Board of Pharmacy
Initial Statement of Reasons

Subject Matter of Proposed Regulation: Compounded Drug Preparations

Sections Affected: Amend Section 1735.1 of Article 4.5 of Division 17 of Title 16, California Code Regulations
Amend Section 1735.2 of Article 4.5 of Division 17 of Title 16, California Code Regulations
Amend Section 1735.6 of Article 4.5 of Division 17 of Title 16, California Code Regulations
Amend Section 1751.1 of Article 7 of Division 17 of Title 16, California Code Regulations
Amend Section 1751.4 of Article 7 of Division 17 of Title 16, California Code Regulations

Problems Addressed

The California State Board of Pharmacy (board) is a state agency vested with the authority to regulate the pharmacy industry, including pharmacies and pharmacists. (Bus. & Prof. Code, (B&P) § 4000, et seq.) The board's mandate and its mission is to protect the public. (B&P § 4001.1.) Pharmacies and pharmacists are permitted to compound drug preparations for patients. (B&P §§ 4029, 4036, 4037, 4051, 4052, 4127, 4129.) If, however, compounding is done in an unsafe or unsanitary manner, a compounded drug preparation can pose a significant and potentially fatal threat to the public. A pharmacist is required to label any prescription dispensed with the expiration date of the effectiveness of the drug dispensed. (B&P § 4076.) To minimize unnecessary risks to the public, the board establishes standards for compounding including, but not limited to, how to establish beyond use dates (BUDs) for compounded drug preparations, and standards for the locations and environment where compounding occurs.

On January 1, 2017, following three years of discussion and development, the board's regulations related to compounded drug preparations were extensively amended. (California Code of Regulations, tit. 16, div. 17, articles 4.5 and 7.) Following implementation of the amended regulations, the board and the public identified concerns, and requested clarifications and amendments to the compounding regulations. Specifically, the regulations relating to BUDs for non-sterile compounded drug preparations adversely impacted patient accessibility to the drugs. In addition, there was confusion between use of the terms "venting" and "exhaust"; concern about the methods for venting air from devices during hazardous drug compounding; confusion about which compounding environments require smoke studies and the necessary frequency for conducting the studies; and the board sought to clarify the maximum temperature for a sterile compounding area consistent with national standards.

Benefits

The anticipated benefits of proposed amendments to the regulations include: protecting the health and safety of the public, worker and environmental safety, and increasing openness and transparency in business and government. More specific benefits include: keeping drug compounding safe for the public, making it more likely that individuals compounding the drugs are safe, making compounded drugs more accessible to patients, making the drug compounding standards clearer to the regulated public and other agencies, and making the standards easier for the board to enforce.

The regulations would also create certainty about specified standards for compounding drugs that were adopted as an emergency effective December 19, 2017.

Specific Purpose of Proposed Changes and Rationale

Each regulation section being amended is discussed in turn below.

Proposed Change to Amend 16 CCR Section 1735.1, Compounding Definitions:

Subdivisions (c) and (f) would be amended to change the terminology from "ventilation" and "venting" to "exhausting" and "exhaust." The changes clarify that, where hazardous drugs are being compounded in a biological safety cabinet or an isolator, the exhaust air must be removed from the device by external building exhaust. This will clarify that exhaust air must travel from the device to the outside of the building.

Rationale for board's determination that the changes are necessary: The Office of Statewide Health Planning and Development (OSHPD), which has a role in reviewing construction projects at licensed hospitals, explained to the board that the correct industry term in the California Mechanical Code used to describe this specific type of air flow or movement out or away from a hood or biological safety cabinet is "exhaust." The word exhaust means air is being expelled, pushed or moved through the opening or outlet to the outside. This exhausting requirement is required to ensure worker safety. Additionally, OSHPD advises that in the California Mechanical Code the term venting is only used for heat producing or fuel burning applications like a gas range and therefore is not the most appropriate term in these contexts. This change should also help to avoid any confusion from or by pharmacies regulated both by the board and OSHPD.

Proposed Change to Amend 16 CCR Section 1735.2, Compounding Limitations and Requirements; Self-Assessment:

Subdivision (i)(1)(D) would be amended from "180 days for non-aqueous formulations," to "for non-aqueous formulations, 180 days or an extended date established by the pharmacist's research, analysis, and documentation." This change permits a pharmacist, using professional judgment, to extend the BUD for a non-aqueous formulation beyond 180 days, based on the pharmacist's research, analysis and documentation. The nature of the research, analysis, and documentation is further clarified in subdivision (G). A pharmacist's ability to extend the BUD for the specified

formulation will make the drug preparations more readily available to public. The pharmacist's exercise of professional judgment under the circumstances should adequately protect the public from any risks associated with the extended BUD.

