Finding of Emergency

On January 1, 2017, following three years of discussion and development, the California State Board of Pharmacy's (board) regulations related to compounded drug preparations were extensively amended. Following implementation of the amended regulations, stakeholders expressed concern that some of the new requirements were having a significant unintended impact on patients' ability to receive their medications. The board held two public committee meetings to discuss the issue and received comments from stakeholders. After considering public impact, the board finds that there is a significant adverse impact to patients related to the current requirements for establishing beyond use dates (BUDs) for non-sterile compounded drug preparations. Each day that the board's existing regulations are in place, there is a significant risk that patients will be deprived access to needed medications. In addition, the board finds that it is necessary to clarify the requirements to extend the BUDs for *sterile* compounded drug preparations in order to allow for the BUDs of non-sterile to be extended. Because of the immediate need for relief from the board's existing regulations that restrict patients' access to drugs, the board is adopting these changes on an emergency basis.

Section 1735.2, subdivision (i), of title 16, California Code of Regulations (section 1735.2), as currently written, establishes the BUDs of compounded drug preparations. Subdivision (i)(2) of that section does not include an option to extend the BUD specific to non-sterile compounded drug preparations. Each BUD exists for public protection because it represents the date after which the preparation should not be used – either because it may no longer be effective (or as effective) as a medication or because the preparation may develop impurities. United States Pharmacopeia - National Formulary (USP) <795>, an industry standard for pharmaceutical compounding of non-sterile preparations, anticipates that the BUD of non-sterile compounded drug preparations may be determined using stability information that is applicable to a specific drug and preparation, which may include drug-specific information as well as general documentation and literature.

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 most notable example of direct patient impact was in the area of pediatric oral suspensions, where the board's current BUD requirements are impacting patient access to 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.

Further, 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. Further, 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. Without this regulatory change, patients may suffer due to increased prices and restricted access to necessary medications. In the context of less risky, non-sterile compounded drugs, the consequences of the decreased access to compounded medications far outweigh the minimal additional public protections that come with the more restrictive BUD.

Another impact described was on the compounded medications that 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. Currently, such medications have 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 on a given day 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. The inability of patients to timely receive non-sterile compounded medication poses a serious threat to public health, safety, and welfare.

The board is proposing an emergency action to amend its regulations related to the establishment of beyond use dates for compounded drug preparations to allow for an extension of the beyond use date of non-sterile compounded drug preparations and to clarify that method suitability tests, container closure integrity tests, and stability studies

are only required to extend the beyond use date of sterile compounded drug preparations.

The Board approved the emergency rulemaking on July 25, 2017 and submitted the emergency rulemaking documents to the Department of Consumer Affairs for review and approval on August 18, 2017.

The Board will also pursue the non-emergency rulemaking process. However, to preserve the peace, health, safety and general welfare of the residents of the State of California, the board will adopt these amendments to existing regulation on an emergency basis.

INFORMATIVE DIGEST

Summary of Existing Laws and Regulations

The Pharmacy Law provides for the licensure and regulation of pharmacists and pharmacies in this state by the California State Board of Pharmacy. Existing law requires the board to adopt regulations establishing standards for compounding drug products in a pharmacy. Existing law requires licensure to operate as a pharmacy, subject to annual renewal. Existing law requires pharmacies to obtain a license from the board in order to compound sterile drug preparations, which is also subject to annual renewal. Similar licensing requirements apply to nonresident pharmacies shipping drug products (compounded or otherwise) into California. Existing law subjects pharmacies who compound sterile products to a cease and desist order issued by the board as well as other enforcement or disciplinary actions.

There are compounding professional standards that are used across the nation known as the United States Pharmacopeia and the National Formulary (USP–NF). USP-NF is a book of pharmacopeial standards. USP–NF is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). Monographs for drug substances, dosage forms, and compounded preparations are featured in the USP. As it pertains to this rulemaking, it contains standards for compounded preparations, for both sterile and non-sterile. The U.S. Federal Food, Drug, and Cosmetics Act designates the USP–NF as official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the standards in USP–NF; failure to do so may result in adulteration and misbranding of the drugs.

Business and Professions Code (B&P) section 4005 generally authorizes the board to adopt and amend rules and regulations pertaining to the practice of pharmacy and the administration of Chapter 9 of Division 2 of that code. B&P section 4127 generally authorizes the board to adopt and amend regulations establishing standards for compounding sterile drug products in a pharmacy.

Existing regulations establish standards and expectations for pharmacies compounding drug preparations. Existing regulations specify the beyond use dates (BUD) that apply

to sterile and non-sterile compounded drug preparations. Subdivision (i)(3) of section 1735.2 specifies a method to extend BUDs for all compounded drugs.

Policy Statement Overview

This regulation will revise and specify new requirements for a pharmacist establishing beyond use dates (BUDs) for non-sterile compounded drug preparations. In addition, it clarifies that an existing provision that permits extending the BUD will only apply to *sterile* compounded drug preparations.

Specific Changes

The specific changes, which are all to section 1735.2, subdivision (i), are as follows:

Subdivision (i)(1)(D) will 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 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) (E) will 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) was 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 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) (G) was added and reads as follows:

> "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:
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> (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) was 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 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) was 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 section, 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 the existing regulation are more appropriate to, and are practically feasible only for, sterile compounded preparations. The board determined that without making this change, 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.

Consistency and Compatibility with Existing Regulations

The board conducted a search of the California Code of Regulations and determined that the proposed regulation is neither inconsistent nor incompatible with existing state regulations.

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. 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/#)

Authority and Reference

Authority: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4126.9, 4127, 4127.1, 4127.2, 4127.3, and 4127.9 Business and Professions Code.

Fiscal Impact Estimates

Cost to Any Local Agency or School District for Which Government Code Sections 17500 – 17630 Require Reimbursement: None

Fiscal Impact on Public Agencies Including Costs or Savings to State Agencies or Costs/Savings in Federal Funding to the State: Minimal

Nondiscretionary Costs/Savings to Local Agencies: None

Effect on Housing Costs: None

Local Mandate: None

Mandate on Local Agencies or School Districts

This regulatory action does not impose a mandate on local agencies or school districts.

Contact Person

Inquiries or comments concerning the proposed rulemaking action may be addressed to:

Name:	Lori Martinez
Address:	1625 N. Market Blvd., N219 Sacramento, CA 95834
Telephone No.:	(916) 574-7917
Fax No.:	(916) 574-8617
E-Mail Address:	Lori.Martinez@dca.ca.gov

The backup contact person is:

Name:	Anne Sodergren
Address:	1625 N. Market Blvd., N219 Sacramento, CA 95834
Telephone No.:	(916) 574-7910
Fax No.:	(916) 574-8617
E-Mail Address:	Anne.Sodergren@dca.ca.gov

Website Access: Materials regarding this proposal can be found at www.pharmacy.ca.gov.