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

ENFORCEMENT AND COMPOUNDING COMMITTEE
CHAIR REPORT

Allen Schaad, Licensee Member, Chair
Amy Gutierrez, Licensee Member, Vice Chair
Greg Lippe, Public Member
Stan Weisser, Licensee Member
Valerie Muñoz, Public Member

a. Discussion and Consideration of Possible Board Policy Relating to Disclosure of Enforcement Actions Involving Board Members

Background

On the Department of Consumer Affairs' list of the "Top 10 Traits of an Effective Board Member" is "Be aware of conflicts of interest" and clarifies that such conflicts could be real or perceived.

One area where board members should be transparent is in the area of enforcement actions (whether they are directly or indirectly involved). Board members should determine whether recusal should occur based on the real or possible appearance of self- interest. For example, an enforcement matter involving a board member could influence a member's objectivity in future decision making.

Committee Discussion

The committee noted that to ensure greater transparency, the board should provide public reporting of any enforcement action affecting a board member. Examples of items that would trigger this reporting would be disciplinary or administrative actions. Such reporting could be completed as part of the board's Organizational Development Committee's report.

Committee Recommendation (Motion): Board member involvement in disciplinary or administrative action will be reported in the Organizational Development Report.

---

b. Discussion and Consideration of FDA Draft Guidance for Industry Relating to "Grandfathering Policy for Packages and Homogenous Cases of Product without a Product Identifier"

Attachment 1

Background

The Drug Supply Chain Security Act (DSCSA), signed into law in November 2013, established the federal track and trace requirements. The requirements encompass the entire drug supply chain and are phased in over a period of 10 years.

The FDA previously released a guidance document delaying some provisions of the DSCSA. Specifically, the FDA indicated that it did not intend to take action against manufacturers who do not add a product identifier to each package and homogenous case intended to be introduced into

commerce before November 27, 2018. (This represents a one-year delay in implementation of the track and trace requirements for manufacturers.)

Committee Discussion
The committee discussed the draft guidance detailing the circumstances under which the FDA would exempt packages and homogenous cases of products to be sold that are not labeled with the required product identifier. Such products may be grandfathered if there is documentation that it was packaged by a manufacturer or repackager prior to November 27, 2018.

As part of the discussion, the committee noted that the guidance document also highlights resulting downstream changes to the remaining partners in the supply chain. Similar wholesaler requirements regarding the sale of products without the required product identifier will be delayed until November 27, 2019 and the related dispenser requirements will be delayed until November 27, 2020.

The committee was advised that information on the delay in enforcement of these federal provisions by the FDA will be included in a future edition of *The Script*.

A copy of the draft guidance is provided in **Attachment 1**.

c. Discussion and Consideration of "CURES 2.0 Survey of California Physicians' and Pharmacists' Experience with and Attitudes about CURES 2.0"

Attachment 2

Background
In September 2013, California enacted a new law to update t h e Controlled Substance Utilization Review and Evaluation System (CURES). This law (SB 809) provided a dedicated funding source for CURES. It also required CURES to streamline the registration process and mandated registration for dispensers and DEA-licensed prescribers.

As part of the upgrade, CURES personnel added the following new features: a streamlined electronic registration process, automatic alerts for certain high-risk prescribing practices, ability to send peer-to-peer messages within CURES, ability to flag patient-provider agreements in CURES, and ability for CURES users to identify delegates who can initiate CURES patient reports. The bundle of upgrades authorized by SB 809 is collectively referred to as "CURES 2.0."

As approved by the Board at the July 2016 meeting, the board participated in assisting researchers from the University of California, Davis in surveying pharmacists. Questions were designed to learn about their use, access to, likes, dislikes and concerns with CURES. Physicians also participated in a related survey at the same time. The survey also evaluated physicians' and pharmacists' attitudes about prescription drug misuse and abuse, prescribing practices, and expectations about using prescription drug monitoring programs when prescribing or dispensing controlled substances.

Committee Discussion
The committee discussed the recently published survey results.

The survey was sent to a sample group comprised of a quasi-random sample of:

- one-twenty-fourth of all California pharmacists (*n* = 1626) ***{498 responded}***
- allopathic physicians (*n* = 5701)
- one-twelfth of all California osteopathic physicians (*n* = 577)

The survey received 1904 responses, for an overall response rate of 24% including:

- Pharmacists listed information from CURES the most common reason for changes in their dispensing practices (63 percent)
- Nearly all pharmacists and 92 percent of physicians reported that they had heard of CURES.
- Among respondents who were required to register for CURES, 96 percent of pharmacists reported that they were either registered or in the process of registering for CURES.
- Pharmacists reported having used CURES for longer than physicians. Over half (54 percent) of pharmacists reported using CURES for more than a year, and 70 percent reported using CURES for 7 months or more. In contrast, only 33 percent of physicians reported using CURES for more than a year, and 49 percent of physicians reported using CURES for 7 months or more.
- 32 percent of pharmacists rated registering for CURES as "difficult" or "very difficult" compared to 43 percent of physicians.
- 36 percent of pharmacists indicated that they check CURES for at least 50 percent of the controlled substance prescriptions they dispense or manage, while 28 percent of physicians indicated that they check CURES for least 50 percent of the patients to whom they prescribe controlled substances.
- For overall ease of use, 47 percent of pharmacists rated CURES 2.0 as an improvement over the prior system. For Patient Activity Reports, 52 percent of pharmacists reported that CURES 2.0 was an improvement over the prior system.
- When asked whether they felt they needed additional training or education about CURES, 40 percent of pharmacists responded affirmatively.
- A substantial majority of physicians (81 percent) and pharmacists (91 percent) agreed that their colleagues should check CURES when prescribing or dispensing a controlled substance.
- 39 percent of pharmacists supported mandatory CURES use for their colleagues.

The survey results suggest that access to CURES has a major impact on pharmacists dispensing practices, and that increased professional awareness of risks and benefits plays a major role in decreased prescribing /dispensing for both physicians and pharmacists. These survey results indicate that pharmacists have near perfect compliance with mandatory CURES registration.

A copy of the survey is provided in **Attachment 2.**

d. <u>Discussion and Consideration of Noncompliant California Security Prescription Forms</u>

Attachment 3

<u>Background</u>

The California Health and Safety Code contains specific provisions for California security forms, which are specialized prescription forms used for prescribing controlled substances in California.

There are 14 security features that are required to appear on the form, and the California Department of Justice licenses the printers who are authorized to print these forms.

Over the last year, the board has identified noncompliant security forms in use. When identified, the board typically cites and fines the pharmacy, and advises the prescribing board that one of its practitioners is using noncompliant forms. Sometimes the board also identifies fraudulent security forms in use which are used to divert drugs or obtain them illegally. These cases are handled differently and more aggressively.

Committee Discussion

The committee was advised that in early November 2017, two pharmacy chains stopped dispensing medications when a noncompliant security form was provided. In speaking with the Department of Justice at the end of November, the board learned that in October 2017 a DOJ audit of California licensed security printers identified 12 California licensed printers that were producing security forms that were not compliant with California's Health and Safety Code.

As part of its discussion, the committee was advised that there are 33 DOJ licensed security printers and at the time of the discussion, four licensed security printers continued to print non-compliant forms. The committee discussed the two major areas of noncompliance: no checkoff box for the number of refills and absence of a watermark on the reverse of the form.

When the program was initially established, the board was responsible for approval of the security printers. However in 2006, licensure responsibility was transferred to DOJ. The committee considered if such licensure should return to the Board of Pharmacy, due to our ability to license and regulate.

The committee discussed a subscriber alert that was released by the executive officer to resolve the problem without harm to patients. A copy of the alert is included in **Attachment 3**.

Committee Recommendation (Motion): Direct the executive officer to work with Department of Justice to ensure that prescribers are receiving compliant forms.

---

e. Update on Emergency Regulation to Amend California Code of Regulations, Title 16 Section 1735.2, Relating to Compounding Beyond Use Dates

Attachment 4

Background

During its July 2017 Board Meeting, the board voted to pursue an emergency regulation to amend section 1735.2 relating to establishing beyond use dating for nonsterile drug compounded preparations.

Committee Discussion

The committee was advised that the emergency regulation took effect December 11, 2017 and will be effective for 180 days, during which time the regular rulemaking must be promulgated to make the changes permanent. Two 90-day readoptions of the emergency regulation are allowed if the board is making progress towards adopting the permanent regulations.

Recent Update

The permanent regulations are currently in the DCA's pre-notice review period. Board staff are monitoring progress of the pre-notice review and working with the department to address concerns as they arise.

Attachment 4 includes a copy of the emergency regulation language and the proposed permanent regulation language.

f. Discussion and Consideration of Draft Frequently Asked Questions Relating to Compounding Requirements, California Code of Regulations, Title 16, Sections 1735 et seq. and 1751 et seq.

Attachment 5

Background

As part of its ongoing evaluation of the board's compounding requirements, some requested changes were proposed and are included in the board's emergency rulemaking and/or the rulemaking to make the emergency rulemaking permanent as referenced above.

During the meeting when considering some other requested changes, members determined that a change to the regulation was not currently necessary, but additional guidance documents should be provided in the form of a FAQ.

Committee Discussion

The committee reviewed the draft FAQs and invited the public to submit additional topics for a FAQs.

Attachment 5 includes draft FAQs in the following areas:

- Electronic monitoring of refrigerator and freezer temperatures
- Definition of Sterility
- Definition of Stability
- "Identical" as applied in CCR Section 1735.2(i)(4)
- Quality assurance minimum testing requirements

g. Discussion and Consideration of Requested Changes to Board Compounding Regulations, California Code of Regulations, Title 16, Sections 1735 et seq. and 1751 et seq., Including Presentation Regarding Beyond Use Date Testing

Attachment 6

Relevant Law

CCR Section 1735 et seq., and CCR section 1751 et seq., establish the requirements for compounding drug preparations.

