differences in cleaning and garbing.

As such, we recommend the following modification to Section 1751.5:

(c) The requirements of subdivision (a) and (b) shall not apply if a barrier isolator is used to compound sterile products from one or more non-sterile ingredients, except when cleaning the barrier isolator or at any time the barrier isolator hood is open and as such breaks positive air flow rendering an ISO 5 environment.

Comment 10: 1751.7 (e), Sterility Testing of Batch-Produced Sterile Drug Products

The proposed regulations amend existing standards for sterile compounding quality assurance and process validation. In particular, Section 1751.7 (e) mandates that products submitted for sterility testing include preparations from the beginning, middle, and end of each batch. We suggest a few modifications to this subsection.

First, where the draft regulation would require sterility testing at the beginning, middle, and end of each batch, we suggest a modification to have sterility testing apply to the finished preparation. No evidence shows that testing each ingredient that is part of a finished preparation increases the likelihood of sterility or increases patient safety. Sterility testing conducted at the beginning, middle, and end of each batch only increases the cost of sterile compounding, without any clear consumer benefit.

If the goal is to ensure the highest standards of quality and safety of sterile compounded drug products, then those promulgated regulations tailored to achieve this goal should directly promote those activities that best directly ensure attainment of the same. Industry best practices recommended by the federal Food and Drug Administration call for personnel and process validation as the key components to ensuring patient sterility. These best practices call for finished preparation testing as a means of verifying personnel and process validation.

Second, the wording of the requirement could be misinterpreted, as it is unclear whether sterility testing requirements are intended to apply to both active and inactive ingredients that are part of the finished preparation or to the various solutions resulting from manipulation during the compounding of the finished preparation. We recommend referring to "active ingredients"

As such, we recommend the following modification to Section 1751.7 (e):

(e) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include finished preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any active ingredient or combination of active ingredients that were previously non-sterile outside of the Beyond-Use-Dating guidelines in USP <797> or autoclaved as the terminal sterilization process.

Comment 11: Section 1751.8, Beyond Use Dating for Sterile Compounded Drug Products

The proposed regulations amend existing Section 1571.8, inserting entirely new text to establish minimum requirements for beyond use dating for sterile compounded drug products. The requirements are based on the standards contained in USP <797>.

We are supportive of consistency between USP <797> and California regulations, and the Board's proposed regulations make much progress toward this goal. This consistency helps prevent conflict between a nationally recognized professional standard and the state's legal practice requirements. However, it is important to note that there is a difference between a standard and a rule. Whereas a standard such as those contained in USP <797> represents a generally accepted model, a rule established by the Board is a specific requirement with the force of law. A professional standard should be followed in most cases, but a rule is strictly enforced in every instance. Regulations based on standards need to be written with this in mind. The standards in USP <797> should guide the Board's regulations, but cannot always be verbatim copied into a regulation.

The standards for beyond use dating are an area where regulatory language should reflect that exceptions to the model do exist. USP <797> standards should generally be followed, but there are times where these standards are not applicable. Some products should be given a shorter beyond use date than the general standard and some products can safely be given a longer beyond use date.

We suggest modifying the proposed regulation to allow for exceptions to the beyond use dating formula when a different standard is provided for in scientific literature or specified by the manufacturer. This would not result in a different standard, but would ensure that the USP <797> standards applying to all

sterile compounding, except when specific information justifies operating outside of the general standard.

As such, we recommend the following modification to Section 1751.8:

1751.8. Beyond Use Dating for Sterile Compounded Drug Products.

In addition to the requirements and limitations of section 1735.2, subdivision (h), every sterile compounded drug product shall be given and labeled with a beyond use date as follows, unless otherwise provided for in scientific literature or specified by the manufacturer.

...

Comment 12: Section 1751.9 (a)(1), Time Limitations on Use of Opened Containers

The proposed regulations add a new Section 1571.9, establishing limitations on use for opened or needle-punctured sterile drug products and compounded sterile products in single-dose and multiple-dose containers. These limitations are based on the standards contained in USP <797>.

As stated above, we support consistency between USP <797> and California regulations but stress that because the Board's regulations have the force of law the regulatory language often needs to be written slightly differently than USP <797>.

The standards for use of opened or needle-punctured single-dose and multiple-dose containers are another area where regulatory language should reflect that exceptions to the model do exist. USP <797> standards should generally be followed, but there are times where these standards are not applicable. It is possible that some products should be discarded sooner than provided for in the standard and others may be safe to use for a period longer than provided for in the standard.

The proposed regulation already includes an exception for multi-use containers when a manufacturer specifies a use date of longer than the general standard (in subsection (c) of Section 1751.9). We suggest modifying the proposed regulation to add the text "unless otherwise provided for in scientific literature or specified by the manufacturer," applicable to subsections (a), (b), and (c). This would not result in a different standard, but would result in the USP <797> standards applying to all sterile compounding, except when specific information justifies operating outside of the general standard.

As such, we recommend the following modification to Section 1751.9:

1751.9 Single-Dose and Multi-Dose Containers; Limitations on Use

Unless otherwise provided for in scientific literature or specified by the manufacturer, the following limitations on use shall apply:

(a) Any single-dose container of sterile drug product or compounded sterile drug product other than an ampule, such as a bag, bottle, syringe or vial, shall be used in its entirety or its remaining contents discarded within the following time limit, depending on the environment:

(1) When opened or needle-punctured in an environment with air quality worse than ISO Class 5, within one (1) hour;

(2) When opened or needle-punctured in an environment with ISO Class 5 or better air quality, within six (6) hours.

(b) Single-dose ampules are for immediate use only, and once opened or needle-punctured shall not be stored for any time period.

(c) ~~Unless otherwise specified by the manufacturer, a~~ A multi-dose container shall be used in its entirety or its remaining contents discarded within twenty eight (28) days from initial opening or puncture.



Michael A. Moné

Vice President – Associate General Counsel

Regulatory Affairs

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January 13, 2014

Debbie Damoth
California Board of Pharmacy
1625 N. Market Blvd., N219
Sacramento, CA 95834
Debbie.Damoth@dca.ca.gov

RE: Comments on Proposed Amendments to Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations

Dear Ms. Damoth:

Cardinal Health Nuclear Pharmacy Services appreciates this opportunity to provide public comments on the proposals by the California Board of Pharmacy to amend sections of Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations. Cardinal Health Nuclear Pharmacy Services operates eleven nuclear pharmacies in California, dispensing approximately 85,000 patient doses of diagnostic and therapeutic radiopharmaceuticals every month. Cardinal Health Nuclear Pharmacy Services has 254 employees in California of which 39 are pharmacists, accounting for approximately \$16 million dollars in salary paid.