Subdivision (i)(1)(E) would be amended from "14 days for water-containing oral formulations, and" to "for water-containing oral formulations, 14 days or an extended date established by the pharmacist's research, analysis, and documentation." This change permits a pharmacist, using professional judgment, to extend the BUD for a water-containing oral formulation, beyond 14 days based on the pharmacist's research, analysis and documentation. The nature of the research, analysis, and documentation is further clarified in subdivision (G). A pharmacist's ability to extend the BUD for the specified formulation makes will make the drug preparations more readily available to public. The pharmacist's exercise of professional judgment under the circumstances should adequately protect the public from any risks associated with the extended BUD.

Subdivision (i)(1)(F) would be amended from "30 days for water-containing topical/dermal and mucosal liquid and semisolid formulations" to "for water-containing topical/dermal and mucosal liquid and semisolid formulations, 30 days or an extended date established by the pharmacist's research, analysis, and documentation." This change permits a pharmacist, using professional judgment, to extend the BUD for a water containing topical/dermal and mucosal liquid and semisolid formulations beyond 30 days based on the pharmacist's research, analysis and documentation. The nature of the research, analysis, and documentation is further clarified in subdivision (G). A pharmacist's ability to extend the BUD for the specified formulation will make the drug preparations more readily available to public. The pharmacist's exercise of professional judgment under the circumstances should adequately protect the public from any risks associated with the extended BUD.

Subdivision (i)(1)(G) would be added to read:

> "A pharmacist, using his or her professional judgment may establish an extended date as provided in (D), (E), and (F), if the pharmacist researches by consulting and applying drug-specific and general stability documentation and literature; analyzes such documentation and literature as well as the other factors set forth in this subdivision, and maintains documentation of the research, analysis and conclusion. The factors the pharmacist must analyze include:
>
> (i) the nature of the drug and its degradation mechanism,
> (ii) the dosage form and its components,
> (iii) the potential for microbial proliferation in the preparation,
> (iv) the container in which it is packaged,
> (v) the expected storage conditions, and
> (vi) the intended duration of therapy.
>
> Documentation of the pharmacist's research and analysis supporting an extension must be maintained in a readily retrievable format as part of the master formula."

Subdivision (i)(1)(G) would be added to clarify how the pharmacist must use professional judgment to research, analyze and document his or her findings in extending a BUD pursuant to one of the identified subdivisions. It requires the pharmacist to research, at a minimum, by consulting and applying drug-specific and general stability documentation and literature. It requires the pharmacist, at a minimum, to analyze the identified documentation and literature, as well as items (i) – (vi) above, before reaching a conclusion. The board determined that items (i) – (vi) were the appropriate standards based on the factors specified in Chapter <795> of the United States Pharmacopeia - National Formulary (USP <795>) for determining BUDs. The board requires the pharmacist to exercise professional judgment in these ways because it is less likely under these circumstances that the public will be harmed by an extended BUD. The section also requires that the pharmacist maintain documentation of his or her research, analysis and conclusion, and to maintain such documents as part of the master formula in a readily retrievable format. The board requires the documentation and maintenance so that the board can readily inspect and verify whether the pharmacist complied with the regulation, and so that the board can take action if it finds that any non-compliance poses a risk to the public.

Subdivision (i)(3) would be amended to add "For sterile compounded drug preparations," to the beginning of the subdivision. This was done to clarify that, with the changes described above, this subdivision, which specifies a different method for extending a BUD, will only apply to sterile compounded drug preparations, and will not apply to non-sterile compounded drug preparations. The standards in subdivision (i)(3) are more appropriate to, and are practically feasible only for, sterile compounded preparations. The board determined that if it did not clarify that subdivision (i)(3) applies only to sterile compounding, the changes the board is proposing to subdivision (i)(1) would create confusion about the means to extend a BUD for both sterile and non-sterile compounded drug preparations.

Rationale for board's determination that the above changes are necessary: After implementation of the revised regulations, the board received significant testimony from the public that patients were not able to receive timely access to medications because of the restrictive BUD for non-sterile compounded preparations. The board's concern was so significant that it adopted emergency regulations on this subject effective December 19, 2017. The analysis below describes the impact of the board's regulations prior to the emergency rulemaking.

