100 Daingerfield Road, Suite 100
Alexandria, VA 22314
www.a4pc.org

Alliance for Pharmacy Compounding

Compounding the Joy of Living

April 12, 2023

Anne Sodergren, Executive Officer
Seung Oh, Board President
California Board of Pharmacy
2720 Gateway Oaks Drive, Suite 100
Sacramento, CA 95833

Dear President Oh and Director Sodergren:

Thank you for the opportunity to comment on the California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposed new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.

The Alliance for Pharmacy Compounding is the voice for pharmacy compounding, representing more than 600 compounding pharmacies and facilities across the U.S., including compounding pharmacists and technicians in both 503A and 503B settings, as well as prescribers, educators, researchers, and suppliers.

APC supports the Board's statutory mission to protect California consumers, and we believe it's in the interest of the pharmacy compounding profession to have robust enforcement of reasonable regulation that safeguards patient safety. Yet it is not clear how many of the current proposed changes protect patients. In fact, in some cases, the effect of these proposals will be to eliminate patient access entirely – an action at odds with the agency's stated mission.

We urge the Board to communicate its rationale for proposing regulations that impose more restrictive rules and procedures than USP standards or FDA guidance. Is there evidence that the Board's proposals advance patient safety? Licensees would benefit from access to the research, testing, or other data the Board has collected that validate the need for many of these proposals. Sharing that evidence will be invaluable in training and compliance for compounding pharmacies licensed in your state.

Without such evidence, many of these proposals appear arbitrary. The Board seems to be taking the stance that some licensees have failed to adhere to current regulations and the entire profession needs new, even more stringent regulations. But a result of some of the proposed regs, if approved, will be a chilling effect on access to sterile compounded preparations for California residents.

Our specific concerns, suggestions, and questions are itemized in the attached document. To summarize here:

- Many of these proposals exceed USP standards and FDA guidance with no clear or verifiable rationale stated for why the more stringent regulation is necessary. The Board should share the research and testing it has conducted that demonstrates that California patients will be safer and better protected as a result of those proposals.

- Some proposals – particularly the prohibition on compounding substances that appear on the FDA's interim bulk substances list – will result in an immediate loss of access to essential medications for many California patients.

We certainly respect your desire to protect Californians. Yet we are concerned that many of these proposed regulations, while advocated for by Board staff, have not yet been thoroughly considered and discussed by the Board itself. We urge that the Board delay action on these proposals so that it can invite and carefully hear and consider further stakeholder input and then better enunciate a rationale for any resulting proposed regulatory changes.

With patient access to essential medications at risk, incorporating these considerations can help improve outcomes for all involved.

Thank you for the opportunity to comment. If I may be helpful to the Board, please contact me at scott@a4pc.org.