Cardinal Health Nuclear Pharmacy Services believes that special consideration for nuclear pharmacy preparation of radiopharmaceuticals should be considered by the Board. At the outset of this discussion is a recognition that the preparation and the very nature of radiopharmaceuticals, among others: an extremely short half-life; the regulation of the preparation of radiopharmaceuticals by the California Board of Pharmacy, the California Radiologic Health Branch and the Nuclear Regulatory Commission; and the unique relationship between the prescribing practitioner and the nuclear pharmacist that prepares the prescription, are such that special consideration is warranted.

As proposed the changes to amend sections of Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations creates significant complications for the operation of nuclear pharmacies in California. Cardinal Health Nuclear Pharmacy Services proposes either:

1. The adoption of the proposed changes in language contained in this response, or
2. The adoption of a statement by the Board of Pharmacy that these changes do not apply to nuclear pharmacy and the establishment of a Task Force to draft nuclear pharmacy specific regulations for the preparation of radiopharmaceuticals. Should

the Board decide to establish such a Task Force, we would welcome that and offer our support and participation on that Task Force.

In response to the proposed amendments to sections of Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations, we make the following suggestions:

Issue 1

- Where the Board proposes to amend 16 CCR §1735.1 the Board states “The purpose of the board’s proposal to add subdivision (e) is to add a definition of “cleanroom” for purposes of compounding drug products. The definition clarifies and specifies “cleanroom” as a separate room meeting an ISO Class 7 or better air quality.”

1735.1. Compounding Definitions.

(e) “Cleanroom” means a separate room meeting an ISO Class 7 or better air quality.

Comment 1

The Board’s proposal to add a definition of “cleanroom” has substantial impacts upon the preparation of radiopharmaceuticals and its language appears to have overlooked the special handling requirements of radiopharmaceuticals. USP 36 <797> recognizes the special handling requirements with radiopharmaceuticals where it states “These radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 (see Table 1) PEC located in an ISO Class 8 (see Table 1) or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.”

Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1735.1:

1735.1. Compounding Definitions.

(e) “Cleanroom” means a separate room meeting an ISO Class 7 or better air quality. For purposes of preparing radiopharmaceuticals, they shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO Class 5 PEC located in an ISO Class 8 or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.

Issue 2

- Where the Board proposes to amend 16 CCR §1735.3 subdivision (c) The board states the proposal further clarifies by deleting “any available” and adding requirements for certificates of purity or analysis are to be matched to the product received. The requirement that all certifications of purity or analysis are to be kept and matched to the product received also includes the now required FDA-registered suppliers.

(c) Chemicals, bulk drug substances, and drug products, and components used to compound drug products shall be obtained from reliable FDA-registered suppliers. The pharmacy shall acquire and retain ~~any available~~ certificates of purity or analysis for chemicals, bulk drug substances, *and* drug products, ~~and components~~ used in compounding. ~~Certificates of purity or analysis are not required~~

~~for drug products that are approved by the Food and Drug Administration. Certificates of purity or analysis are to be matched to the product received.~~

Comment 2

Radiopharmacies prepare short lived radiotracers manufactured by FDA licensed drug manufacturers and only use FDA approved drug "kits". When all drugs sourced and procured are FDA approved commercially available drugs, there is no benefit to be achieved by requiring the manufacturer to provide certificates of purity or certificates of analysis (COA) to be matched to the product received as the products are manufactured pursuant to cGMPs.

Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1735.3:

(c) Chemicals, bulk drug substances, and drug products, and components used to compound drug products shall be obtained from reliable FDA-registered suppliers. The pharmacy shall acquire and retain ~~any available~~ certificates of purity or analysis for chemicals, bulk drug substances, *and* drug products, ~~and components~~ used in compounding. ~~Certificates of purity or analysis are not required for drug products that are approved by the Food and Drug Administration. Certificates of purity or analysis are to be matched to the product received.~~ When radiopharmaceuticals are prepared from commercially available FDA-approved drugs, no certificates of purity or certificates of analysis are required.

Issue 3

- 16 CCR §1751.1 specify requirements for sterile compounding recordkeeping requirements. The purpose of the board's proposal will amend subdivision (b) to add a new paragraph (6) to require recordkeeping requirements for the logs of room pressure differentials.

1751.1. Sterile ~~Inje~~ctable Compounding Recordkeeping Requirements.

(6) Logs of room pressure differentials.

Comment 3

In radiopharmacy practice the ante and buffer rooms are both ISO Class 8 air quality

Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.1:

(6) Logs of room pressure differentials. For the preparation of radiopharmaceuticals where the ante and buffer rooms are both ISO Class 8 air quality or better, no logs of room pressure differentials are required.

Issue 4

- 16 CCR §1751.4 specify requirements for facility and equipment standards for sterile compounding. The purpose of the board's proposal will add subdivision (d) to specify cleaning and disinfecting surfaces in the ISO Class 5 hood shall occur frequently, including: at the beginning of each shift; before each batch; every 30 minutes during continuous compounding of individual compounded sterile drug products; after each spill; when surface contamination is known or suspected; and when switching between cytotoxic and non-cytotoxic ingredients. This change outlines minimum safety requirements and the required documentation for the minimum safety requirements.

1751.4. Facility and Equipment Standards for Sterile ~~Injectable~~ Compounding [from Non-Sterile Ingredients].

Comment 4

The nature of the preparation of radiopharmaceuticals is unique. It takes an authorized licensed Nuclear Pharmacist less than 2 minutes to prepare an FDA approved vial of Tc-99m medronate for imaging skeletal metastases. It is prepared by aseptically adding sterile Tc-99m sodium pertechnetate and sterile normal saline to the kit vial (all FDA approved sterile ingredients).

Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.4:

(i) When preparing radiopharmaceuticals the nuclear pharmacist shall be responsible for cleaning and disinfecting surfaces in the ISO Class 5 hood frequently, including: at the beginning of each shift; after each spill; when surface contamination is known or suspected and prior to each unique radiopharmaceutical preparation cycle.

Issue 5

- Regulations at 16 CCR §1751.5 specify requirements sterile compounding attire. The purpose of the board's proposal will delete subdivision (a) removing the requirement for gowns and gloves to be worn when preparing cytotoxic agents. The section is further expanded the addition of requirements for gowns and gloves to be worn for all sterile compounding and not only compounding of cytotoxic agents.
- Additionally, the board's proposal will amend paragraph (1) of subdivision (a) to specify cleanroom garb requirements. Specifically, the "low-shedding coverall" is revised to a "non-shedding gown." The change is required to prevent particles from the gown worn during compounding to fall off the gown and into the compounded drug products.
- The board's proposal will add paragraph (3) of subdivision (a) to specify the donning of personal protective equipment. Specifically, "Personnel shall don personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water and then the donning of a non-shedding gown. Cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves must occur

(e) (e) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile.