The most notable example of direct patient impact was in the area of pediatric oral suspensions where the board's then-current BUD requirements were impacting patient access and ability to maintain appropriate drug therapy. According to the United Network of Organ Sharing (UNOS) online database system (UNet), there were over 1,800 transplants in patients under the age of 18 in 2016 nationwide (based on Organ Procurement and Transplantation Network data as of November 24, 2017). Pediatric patients who have undergone an organ transplant use a compounded medication to prevent the body from rejecting the transplant. Failure to have timely and consistent access to this medication may result in transplant rejection.

For pediatric patients with autism, compounded medications play a vital role. When nutritional therapy is required, pharmacies combine vitamins, minerals, and supplements in specific dosage forms for such patients. According to the Professional Compounding Centers of America, children affected by autism often have unique physical or psychological challenges that can be exacerbated by ingredients found in food and medicine. Compounded medications are necessary to overcome these challenges.

Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients (humans and animals) whose health care needs cannot be met by manufactured medications. Compounding preserves the prescribers' ability to prescribe medications that best fit the needs of their patients. Pharmacies may either cease compounding, or they pass the costs associated with the higher testing standards to extend BUDs on to patients. The BUDs and high-test standards also restrict access to compounded drugs. Accordingly, patients may have suffered under the board's regulations because they paid higher costs than necessary and had limited access to necessary medications. In the context of less risky, non-sterile compounded drugs, the potential consequences of the decreased access to compounded medications far outweigh the additional public protections that come with the more restrictive BUD.

Another impact described was on the compounded medications that are available for prescriber office use. Under board regulations, a pharmacy may provide a reasonable quantity of a medication to a prescriber for office use. Specific to veterinary practices, most non-sterile compounded medications for animals are aqueous, or water-containing, oral formulations. Such medications had a BUD of 14 days. Because the patient population in a veterinary practice ranges in species and sizes (from birds to horses), the reasonable quantity a veterinarian might need to keep on hand varies greatly, and the supply cannot easily be managed without the ability of the compounder to extend the BUD of non-sterile compounded products beyond 14 days. Without the appropriate supply, the veterinarian cannot easily provide sufficient medication to the animal patient until the regular prescription can be filled.

Under the existing regulation, the restrictive BUDs mean that the medication is less accessible for patients because 1) patients can obtain only a limited quantity and must return to the pharmacy more frequently for refills, 2) the expense required to extend BUDs makes drugs prohibitively expensive for patients, or 3) the expense required to extend BUDs will mean that fewer pharmacies will compound and patients will have a harder time finding a pharmacy from which to obtain medications. The patients' restricted access, in turn, directly impacts patients' medication adherence. Patient medication adherence, where the patient takes medication in the dosage and in the pattern prescribed, is necessary for patient health. The lack of ready access to medications decreases patient medication adherence and, consequently, patient health.

This proposal is necessary to allow for the extension of the BUD of non-sterile compounded drug preparations in a manner consistent with national practice standards,

eliminate possible confusion about the means to extend a BUD for both sterile and non-sterile compounded drug preparations, and ensure timely access to non-sterile compounded drug preparations.

Proposed Change to Amend 16 CCR Section 1735.6 Compounding Facilities and Equipment:

Subdivision (e) was amended to change "vented" to "exhausted" for consistency with the changes in 16 CCR section 1735.1.

Subdivision (e)(1) would be amended to change the abbreviation from "hrs" to "hours." This is a non-substantive change made for grammatical clarity.

Subdivision (e)(3) would delete the word "PEC" (Primary Engineering Control) and replaces it with "BSC" (Biological Safety Cabinet). This provision would specify the type of PEC that must be externally vented. The board is providing clarity to this section by adding the more specific compounding terminology of BSC.

Rationale for board's determination that the above changes are necessary: The word PEC is a broad term as defined in 16 CCR section 1735.1(ab). When compounding with hazardous drugs one should only use a negative pressure PEC. A negative pressure PEC is a BSC. The use of a negative pressure PEC is already required in 16 CCR section 1735.4(g).

Subdivision (e)(3) would also be amended to add "except that a BSC used only for nonsterile compounding may use a redundant-HEPA filter in series" to permit a BSC used for nonsterile compounding to use redundant-HEPA filters in series. Additionally, this subdivision was further amended to change "vented" to "exhausted" for consistency with the changes in 16 CCR section 1735.1.

Rationale for board's determination that the above changes are necessary: External exhaustion protects worker safety by removing any contaminants from the immediate air where compounding is occurring. In series filtering of the air is, however, also an accepted air filtering method in USP <800> for nonsterile compounding (see section 5.3.1). This means there would be more than one HEPA filter linked together, each of which would filter the air before it could be recirculated into the compounding room, thereby further cleansing the air for the safety of employees and the environment. The board would be aligning its regulations with the current national compounding practice standards by updating this language. This will continue to protect the public while providing more options to protect worker safety during nonsterile compounding of hazardous drugs.