Sincerely,

Scott Brunner, CAE
Chief Executive Officer

Alliance for Pharmacy Compounding
Compounding the Joy of Living

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
153	1736(a)	"Certificate of Analysis" (COA) means a document produced by the manufacturer that certifies the quality of the component and demonstrates that the component conforms to the defined specifications, has been manufactured under recognized principles of current good manufacturing practices and is suitable for use in pharmaceuticals and meets the requirements in USP.	As per the new USP chapter <797>, CofA is a report from the SUPPLIER of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material. The manufacturer COA as a stand-alone doc may not capture the evidence of GMP and pharmaceutical use, but that info may be found on such documents as an FDA registration, inspection report, GMP certificate, product label. In addition, not all chemicals have a USP monograph, meaning a COA cannot meet USP requirements.
153	1736(d)	"Essentially a copy" of a commercially available drug product means all preparations that are comparable in active ingredients to commercially available drug products, except that it does not include any preparations in which there has been a change, made for an identified individual patient, which produces for that patient a clinically significant difference, as determined by a prescribing practitioner, between that compounded preparation and the comparable commercially available drug product.	A commercially available drug product includes 503B products. "FDA-approved" drug products would be more appropriate language. What is the definition of "comparable"' in active ingredients to commercial products, and does this account for routes of administration?
153	1736(e)	"Diluent" means a liquid with no pharmacological activity used in reconstitution, such as sterile water for injection.	Diluents such as lactated ringers, dextrose or sodium chloride in many cases do encompass pharmacological activity. How are these accounted for?
	1736(h)	"Preparation" means a compounded drug or nutrient.	What is the definition of nutrient?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
154	1736(j)	"Quality" means the degree to which the components and preparation meets the intended use or purpose, complies with relevant law and regulation, and means the absence of harmful levels of contaminants, including but not limited to filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, or the absence of inactive ingredients other than those listed on the master formula record as specified in USP 797.	FDA-approved drugs contain a small allowable limit of impurities. Will this limit for compounded preparations be in place as well?
154	1736.1©	A limited quantity of CNSP may be prepared and stored in advance of receipt of a patient specific prescription document where, and solely in such quantity, as is necessary to ensure continuity of care for individual patients of the pharmacy based on a documented history of prescriptions for those individual patients. This includes authority to prepare and furnish a limited quantity of CSPs to veterinarians for office dispensing of not more than a 120-hour supply, solely to the prescriber's owner veterinary patients seen as part of regular treatment in the prescriber's officer, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing	This references a cNsp when this is a section talking about sterile compounding, should be CSP. A VCPR documentation on the purchase order may be difficult when patients may not be known in advance particularly for office use drugs.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
155	1736.1(d)(3)	In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that is made with a component for which a conventionally manufactured sterile product is available and appropriate for the intended CSP.	Depending on the batch size and compounding set-up, using a conventionally manufactured sterile product as opposed to bulk ingredients could cause more sterility assurance issues and potency variability among units prepared (e.g., exponentially increased manual manipulations by repetitively entering vials or bags to transfer a portion of liquid to the finished preparation increases the potential for contamination and variability as these processes are primarily manual).
155	1736.1(d)(4)	In addition to prohibitions established in federal law, no licensed pharmacy personnel shall compound a CSP that cannot be sterilized within the licensed location.	The revised <797> states: "Injectable compounded preparations that contain nonsterile components or that come into contact with nonsterile devices (e.g., containers, tubing) during any phase of the compounding procedure must be sterilized within 6 h after completing the preparation to minimize the generation of endotoxins in CSPs." If one were to successfully have the CSPs transferred to a local third party for terminal sterilization within the 6-hour window, would this be acceptable?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
156	1736.2©	Aseptic manipulation ongoing training and competency shall occur each time the quality assurance program yields an unacceptable result as defined in the SOPs referenced in section 1736.17 that may indicate microbial contamination of CSPs. Aseptic manipulation ongoing training and competency procedures shall be defined in the facilities SOPs.	Requiring a media fill each time there is a sterility failure of a CSP implies that all sterility failures are due to poor aseptic technique, which may not be accurate. A more scientific approach would be to require an investigation with each OOS result, and personnel retraining / repeat compentency as appropriate/applicable.
	1736.4 (f)	No CSP shall be compounded if the compounding environment fails to meet criteria specified in the law or the facilities SOPs.	USP 797 states that BUDs revert to the most limited BUDs if pressure differential is different. BUD could go to Category 1 in this situation rather than Category 2. This is an important distinction for patient care to continue. If you can compound in a SCA for sterile with Category 1 BUDs then it would seem that you could revert to those BUDs as well
159	1736.6(a)	SOPs shall specify steps to be taken when the microbiological air and surface monitoring action levels are exceeded including the investigative and corrective actions, allowable activities, and resampling procedures.	Implies the SOP has to predict all possible reasons why a microbiological excursion could happen in a hypothetical future and outline all possible corrective actions to take. A more scientific approach would be to require the SOP to state that a root cause investigation and associated corrective actions appropriate to the root cause(s) identified are carried out.
	1736.7 (b)	Reusable cleaning supplies shall not be stored within 1 meter of the PEC.	Can the Contec Easy Reach tool be stored within a meter of the PEC?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
	1736.8	SOPs shall specify the process and products to be used on any equipment and other items entering from an unclassified area into the clean side of the ante-room, entering a PEC, and entering the SCA. These SOPs will define at a minimum, what product is to be used, the dwell time required, and how dwell time will be monitored and documented.	Items would go from the unclassified area to the dirty side of the ante-room and then to the clean side of the ante-room, then to buffer room, and then to a PEC. This could be read as a somewhat random list of areas, but staging happens between more areas than this.
160	1736.9(d)	All components used to compound a CSP shall be manufactured by an FDA-registered facility and suitable for use in sterile pharmaceuticals. A Certificate of Analysis (COA) which includes the compendial name, the grade of the material, and the applicable compendial designations on the COA must be received and evaluated prior to use.	**All** components, including excipients? All components cannot come from an FDA-registered manufacturer. APIs come from FDA registered manufacturers as required by 503A and other components may not all be available from FDA registered manufacturers. Also, what is meant by 'suitable for use in sterile pharmaceuticals'? A limited number of chemicals within USP have additional specifications when the chemical will be used in a parenteral preparation. Does the board have specific criteria or expectations for what makes a chemical suitable for this use?