Comment 6

In the preparation of radiopharmaceuticals where all drugs sourced and prepared are FDA approved commercially available sterile drugs, the performance of sterility and pyrogen testing is performed by the manufacturer as a component of its cGMP process. Applying this requirement to the preparation of radiopharmaceuticals from FDA-approved commercially available pharmaceuticals creates an impractical situation with the dispensing of a radiopharmaceutical: the sterility test takes 14 days to complete, whereas the radiopharmaceutical has a half-life of 6 hours and a beyond-use date of 12 hours. For example: it takes less than 2 minutes to prepare an FDA approved vial of Tc-99m medronate for imaging skeletal metastases. It is prepared by aseptically adding sterile Tc-99m sodium pertechnetate and sterile normal saline to the kit vial (all FDA approved sterile ingredients).

Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.5:

(e) (e) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile. Nuclear pharmacies that prepare and dispense only FDA-approved commercially available pharmaceuticals shall perform quarterly random representative retrospective sterility testing

Issue 7

- The proposed regulation at 16 CCR specifies the title of §1751.9 to be “Single-Dose and Multi-Dose Containers; Limitations on Use.” The purpose of the board’s proposal will outline the requirements for the use of single-dose containers in accordance with the usage and intended use of one time when meeting the outlined requirements. The board’s proposal will also outline the restriction of a multi-dose container absent the manufacturer’s specifications.

Comment 7

The proposed addition would limit the pharmacist’s ability granted under USP 36 <797> to validate alternate technologies. USP 36 <797> provides for “The use of technologies, techniques, materials, and procedures other than those described in this chapter are not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.”

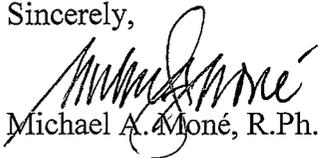
Cardinal Health proposes the following language change to add to the proposed amendments to 16 CCR §1751.9:

1751.9 Single-Dose and Multi-Dose Containers; Limitations on Use

(3) With respect to the preparation of radiopharmaceuticals, an authorized licensed nuclear pharmacist may employ the use of technologies, techniques, materials, and procedures other than those described in USP 36 <797> that are not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described therein.

Cardinal Health Nuclear Pharmacy Services thanks the California Board of Pharmacy for its consideration of these proposed changes to the regulations affecting nuclear pharmacy practice in California. As stated above, we wish to offer our time and commitment to the citizens of California should the Board of Pharmacy establish a Task Force on nuclear pharmacy practice.

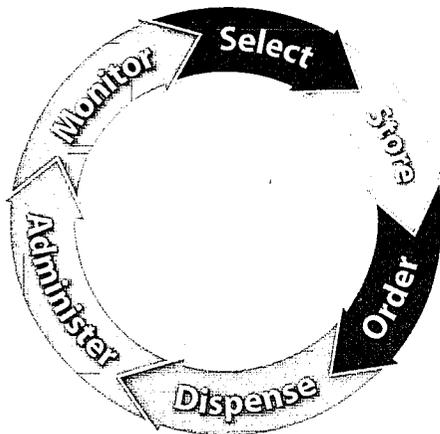
Sincerely,



Michael A. Moné, R.Ph., J.D., FAPhA

FDA-approved radiopharmaceuticals

Medication Management



This is a current list of all FDA-approved radiopharmaceuticals. Nuclear medicine practitioners that receive radiopharmaceuticals that originate from sources other than the manufacturers listed in these tables may be using unapproved copies.

	Radiopharmaceutical	Manufacturer	Trade Names	Approved Indications in Adults (Pediatric use as noted)
1	Carbon-11 choline	Mayo Clinic	-	Indicated for PET imaging of patients with suspected prostate cancer recurrence based upon elevated blood prostate specific antigen (PSA) levels following initial therapy and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging (MRI) to help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation
2	Carbon-14 urea	Kimberly-Clark	PYtest	Detection of gastric urease as an aid in the diagnosis of H.pylori infection in the stomach
3	Fluorine-18 florbetapir	Eli Lilly	Amyvid™	
4	Fluorine-18 sodium fluoride ¹	Various	-	PET bone imaging agent to delineate areas of altered osteogenesis
5	Fluorine-18 fludeoxyglucose ¹	Various	-	As a PET imaging agent to: <ul style="list-style-type: none"> • Assess abnormal glucose metabolism in oncology • Assess myocardial hibernation • Identify regions of abnormal glucose metabolism associated with foci of epileptic seizures

Package Inserts may be viewed at <http://nps.cardinal.com/MSDSPI/Main.aspx>

Note: See page six for footnotes

Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.

	Radiopharmaceutical	Manufacturer	Trade Names	Approved Indications in Adults (Pediatric use as noted)
6	Gallium-67 citrate	Covidien Lantheus Medical Imaging	- -	Useful to demonstrate the presence/extent of: <ul style="list-style-type: none"> • Hodgkin's disease • Lymphoma • Bronchogenic carcinoma Aid in detecting some acute inflammatory lesions
7	Indium-111 capromab pentetide	Jazz Pharmaceuticals	ProstaScint®	<ul style="list-style-type: none"> • A diagnostic imaging agent in newly-diagnosed patients with biopsy-proven prostate cancer, thought to be clinically-localized after standard diagnostic evaluation (e.g. chest x-ray, bone scan, CT scan, or MRI), who are at high-risk for pelvic lymph node metastases • A diagnostic imaging agent in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease
8	Indium-111 chloride	Covidien GE Healthcare	- Indiclor™	Indicated for radiolabeling: <ul style="list-style-type: none"> • ProstaScint® used for in vivo diagnostic imaging procedures
9	Indium-111 pentetate	GE Healthcare	-	For use in radionuclide cisternography
10	Indium-111 oxyquinoline	GE Healthcare	-	Indicated for radiolabeling autologous leukocytes which may be used as an adjunct in the detection of inflammatory processes to which leukocytes migrate, such as those associated with abscesses or other infection
11	Indium-111 pentetreotide	Covidien	Octreoscan™	An agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors
12	Iodine I-123 iobenguane	GE Healthcare	AdreView™	<p>Indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests.</p> <p>Indicated for scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the heart to mediastinum (H/M) ratio of radioactivity uptake in patients with New York Heart Association (NYHA) class II or class III heart failure and left ventricular ejection fraction (LVEF) ≤ 35%. Among these patients, it may be used to help identify patients with lower one and two year mortality risks, as indicated by an H/M ratio ≥ 1.6. Limitations of Use: In patients with congestive heart failure, its utility has not been established for: selecting a therapeutic intervention or for monitoring the response to therapy; using the H/M ratio to identify a patient with a high risk for death.</p>
13	Iodine I-123 ioflupane ²	GE Healthcare	DaTscan™	Indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS) in whom it may help differentiate essential tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy)
14	Iodine I-123 sodium iodide capsules	Cardinal Health Covidien	- -	Indicated for use in the evaluation of thyroid: <ul style="list-style-type: none"> • Function • Morphology
15	Iodine I-125 human serum albumin	IsoTex Diagnostics	Jeanatope	Indicated for use in the determination of: <ul style="list-style-type: none"> • Total blood • Plasma volume
16	Iodine I-125 iothalamate	IsoTex Diagnostics	Glofil-125	Indicated for evaluation of glomerular filtration