Proposed Change to Amend 16 CCR Section 1751.1 Sterile Compounding Recordkeeping Requirements:

Subdivision (a)(5) would be amended to add "Biannual" and "Class 5" to the requirements of the video smoke studies. This language is added to clarify the

frequency of the smoke studies and the class environment where the smoke studies must be performed. These changes further align the board's regulation with USP <797>. Smoke studies are used to verify air flow within a specified area. For purposes of this regulation, the smoke study is conducted to verify unidirectional airflow and sweeping action over and away from the compounding area and must be conducted under dynamic conditions.

Rationale for board's determination that the above changes are necessary: The board determined that biannual, meaning twice a year, was the appropriate frequency to perform such studies as it is the same requirement for smoke studies in an ISO Class 5 area and is consistent with USP <797>. The smoke studies help ensure public, worker and environmental protection by demonstrating the airflow in the compounding environment. The smoke study requires that fire alarm systems in a hospital to be turned to test mode (turns off the fire alarm) and it closes the compounding room for the duration of the test. On balance, the benefits of more frequent testing do not outweigh the time, effort and expense of the study; less frequent testing poses an unacceptable risk that the public and workers could be exposed to potentially harmful particles from air circulation.

Proposed Change to Amend 16 CCR Section 1751.4 Facility and Equipment Standards for Sterile Compounding:

Subdivision (k) would be amended to remove the higher figure in the temperature range (24 degrees (Celsius) and 75 degrees Fahrenheit, respectively), leaving only a single maximum temperature for the room where the sterile compounding occurs.

Rationale for board's determination that the above changes are necessary: The temperature where compounding occurs must be comfortable for all employees working in all required protective compounding garments and equipment so that the employees do not perspire; perspiration can expose the area, ingredients and drug products to contaminants. The prior room temperature range requirement was based on the conditions for an operating room. The revised maximum room temperature, 20 degrees Celsius (and its equivalent of 68 degrees Fahrenheit), is a reasonable temperature for a person when garbed for compounding, and it also consistent with USP <797>, which suggests 20 degrees Celsius as the maximum room temperature. (See USP <797>, *Environmental Quality Control* section, under the subheading *Facility Design and Environmental Controls*.)

Underlying Data

1. Relevant Meeting Materials and Minutes from Board Meeting held January 24-25, 2017
2. Relevant Meeting Materials and Minutes from Board Enforcement Committee Meeting held April 18, 2017
3. Relevant Meeting Materials and Minutes from Board Enforcement Committee Meeting held June 2, 2017

4. Relevant Meeting Materials and Minutes from Board Enforcement Committee Meeting held July 12, 2017
5. Relevant Meeting Materials and Minutes from Board Meeting held July 25-26, 2017
6. Chapter <795> of the United States Pharmacopeia - National Formulary (USP37 - NF32 through 2nd Supplement) (37th Revision, Effective December 1, 2014).
7. Chapter <797> of the United States Pharmacopeia - National Formulary (USP37 - NF32 through 2nd Supplement) (37th Revision, Effective December 1, 2014).
8. Chapter <800> of the United States Pharmacopeia - National Formulary (USP37 - NF32 through 2nd Supplement) (40thRevision, Effective December 1, 2017).
9. United Network for Organ Sharing (UNOS) Organ Procurement and Transplantation Network (OPTN) as of November 24, 2017 (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#)

Business Impact

The board has made a determination that the proposed regulatory action would have no significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. This initial determination is based on the absence of testimony to that effect during the development of the proposed regulation, which occurred over several months. Additionally, the proposed amendments more closely align the board's regulations with national practice standards for compounding in USP <795>, <797>, and <800>, allow for the extension of the BUD of non-sterile compounded drug preparations, eliminate possible confusion about the means to extend a BUD for both sterile and non-sterile compounded drug preparations, and ensure timely access to non-sterile compounded drug preparations. These amendments will positively impact California businesses.

Economic Impact Assessment/Analysis

There are approximately 7,627 pharmacies licensed in the state. There are approximately 7,150 licensed California community and outpatient pharmacies and 477 licensed hospital pharmacies. Each of these pharmacies may perform nonsterile compounding in accordance with board regulations.

The proposed changes to the terms "exhaust" and "vent" in the definitions of BSC and CACI are for clarity and to avoid confusion, and the board believes its licensees are currently following industry standards, which are consistent with these clarifications. It does not believe pharmacies will actually modify the equipment or facilities based on these changes. As a result, the board anticipates no economic impact from these changes, including the creation or elimination of jobs, businesses, or the expansion of businesses doing business with the state.