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
161	1736.9(e)	If a bulk drug substance, or API, is used to compound a CSP, it shall comply with a USP drug monograph, be the active substance of an FDA approve drug, or be listed in CFR List of Bulk Drug Substances That Can Be Used To Compound Drug Products, 21 CFR 216, unless authorized by a public health official in an emergency use situation for a patient specific compounded sterile preparation.	FDA made it clear the purpose of the interim list is to prevent the lapse in patient access to legacy compounds until FDA can review each substance and make the final determination. This proposed regulation will eliminate patient access to several compounds in California while FDA reviews each bulk substance. Take note other states have not imposed such an unnecessarily restrictive regulation, and this proposal will cause Californians to go to other states to obtain these medications while they wait (most of the time many years) for FDA to review and approve or deny the use of the bulk in compounding.
161	1736.10.(a-d, f)	(a) Dry heat depyrogenation shall be done in compliance with USP Chapter 1228.1, Dry Heat Depyrogenation. (b) Sterilization by filtration shall be done in compliance with USP Chapter 1229.4, Sterilizing Filtration of Liquids. (c) Steam sterilization shall be done in compliance with USP Chapter 1229.1, Steam Sterilization by Direct Contact. (d) Dry heat sterilization shall be done in compliance with USP Chapter 1229.8, Dry Heat Sterilization. (f) Sterilization and depyrogenation of supplies and/or container–closure systems shall be done in compliance with USP Chapter 1229, Sterilization of Compendial Articles.	This is a misapplication of the USP Chapters in a way that USP itself states the chapters above 1000 are not intended to be applied. While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, General chapters numbered 1000 to 1999 are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these General Notices.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
161	1736.10(e)	No compound of a CSP from nonsterile components shall be prepared when the licensed location cannot also sterilize the CSP as described in this section.	Implies that CSPs made from nonsterile starting materials must have the option of being sterilized via filtration (as most compounds currently are) as well as being terminally sterilized via dry heat or steam. Many CSPs are heat sensitive and cannot maintain their physicochemical properties after exposure to extreme heats as seen in dry heat ovens and autoclaves. This seems to remove ebeam/radiation sterilization since its not a described method, limiting compounds utilizing this method.
162	1736.11 ©	A compounding record shall be a single document. The document shall satisfy the requirements of USP Chapter 797, as well as the following:	The expectation that a compounding record be a single document is unweildy and impractical, as proper documentation of the process will produce numerous attachments and become several pages in length (e.g., quality control tests such as visual inspection, photos of in-process and/or finished preparation, release test results from a 3rd party lab, microbiological and environmental monitoring results, etc.).

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
162	1736.11©(3)	The manufacturer, lot number, and expiration date shall be recorded for each component for CSPs.	As most compounders engaged in nonsterile to sterile compounding purchase bulks from FDA-registered repackers, they have been historically limited to the identity of the original manufacturer. As such, these compounders often are limited to stating the wholesaler in place of the manufacturer. Recommend allowing the name of the wholesaler in place of the manufacturer in such situations.
163	1736.12(b)	Validation of an alternative method for sterility testing shall be done in compliance with USP Chapter 1223, Validation of Alternative Microbiological Methods and shall document the method-suitability for each CSP formulation for which the alternate method is used.	While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, General chapters numbered 1000 to 1999 are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these General Notices.
	1736.12 ©	Injectable CSP's made from nonsterile components regardless of Category, must be tested to ensure that they do not contain excessive bacterial endotoxins, as established in Chapter 85. Results must be reviewed and documented in the compounding record prior to release.	It is unreasonable to test all CSPs made from a nonsterile ingredient for endotoxin, and it's not a requirement of USP. Doing so would delay the release of these Cat 1 compounds that are already short-dated. This requirement also does not fit the model of Category 2 where CSPs can be released without sterility testing using a limited BUD.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
	1736.15	A single-dose container entered or punctured inside of an ISO class 5 area must be discarded within 12 hours.	Is the container expected to be kept in the ISO 5 area after being punctured?
165	1736.16	A compounded stock solution intended for use in a CSP must comply with all provisions of this article including Category 1, Category 2, and Category 3.	What is the definition of a compounded stock solution? Is it one that is prepared well in advance of an intended preparation for compounding that may be used for several different lots? Or is the definition akin to a subformula, where a starting ingredient must be manipulated/mixed into an intermediate ingredient, which is then used to prepare the final parent compound? Also, it is not possible to comply with all 3 Categories of CSP. Suggest changing "and" to "or" in that sentence so that you comply with one of the CSP Categories instead of all of them.
165	1736.17(a)	(1) Comply with USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. (2) In addition to the SOPs required in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding, SOPs must also be developed to describe the following:	While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, General chapters numbered 1000 to 1999 are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these General Notices.

California Board of Pharmacy's Proposed Changes to Regulations Related to Pharmaceutical Compounding of Sterile Preparations (Repeal Article 7 and sections 1751-1751.10 and proposal to add new titles and sections 1736-1736.21 to Article 4.5 of Division 17 of Title 16 of the California Code of Regulations) Relevant California Law.			
Page	**Section**	**Statement**	**Clarification Requested**
166	1736.18(a)	The quality assurance program shall comply with section 1711 and the standards contained in USP Chapter 1163, Quality Assurance in Pharmaceutical Compounding. In addition, the program shall include the following:	While pointing a compounder to the USP chapters referenced to carry out best practices and to learn more about a given subject is encouraged, according to USP General Notices, General chapters numbered 1000 to 1999 are for informational purposes only. They contain no mandatory tests, assays, or other requirements applicable to any official article, regardless of citation in a general chapter numbered below 1000, a monograph, or these General Notices.
167	1736.21(b)	Compounding of allergenic extracts are limited to patient-specific prescriptions and the conditions limited to Category I and Category 2 CSPs as specified in USP 797.	Are there are no situations in which BUDs can be extended? Both USP and FDA state that a BUD of up to one year can be provided to these preparations.