	Radiopharmaceutical	Manufacturer	Trade Names	Approved Indications in Adults (Pediatric use as noted)
17	Iodine I-131 human serum albumin	IsoTex Diagnostics	Megatope	Indicated for use in determinations of: <ul style="list-style-type: none"> • Total blood and plasma volumes • Cardiac output • Cardiac and pulmonary blood volumes and circulation times • Protein turnover studies • Heart and great vessel delineation • Localization of the placenta • Localization of cerebral neoplasms
18	Iodine I-131 sodium iodide	Covidien	–	Diagnostic: <ul style="list-style-type: none"> • Performance of the radioactive iodide (RAI) uptake test to evaluate thyroid function • Localizing metastases associated with thyroid malignancies Therapeutic: <ul style="list-style-type: none"> • Treatment of hyperthyroidism • Treatment of carcinoma of the thyroid
		DRAXIMAGE	HICON™	
19	Iodine I-131 tositumomab	GlaxoSmithKline	BEXXAR®	Indicated for: Treatment of patients with CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with Rituximab-refractory non-Hodgkin's lymphoma
20	Molybdenum Mo-99 generator	Covidien	Ultra-TechneKow® DTE	Generation of Tc-99m sodium pertechnetate for administration or radiopharmaceutical preparation
		Lantheus Medical Imaging	Technelite®	
21	Nitrogen-13 ammonia ¹	Various	–	Indicated for diagnostic Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease
22	Radium-223 dichloride	Bayer HealthCare Pharmaceuticals Inc.	Xofigo®	Indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease
23	Rubidium-82 chloride	Bracco Diagnostics	Cardiogen-82®	PET myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction
24	Samarium-153 lexidronam	Jazz Pharmaceuticals	Quadramet®	Indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan
25	Strontium-89 chloride	Bio-Nucleonics	–	Indicated for the relief of bone pain in patients with painful skeletal metastases that have been confirmed prior to therapy
		GE Healthcare	Metastron™	
26	Technetium-99m bicisate	Lantheus Medical Imaging	Neurolite®	SPECT imaging as an adjunct to conventional CT or MRI imaging in the localization of stroke in patients in whom stroke has already been diagnosed

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Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.

	Radiopharmaceutical	Manufacturer	Trade Names	Approved Indications in Adults (Pediatric use as noted)
27	Technetium-99m disofenin	Pharmalucence	Hepatology®	Diagnosis of acute cholecystitis as well as to rule out the occurrence of acute cholecystitis in suspected patients with right upper quadrant pain, fever, jaundice, right upper quadrant tenderness and mass or rebound tenderness, but not limited to these signs and symptoms.
28	Technetium-99m exametazine	GE Healthcare	Ceretec™	<ul style="list-style-type: none"> • As an adjunct in the detection of altered regional cerebral perfusion in stroke • Leukocyte labeled scintigraphy as an adjunct in the localization of intra abdominal infection and inflammatory bowel disease
29	Technetium-99m macroaggregated albumin	DRAXIMAGE	–	<ul style="list-style-type: none"> • An adjunct in the evaluation of pulmonary perfusion (adult and pediatric) • Evaluation of peritoneo-venous (LaVeen) shunt patency
30	Technetium-99m mebrofenin	Bracco Diagnostics	Choletec®	As a hepatobiliary imaging agent
		Pharmalucence	–	
31	Technetium-99m medronate	Bracco Diagnostics	MDP-Bracco™	As a bone imaging agent to delineate areas of altered osteogenesis
		DRAXIMAGE	–	
		DRAXIMAGE	MDP-25	
		GE Healthcare	MDP Multidose	
		Pharmalucence	–	
32	Technetium-99m mertiatide	Covidien	Technescan MAG3™	<p>In patients > 30 days of age as a renal imaging agent for use in the diagnosis of:</p> <ul style="list-style-type: none"> • Congenital and acquired abnormalities • Renal failure • Urinary tract obstruction and calculi <p>Diagnostic aid in providing:</p> <ul style="list-style-type: none"> • Renal function • Split function • Renal angiograms • Renogram curves for whole kidney and renal cortex
33	Technetium-99m oxidronate	Covidien	Technescan™ HDP	As a bone imaging agent to delineate areas of altered osteogenesis (adult and pediatric use)
34	Technetium-99m pentetate	DRAXIMAGE	–	<ul style="list-style-type: none"> • Brain imaging • Kidney imaging: <ul style="list-style-type: none"> - To assess renal perfusion - To estimate glomerular filtration rate
35	Technetium-99m pyrophosphate	Covidien	Technescan™ PYP™	<ul style="list-style-type: none"> • As a bone imaging agent to delineate areas of altered osteogenesis • As a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction • As a blood pool imaging agent useful for: <ul style="list-style-type: none"> - Gated blood pool imaging - Detection of sites of gastrointestinal bleeding
		Pharmalucence	–	
36	Technetium-99m red blood cells	Covidien	UltraTag™	<p>Tc99m-labeled red blood cells are used for:</p> <ul style="list-style-type: none"> • Blood pool imaging including cardiac first pass and gated equilibrium imaging • Detection of sites of gastrointestinal bleeding

Package Inserts may be viewed at <http://nps.cardinal.com/MSDSP/Main.aspx>

Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.