The proposed changes that reduce the standards for establishing a BUD for nonsterile compounded drug preparations will make it possible for pharmacies to use a longer BUD date and allow patients to get larger supplies of a drug at one time. This proposal will restore and codify the prior standard, which is consistent with national industry

standards for nonsterile compounding. The proposal will make it easier to extend BUDs for nonsterile compounded drugs, meaning the medications may be used for a longer period of time. The board anticipates lower costs for patients because they will obtain a larger supply of medications (fewer visits to the pharmacy), and possible lower health care costs overall because patients who can easily access and follow prescription regimens should have better health and need fewer health care interventions (doctor visits and treatments) long term. Fewer visits to the doctor and pharmacy could result in fewer co-pays, and could result in savings to the State for patients receiving Medi-Cal benefits. Based on public testimony, the board also anticipates that pharmacies will find it easier to continue to provide nonsterile compounding as a result of the change. Several pharmacies provided public comment that complying with the current regulation would be prohibitively expensive, and speculated that they may cease to provide nonsterile compounding services if the regulation was not modified. Fewer pharmacies providing these services may result in less competition in the marketplace.

The pharmacy and pharmacist may expend some additional resources in preparing the record when they exercise professional judgment to extend a nonsterile BUD, but those resources were likely being incurred prior to the board's revisions of its compounding regulation by diligent compounders acting consistent with industry practice. Because the board believes most pharmacy licensees to be diligent, it does not anticipate a significant cost associated with that requirement. The clarification that the existing text of the regulation for BUDs continues to apply to sterile compounding is also not anticipated to have an economic impact because it only makes it clearer that the existing standard still applies to that type of compounding. Therefore, the proposed amendments will not result in the creation or elimination of jobs, businesses, or the expansion of businesses doing business with the state.

The clarification that a biological safety cabinet may be used for nonsterile compounding with redundant, in series HEPA filters, rather than external venting, is unlikely to result in an economic change because it will restore the prior standard with respect to ventilation for nonsterile hazardous compounding. While it may be less expensive for a pharmacy that performs only nonsterile hazardous compounding, the board does not believe that many pharmacies perform only that unique type of compounding. Pharmacies that engage in sterile hazardous compounding will still have to invest in the more elaborate external venting. It is more likely that the modification will enable a nonsterile compounder to sometimes perform the nonsterile hazardous compounding for patients in a cost-effective manner without referring a prescription to another compounding pharmacy. Because this restores the prior industry standard for the unique type of compounding, and because the board believes most of its licensed pharmacies are compliant with such standards, the board does not anticipate an economic impact of this regulation on pharmacies. It is possible that patients may save time by being able to obtain their prescriptions from a pharmacy closer to their home.

The change to the standards to the smoke studies is made for clarification. Because the board believes that most of its licensees are diligent compounders, and existing industry standards require twice yearly studies only in ISO Class 5 environments, it does not anticipate pharmacies will be changing their practices. Without a change to

practices, the board does not anticipate an economic impact in the creation or elimination of jobs, businesses, or the expansion of businesses doing business with the State.

The change to the room temperature standard to remove the upper end of the range (leaving only the lower figure of 20 degrees Celsius) is not anticipated to have an economic impact on pharmacies. Similar to prior analysis, existing national industry standards would require the room temperature for sterile compounding to be not more than 20 degrees Celsius. The board believes that most licensed sterile compounding pharmacies are diligent and follow existing industry standards; without a change to the pharmacies' practices, the board does not anticipate an economic impact based on that change.

The board concludes that it is:

(1) Unlikely that the proposal will create or eliminate any jobs within California;
(2) Unlikely that the proposal will create new, or eliminate existing, businesses in California;
(3) Unlikely that the proposal will expand businesses currently doing businesses within the state;
(4) The benefits to the public are for consumer protection and increased assurance that any compounding services will be provided safely and effectively with minimal risk, that patients will have better access to nonsterile compounded medications, that workers and environments will be protected during the compounding of drugs and that the board will be better able to monitor compliance.

Specific Technologies or Equipment

This regulation does not mandate the use of specific technologies or equipment.

Consideration of Alternatives

No reasonable alternative to the regulatory proposal would be either more effective in carrying out the purpose for which the action is proposed or would be as effective or less burdensome to affected private persons and equally effective in achieving the purposes of the regulation in a manner that ensures full compliance with the law begin implemented or made specific. The only alternative identified would be to not implement the proposed changes. This is not reasonable as it would not mitigate the possible patient harm with the restriction of extending beyond use dates.