	Radiopharmaceutical	Manufacturer	Trade Names	Approved Indications in Adults (Pediatric use as noted)
37	Technetium-99m sestamibi	Cardinal Health	-	<p>Myocardial perfusion agent that is indicated for:</p> <ul style="list-style-type: none"> • Detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) • Evaluating myocardial function • Developing information for use in patient management decisions <p>Planar breast imaging as a second line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass</p>
		Covidien	-	
		DRAXIMAGE	-	
		Lantheus Medical Imaging	Cardiolite®	
		Pharmalucence	-	
38	Technetium-99m sodium pertechnetate	Covidien	-	<ul style="list-style-type: none"> • Brain Imaging (including cerebral radionuclide angiography)* • Thyroid Imaging* • Salivary Gland Imaging • Placenta Localization • Blood Pool Imaging (including radionuclide angiography)* • Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux* • Nasolacrimal Drainage System Imaging <p>(*adult and pediatric use)</p>
		Lantheus Medical Imaging	-	
39	Technetium-99m succimer	GE Healthcare	-	An aid in the scintigraphic evaluation of renal parenchymal disorders
40	Technetium-99m sulfur colloid	Pharmalucence	-	<ul style="list-style-type: none"> • Imaging areas of functioning reticuloendothelial cells in the liver, spleen and bone marrow* • It is used orally for: <ul style="list-style-type: none"> - Esophageal transit studies* - Gastroesophageal reflux scintigraphy* - Detection of pulmonary aspiration of gastric contents* • Aid in the evaluation of peritoneo-venous (LeVeen) shunt patency • To assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or malignant melanoma when used with a hand-held gamma counter. <p>(*adult and pediatric use)</p>
41	Technetium-99m tetrofosmin	GE Healthcare	Myoview™	<p>Myocardial perfusion agent that is indicated for:</p> <ul style="list-style-type: none"> • Detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects) • The assessment of left ventricular function (left ventricular ejection fraction and wall motion)
42	Technetium-99m tilmanocept	Navidea Biopharmaceuticals, Inc.	Lymphoseek®	Indicated for lymphatic mapping with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma
43	Thallium-201 chloride	Covidien	-	<ul style="list-style-type: none"> • Useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction • As an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease) • Localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels
		GE Healthcare	-	
		Lantheus Medical Imaging	-	

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Radiopharmaceuticals that may potentially have unapproved copies of FDA-approved commercially available radiopharmaceuticals in the marketplace.



	Radiopharmaceutical	Manufacturer	Trade Names	Approved Indications in Adults (Pediatric use as noted)
44	Xenon-133 gas	Lantheus Medical Imaging	-	<ul style="list-style-type: none"> The evaluation of pulmonary function and for imaging the lungs Assessment of cerebral flow
45	Yttrium-90 chloride	MDS Nordion	-	Indicated for radiolabeling: <ul style="list-style-type: none"> Zevalin® used for radioimmunotherapy procedures
		Eckert & Ziegler Nuclitec	-	
46	Yttrium-90 ibritumomab tiuxetan	Spectrum Pharmaceuticals	Zevalin®	Indicated for the: <ul style="list-style-type: none"> Treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) Treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy

Package Inserts may be viewed at <http://nps.cardinal.com/MSDSPI/Main.aspx>

¹Subsequent to promulgation of 21 C.F.R. Part 212, Current Good Manufacturing Practices (cGMP) for PET Radiopharmaceuticals, firms manufacturing and distributing this drug are required to submit either a NDA or an ANDA by June 12, 2012 and manufacture following cGMP Part 212 regulations as of December 11, 2011 for its continued distribution and sale.

²This is a Schedule II controlled substance under the Controlled Substances Act. A DEA license is required for handling or administering this controlled substance.

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cardinalhealth.com

Cardinal Health
7000 Cardinal Place
Dublin, Ohio 43017

Damoth, Debbie@DCA

From: Bill.Jones@CAPSpharmacy.com
Sent: Monday, January 13, 2014 10:41 AM
To: Damoth, Debbie@DCA
Subject: Re: FW: Public Comment on CA Pharmacy Compounding Regulations
Attachments: CA BoP _ Letter to comment on proposed compd regs Nov 2013 final.pdf

Hi Debbie,

Yes I would like my comments considered.

Thank you for checking on this.

Bill Jones
Regional Director of Pharmacy Operations
Central Admixture Pharmacy Services, Inc. (CAPS)
Phone: 720-962-4700
Fax: 815-927-0125
Email: Bill.Jones@CAPSpharmacy.com

From: "Damoth, Debbie@DCA" <Debbie.Damoth@dca.ca.gov>
To: "Bill.Jones@CAPSpharmacy.com" <Bill.Jones@CAPSpharmacy.com>, <Bill.Jones@CAPSpharmacy.com>
Date: 01/13/2014 09:28 AM
Subject: FW: Public Comment on CA Pharmacy Compounding Regulations

Hello Mr. Jones,

The board received your comments before the beginning of the comment period for the pending regulation. Would you please confirm via email if you would like these comments to be considered for the pending regulation today as this is the last day to submit comments?

Thank you,

Debbie Damoth
Administration and Regulations Manager
California State Board of Pharmacy
(916) 574-7935

Please note: my name and email changed effective 3/2/13 from Debbie Anderson.

From: Bill.Jones@CAPSpharmacy.com [<mailto:Bill.Jones@CAPSpharmacy.com>]
Sent: Friday, November 22, 2013 9:18 AM
To: Damoth, Debbie@DCA
Subject: Public Comment on CA Pharmacy Compounding Regulations

Dear Debbie,

I appreciate the opportunity that the Board of Pharmacy has given to comment on the proposed changes to Compounding Regulations. I have attached a letter with my comments. Please let me know if you require any clarification.

I will send a hard copy of this letter by FedEx also.

Thank you,
Bill Jones
Regional Director of Pharmacy Operations
Central Admixture Pharmacy Services, Inc. (CAPS)
Phone: 720-962-4700
Fax: 815-927-0125
Email: Bill.Jones@CAPSpharmacy.com

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If you have received this communication in error, please notify us immediately by return e-mail and destroy this communication and all copies thereof, including all attachments.



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November 22, 2013

State of California
Department of Consumer Affairs
Board of Pharmacy

Debbie Damoth, Regulation Manager.
California State Board of Pharmacy
1625 N. Market Blvd, N219
Sacramento, CA 95834
E-mail: Debbie.Damoth@dca.gov
(916) 574-7935 Fax (916) 574-8618

Re: Public Comment to Proposed Compounding Regulations

Dear Ms Damoth:

Central Admixture Pharmacy Services, Inc (CAPS) has a long history of providing compounded sterile preparations within the State of California. Having three registered Sterile Compounding Pharmacies located in California, CAPS appreciates the opportunity provided to comment on the proposed enhancements to the compounding regulations.

CAPS has reviewed the proposed compounding regulations and would like to offer comment on Section 1751.7 Quality Assurance and Process Validations, Section 1751.5 Sterile Compounding Attire, Section 1751.8 Beyond Use Dating for Sterile Compounded Products, and Section 1735.1 Compounding Definitions.

1751.7 Quality Assurance and Process Validations

The proposed requirement in 1751.7 (e) requires quarantining for non sterile to sterile batch compounded CSPs while the preparation is undergoing sterility and pyrogen testing. Further, the requirement includes any compounds made from components that were previously rendered sterile through a non sterile to sterile compounding process. This requirement creates an obstacle for patient care as well as a possible conflict with proposed federal regulations. The Drug Quality and Security Act may become law before these rules are implemented. The new federal law permits "outsourcing facilities" to compound drug shortage items under certain circumstances with the conditional blessing of the FDA. The practice of pharmacies making drug shortage items has been happening apart from this regulation and the new federal statute will now sanction it under the regulation of the FDA. If the proposed 1751.7(e) was in place, pharmacies who have been relying on compounded drug shortage items coming from outsourcing facilities would now be required to sterility test, pyrogen test, and quarantine finished prescriptions made from drug shortage items despite these tests having been performed by the outsourcing facility. An example of this would be magnesium sulfate injection for compounding TPNs, unavailable as an FDA approved drug, but sanctioned by FDA through an outsourcing facility. If this drug were obtained to compound TPN solutions by a hospital in California the TPNs would need to be quarantined until sterility and pyrogen testing was completed. Quarantining and testing thousands of TPN solutions is impractical and this new rule would have the affect of exacerbating the drug shortage issues facing pharmacies.

CAPS agrees that non sterile to sterile preparations should be quarantined and released for use if sterility testing indicates that the sample was sterile. CAPS recommends an exemption placed in the sterility and pyrogen testing provisions of section 1751.7(e) that exempts CSPs used as components that were obtained from federally registered entities that have already passed a sterility and pyrogen test and are packaged with a certificate of analysis.

CAPS proposed language (denoted by *) for 1751.7 (e):

~~(e)~~ (e) Batch-produced sterile injectable drug products compounded from one or more non sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile unless the component that was compounded from nonsterile ingredients was compounded by an entity registered with the State of California and the FDA and they provide a Certificate of Analysis with the component documenting that it was tested for sterility, pyrogens, and chemistry and was within specification.*

1751.5 Sterile Compounding Attire

The proposed regulation lists a specific order of gowning. This order of gowning would not be appropriate in all pharmacy models. CAPS continuously modifies and enhances gowning procedures based on FDA input. Our current gowning procedure, although compliant with FDA inspectional observations, would not meet the letter of the proposed CA 1751 standards. CAPS recommends allowing for an alternate order of gowning if it is shown to be equivalent or superior to the proposed gowning method.

CAPS proposed language (denoted by *) for 1751.5 (a) (3):

~~(b)~~ (a) When compounding sterile drug products from one or more non-sterile ingredients the following standards must be met:

- (1) Cleanroom garb consisting of a low non-shedding coverall gown, head cover, face mask, and shoe covers must be worn inside the designated area at all times.
- (2) Cleanroom garb must be donned and removed in an anteroom or outside the designated area in a designated area immediately outside the segregated compounding area.
- (3) Personnel shall don personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The following order is to be followed unless the pharmacy has a procedure in place that documents a method equivalent to or is superior to the method described here.* The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water and then the donning of a non-shedding gown. Cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves must occur within the buffer area, not prior to entering. Gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol after contact with non-sterile objects.

* Underlined passages in this document indicate language recommended by CAPS to the proposed compounding regulations.

1751.8 Beyond Use Dating for Sterile Compounded Drug Products

USP <797> uses risk levels to classify different levels of compounding and the corresponding standard beyond use dates associated with these risk levels. The proposed compounding regulation does not use these risk levels which have become a standard and this creates confusion when reading section 1751.8 Beyond Use Dating for Compounded Sterile Products. Without the use of the risk level classifications or an alternative classification, Pharmacists are left with no method to reference the compounding process and the associated dating and/or testing requirements. CAPS recommends the use of the USP <797> risk levels to clarify section 1751.8 Beyond Use Dating for Sterile Compounded Drug Products.

1751.8 (b) (2) Beyond Use Dating for Sterile Compounded Drug Products

The refrigerated beyond use date for this 'medium risk' process in the absence of a sterility test is 7 days. This creates an obstacle for homecare patients who would be required to be available for multiple deliveries of their medium risk medications each week. CAPS recommends a refrigerated beyond use date of 9 days which is the USP <797> standard beyond use dating in the absence of a sterility test.

CAPS proposed language (denoted by *) for 1751.8 (b) (2)

(b) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using multiple individual or small doses of sterile products combined or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following:

- (1) 30 hours at controlled room temperature
- (2) 9* days at controlled cold temperature
- (3) 45 days at controlled freezer temperature

1751.8 (c) Beyond Use Dating for Sterile Compounded Drug Products

Section 1751.7(e) and 1751.8(c) appear to conflict. 1751.7(e) requires sterility and pyrogen testing and quarantining for non sterile to sterile batch compounded CSPs. Section 1751.8(c) permits assigning a BUD date for compounds made from non sterile to sterile components "in the absence of passing a sterility test." Assuming the assignment of BUD also indicates that it is permissible to dispense, these two sections are conflicting. The language in section 1751.8(c) appears to mimic USP <797> for High Risk Level CSPs, however, USP 797 included a provision that indicates a sterility test is not required for batch sizes of no more than 25 units. The 1751 language does not include this provision and in fact insists on a sterility and pyrogen test in all cases for non sterile to sterile compounding. Did the board inadvertently leave the 25 unit limit out of the rule? These two sections need to be edited to eliminate the conflict.

1751.8 (c):

(c) Where the sterile compounded drug product was compounded solely with aseptic manipulations entirely within an ISO Class 5 hood located in an ISO Class 7 buffer area with an anteroom, using nonsterile ingredients, including manufactured products not intended for sterile routes of administration, or nonsterile devices, before terminal sterilization, or where the sterile compounded drug product lacks effective antimicrobial preservatives, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, the beyond use date shall specify that storage and exposure periods for the sterile compounded drug product cannot exceed the following:

* Underlined passages in this document indicate language recommended by CAPS to the proposed compounding regulations.

- (1) 24 hours at controlled room temperature
- (2) 3 days at controlled cold temperature
- (3) 45 days at controlled freezer temperature

1751.7 (e):

(e) Batch-produced sterile injectable drug products compounded from one or more non sterile ingredients shall be subject to documented end product testing for sterility in accordance with methodologies and processes found in Chapter 71 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), and pyrogens in accordance with the methods of Chapters 85 and 151 of the United States Pharmacopeia – National Formulary (USP36-NF31 through 1st Supplement) (36th Revision, Effective August 1, 2013), hereby incorporated by reference, and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens before dispensing. Products submitted for sterility testing are to include preparations from the beginning, middle, and end of each batch. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile

1735.1 Compounding Definitions

The proposed regulation creates confusion with established definitions of 'product' and 'preparation'. If the goal of these regulations is to create clarity for Pharmacists and harmonize with USP 797 then CAPS recommends using the terminology already established by USP. The use of the term "sterile drug product" is used throughout the document to refer to the prepared doses that result from compounding. This terminology is in direct conflict with USP Chapter 797 where "products" refer to manufactured goods while "preparations" refer to the articles/doses of drug that result from compounding. Further, the CA 4.5 document mixes the items referred to as "drug products" in section 1735(c) where a manufactured "drug product" is correctly referred to in the context of the USP definition. The document should be rewritten to substitute the term "compounded sterile preparation" or "CSP" where "sterile drug product" is used in the context of the articles/doses that result from compounding.

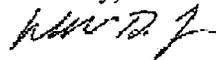
CAPS recommends adding these USP definitions to 1735.1:

Preparation—A preparation, or a CSP, that is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.*

Product—A commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA. Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.*

CAPS would like to thank the Board of Pharmacy and the Enforcement/Compounding Committee for their work to enhance the compounding regulations to ensure patient safety. CAPS looks forward to working with the Board of Pharmacy to clarify the proposed regulations.

Sincerely,



William D. Jones, R.Ph.
Regional Director of Pharmacy Operations

* Underlined passages in this document indicate language recommended by CAPS to the proposed compounding regulations.



Dignity Health.

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Pasadena, CA 91101
direct 626-744-2209
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Submitted Via Electronic Mail
Debbie.Damoth@dca.ca.gov

January 13, 2014

California Board of Pharmacy
Attn: Debbie Damoth
1625 N. Market Blvd., Suite N219
Sacramento, CA 95834

RE: Compounding Regulations, Notice of Proposed Action, Articles 4.5 and 7 of Division 17 and Title 16 of the California Code of Regulations Section 1735 et seq. and 1751 et seq.

Dear Ms. Damoth:

On behalf of Dignity Health and our 30 hospital-based and three infusion center-based pharmacies, we are grateful for the opportunity to offer the following comments for consideration to the proposed changes to compounding regulations set forth in Articles 4.5 and 7 of Division 17 of Title 16 California Code of Regulations Section 1735 et seq. and 1751 et seq.

Dignity Health, one of the nation's five largest healthcare systems, is a 21-state network of nearly 9,000 physicians, 55,000 employees, and more than 380 care centers, including hospitals, urgent and occupational care centers, imaging centers, home health and primary care clinics. Dignity Health is dedicated to providing compassionate, high-quality and affordable patient-centered care with special attention to the poor and underserved.

Central to our healing mission, Dignity Health is committed to patient and employee safety and continuous improvement to quality of care. Since our beginning and as we usher this unprecedented time of health care reform, our values call us to place public protection along with efficient, effective delivery of pharmaceutical care of primary importance. In light of the recent national events with sterile compounding pharmacies, Dignity Health stands with the California Board of Pharmacy and the entire hospital community to further reflect upon the existing Pharmacy Law, including the recently passed Senate Bill 294 (Emerson), and what opportunities we can create to advance meaningful change. We wholeheartedly agree that updating California's compounding regulations to improve overall patient safety is paramount.

As our hospitals have relied on and have been operating under the United States Pharmacopeia (USP) Chapter 797 Guidelines, "Pharmaceutical Compounding – Sterile Preparations" in the National Formulary, Dignity Health urges the California Board of Pharmacy to adopt and codify regulations that are fully aligned with the Guidelines, including key provisions such as the immediate use provision and the hazardous drug compounding that are not present in the proposed regulations.

During this time of transformation for California and the nation, Dignity Health is invested in successfully implementing the Affordable Care Act (ACA) and advancing the triple aim of 1) improving quality of care; 2) improving population health; 3) bending the healthcare cost curve. 2014 marks the year when core provisions of the ACA are being implemented and hospitals are adjusting to tremendous changes. Stewardship of resources is critical as hospitals are still in the early stages of fully realizing the fiscal and operational impacts of ACA and other state reform initiatives. While we welcome changes that support hospitals' ability deliver on our promise of high quality care to the communities we serve, Dignity Health believes that it is essential that final regulations strike the optimal balance between public protection and appropriate regulatory changes that protects access to care and continued hospital solvency.

Dignity Health is encouraged by the Board's desire to ensure California compounding regulations that reflect at minimum the compounding standards used in the profession. Dignity Health urges the Board to finalize regulations that are aligned with USP 797 Guidelines. We have worked closely with the California Hospital Association (CHA) and other member hospitals to develop the hospital community's position on the Board's proposed regulations. We support the Board's principles and efforts to provide uniformity, eliminating redundancies and redefining particular definitions in alignment with national standards for pharmacies that carry out compounding in general, including sterile injectable.

Dignity Health submits the following detailed recommendations for the Board's careful consideration:

- **We recommend adding the immediate use provision with a one-hour beyond use date as stated in USP 797 to allow preparation of sterile compound products outside of an ISO Class 5 hood for emergency or immediate patient administration.**
- **We recommend the use of an ISO Class 5 hood within a segregated compounding area with a 12-hour beyond use date for any hospital or facility currently compounding drugs safely without a cleanroom (ante-area and buffer room).**
- **We recommend allowing hospital pharmacies to compound hazardous drugs in non-negative pressure room, such as a closed system vial transfer device within an ISO Class 5 biological safety cabinet or containment isolator.**

The immediate use provision can eliminate unnecessary physical plant facility upgrade costs. Unnecessary upgrades or upgrades required that do not consider a realistic phased-in approach will run counter to transformative goals. The immediate use provision can prevent untimely patient care in fast-paced treatment areas where construction of a cleanroom is not feasible, such as emergency room departments, operating rooms, therapeutic radiology, cardiac catheterization, and respiratory therapy. Compounding in acute care hospitals requires speed and flexibility. Critical lifesaving medications in acute care hospitals are compounded in areas outside of pharmacies and cleanrooms, including the patient's bedside. Without the immediate use exemption provision, hospitals would be unable to appropriately respond to code blues or other essential

patient care therapies requiring compounding within a one hour or twelve hour time period. Regulations are needed to account for the varying environments and situations when compounding must occur to effectively provide the right care at the right time for our patients. The immediate use provision is fiscally sensible, and more importantly it is a responsive provision that will ensure public health and patient and worker safety.

Our hospitals have successfully compounded cytotoxic or other hazardous agents in non-negative pressure rooms with closed system vial transfer devices. According to USP 797 Guidelines, hazardous drug compounding can occur in a non-negative pressure room if using a closed system vial transfer device within an ISO Class 5 biological safety cabinet or barrier isolator. The ability for hospitals to use this has provided essential patient care to more patients who may otherwise be unable to receive these lifesaving treatments from hospitals due to facility plant space restrictions.

Finally, Dignity Health seeks and supports amendments to the Title 24 section that will be handled through the Building Standards Commission which are in alignment with our recommendations above. **We will recommend that Title 24, Part 2, Chapter 12, 1250.4(5) be changed to reflect inclusion of the environment that will allow hospitals to perform sterile compounding for emergently needed sterile drug preparations both at the bedside or in settings with an ISO Class 5 hood in a segregated sterile compounding area.**

Dignity Health seeks a CSP Licensure process that is fair, consistent, and achievable for hospitals while leveraging the need for public and worker safety and high quality patient care. We seek from the Board a detailed process on how the Board will license and inspect hospitals to meet SB 294's July 1, 2014 deadline. Hospitals recognize the need to apply for licensure. However, absent final regulations, hospitals may not be able to make the changes required in a timely manner. Guidance from the Board is necessary to assure there is no gap in delivery of care to patients receiving medications across the state. Moreover, since compounding self-assessment form must be completed prior to becoming licensed, it is essential that the Board develop and implement a self-assessment form reflecting the approved regulatory amendments. If the projections for this are unlikely to be met, guidance and direction from the Board on what self-assessment form to utilize is necessary.

We thank the Board for its leadership and for your thoughtful consideration of our recommendations and comments. Should you have any questions or if we can be of resource, please do not hesitate to contact us at rachelle.wenger@dignityhealth.org or 626.744.2209 or candace.fong@dignityhealth.org or 916.851.2678.

Sincerely,



Candace Fong, PharmD
Director, Pharmacy and Medication
Safety



Rachelle Reyes Wenger
Director, Public Policy & Community
Advocacy

Damoth, Debbie@DCA

From: Wenger, Rachelle - PAS <Rachelle.Wenger@DignityHealth.org>
Sent: Monday, January 13, 2014 2:00 PM
To: Damoth, Debbie@DCA
Cc: Fong, Candace - SF
Subject: Dignity Health Letter to the California Board of Pharmacy - January 13, 2014
Attachments: Dignity Health Letter to CA Board of Pharmacy - January 13 2014.pdf

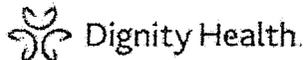
Dear Ms. Damoth:

Attached please find Dignity Health's letter re: Compounding Regulations, Notice of Proposed Action, Articles 4.5 and 7 of Division 17 of Title 16 of the California Code of Regulations Section 1735 et seq. and 1751 et seq.

Thank you for the opportunity to provide our comments.

Best,
Rachelle R. Wenger

Rachelle Reyes Wenger, MPA
Director, Public Policy & Community Advocacy



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SILICON VALLEY PHARMACY

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Debbie.Damoth@dca.ca.gov

Dear California State Board of Pharmacy,

In regards to proposed amendments of the California Code of Regulations as they pertain to the compounding of drug products and including Senate Bill (SB) 294, I respectfully submit these comments for your consideration.

The impact on Silicon Valley Pharmacy, a small business, will be significant. In order to comply with the proposed amendments, we will have to undergo remodeling of our pharmacy at a significant expense. It is reasonable to extrapolate our concern with the independent pharmacies which compound the vast majority of drug products in the State of California, and most of which fall into the category of a small business.

I request that the Board of Pharmacy conduct a survey of California independent compounding pharmacies for the purpose of collecting data in order to determine how these proposed amendments will affect their small businesses. Additionally, I request that that survey collect data on how the cost to implement and practice pharmacy under these changes will impact the cost of care for the people of California who receive compounded drug products.

I request that these proposals not be implemented until the survey can be conducted and the results evaluated.

Also, I respectfully request an opinion from the Board of Pharmacy if a Standardized Regulatory Impact Assessment is required for this determination.

If the Board of Pharmacy decides to implement the proposed amendments, I respectfully request that the Board of Pharmacy allow for a two year implementation period before enforcement begins.

Thank you for your kind consideration of these comments.

Very Truly Yours,

Vivian Matsuo, Pharm.D.
Pharmacist in Charge
Silicon Valley Pharmacy

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Damoth, Debbie@DCA

From: DAVID MATSUO <dvmatsuo@yahoo.com>
Sent: Monday, January 13, 2014 9:05 AM
To: Damoth, Debbie@DCA
Subject: Comments to Proposed Amendments pertaining to compounded drug products.
Attachments: COMMENTS BOARD OF PHARMACY 011314.docx

Debbie,

I respectfully submit the attached comments for review by the Board of Pharmacy.

Thank you.

Vivian Matsuo, Pharm.D.

Damoth, Debbie@DCA

From: Kardasinski, Dan S. <DKardasinski@llu.edu>
Sent: Monday, January 13, 2014 1:49 PM
To: Damoth, Debbie@DCA
Subject: Endotoxin Clarification for New Compounding Regulations

Good afternoon Debbie,

One last question for clarification regarding the new sterile compounding regulations.. The new regulations state "For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets, and for appropriate documentation, and for sterility and bacterial endotoxin testing." The question that my colleagues and I have is that USP 797 requires bacterial endotoxin testing only for high risk non-sterile to sterile compounding. Thus, we are inquiring to verify if sterile to sterile compounding will also require endotoxin testing. Our main concern with this is that if endotoxin testing is required for all sterile to sterile batching with the standard specified beyond use dating of 30 hours @ RT, 7 days @ cold temp, and 45 days @ freezing, then compounded products at room temperature and refrigeration will spend a larger portion, if not all, of their usage time in being sequestered until the endotoxin results are final. This would be especially true if the samples need to be sent out for testing, resulting in increased wasted product.

Thank you,

Dan Kardasinski, Pharm.D.
Director of Adult Pharmacy Services
Loma Linda University Medical Center
Pager: 3916 Ext: 47385
2 Way: 9098140572@my2way.com

Damoth, Debbie@DCA

From: Kardasinski, Dan S. <DKardasinski@llu.edu>
Sent: Friday, January 10, 2014 1:34 PM
To: Damoth, Debbie@DCA
Subject: Question on Proposed Sterile Compounding Regulations

Follow Up Flag: Follow up
Flag Status: Flagged

Hello Debbie,

For clarification on the fingertip sampling (page 18 of the draft), does the set of follow up annual samplings need to be performed only once or three times, like the initial testing? Current USP <797> regulations call for the initial sampling to be performed three times, with the repeat sampling to be performed only once.

Thank you,

Dan Kardasinski, Pharm.D.
Director of Adult Pharmacy Services
Loma Linda University Medical Center
Pager: 3916 Ext: 47385
2 Way: 9098140572@my2way.com

Damoth, Debbie@DCA

From: bramschnur@aol.com
Sent: Monday, January 13, 2014 5:36 PM
To: Damoth, Debbie@DCA
Subject: comments on proposed changes to 1735

Hi Debbie –
Thanks for taking my comments:

1735.1:
(h) Consider allowing for excursions under “controlled room temperature” down to 59 deg F
(g) Consider allowing for freezer temperatures to go lower based on the requirements of the medications stored within.

1735.2
(c) (1) include Health Care Facilities in addition to prescribers' offices

1735.3
(9) (c) Confusing to me why the requirement for certificate of purity or analysis is required for FDA approved products.

1735.5
(a) can the “unprofessional conduct” piece be delineated to include specific serious failures to follow policy? The way it is written allows for unprofessional conduct no matter what the violation of policy – very broad.

Thanks again for considering my input.

Sincerely,
Krista Bramble