Business and Professions Code section 4127.1 requires the board to adopt regulations to establish policies, guidelines and procedures to implement Article 7.5, Sterile Drug Products, and further requires the board to review any formal revisions to General Chapter 797 of the United States Pharmacopeia and the National Formulary (USP-NF) relating to the compounding of sterile preparations no later than 90 days after the revision becomes official.

Background

Since adoption of the board's current compounding regulations, the board has received public comment regarding the impact of the regulations on patient populations, principally for oral compounded preparations, including animals.

The committee held meetings on June 2 and July 11, 2017, to consider both written and verbal comments, and requested changes offered by board staff and members of the public. As noted in prior agenda items, the board initiated an emergency and regular rulemaking to update its regulations in response to some of the requested changes considered by the committee.

During the September 2017 committee meeting, it was requested that the committee continue its consideration of additional requested changes offered by stakeholders during previous meetings.

Committee Discussion

During the meeting, DynaLabs provided the committee with a presentation on stability studies and potency over time. The presentation highlighted the differences between potency over time testing and stability indicating testing. The committee was advised that USP calls for stability indicating testing.

A copy of the presentation is included in **Attachment 6**.

Following the presentation, the committee considered possible changes to the board's current regulations. Below is a brief summary of the requested changes, relevant information considered by the committee and action by the committee.

- **Proposed Change to CCR 1735(b) regarding the use of compounding kits:**

  The committee previously considered a change that would exempt from the definition of compounding the combining of nonhazardous ingredients from prepackaged kits supplied by an FDA-registered manufacturer for nonsterile preparations. In response to public comment, board staff was directed to contact the FDA to determine the level of regulatory oversight these kits have. Staff was subsequently advised that the FDA is not aware of any FDA approved applications for compounding kits and that the FDA has neither conducted premarket review of any instructions provided with such products nor performed any premarket review of the manufacturer's assignment of BUDs. The FDA also advised board staff that it is currently reviewing its policy in this area.

  Committee Action: The committee stated the goal is to move forward with a change while making sure the kits are available and meet all standards. The committee directed staff to develop language for consideration at its next meeting.

- **Proposed Change to CCR Section 1735.1(r) regarding the board's current definition of "hazardous drug"**

  The committee previously considered a request to change the board's definition of "hazardous drug" to mirror the definition provided in USP <800>. In late September 2017 USP announced the postponement of the official date of Chapter <800> until December 1, 2019 to coincide with the anticipated update to Chapter <797>. Consistency between the

board's definition of hazardous and USP <800> would be beneficial to the board's regulated public.

Committee Action: The committee considered language that could be used to update the board's definition of hazardous to coincide with the effective date of USP <800>:

…

(r) Until December 1, 2019, "~~H~~hazardous" means all anti-neoplastic agents identified by the National Institute for Occupational Safety and Health (NIOSH) as meeting the criteria for a hazardous drug and any other drugs, compounds, or materials identified as hazardous by the pharmacist-in-charge. Effective December 1, 2019, "hazardous" means any drug identified by NIOSH and that exhibits at least one of
the following six criteria:

(1) Carcinogenicity
(2) Teratogencitiy of developmental toxicity

(3) Reproductive toxicity in humans

(4) Organ toxicity in low doses in human or animals

(5) Genotoxicity

(6) New drugs that mimic existing hazardous drugs in structure or toxicity.

…

The committee requested that board staff research USP <800> requirements and the provisions for a risk-based approach.

- **Proposed Change to CCR Section 1735.2(a), regarding documentation of a prescriber's authorization to compound**

  During prior discussions, the committee considered if it would be appropriate to remove the requirement to document a prescriber's authorization to compound a product and requested additional research to be conducted by board staff. Without documentation neither the pharmacy nor the board will have any record that the prescriber authorized use of a compounded product. Public comment previously contemplated that such a requirement could result in a delay in therapy.

  Committee Action: The committee directed staff to create language that is not burdensome or redundant to current requirements in law while focusing on consumer protection.

- **Proposed Change to CCR Section 1735.2(i)(2)-(4), regarding BUDs for sterile drug products**

  During prior discussions, the committee considered if changes were necessary to the requirements for the establishment of a BUD for sterile products. (BUD requirements for nonsterile products are currently undergoing changes through the emergency rulemaking.) At the time of its last discussion, the committee was anticipating changes to USP <797> would be in place in 2018.

Committee Discussion

Given the delay in USP 797 changes, the committee considered changes to BUD assignments that may more closely align with current USP <797> requirements

…

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

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

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

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

(D) The beyond use date assigned for sterility in section 1751.8., or-

(~~3~~E) ~~Extension of a beyond use date is only allowable when supported by the following:~~ A beyond use date established by a pharmacist using his or her professional judgment after conducting research and analysis and preparing documentation. The pharmacist's documentation must demonstrate that:

(~~A~~ i) The beyond use date is supported by a USP <671> compliant Method Suitability

Test,

(~~B~~ii) The beyond use date is supported by a USP <1191> Container Closure Integrity

Test, ~~and~~

(~~C~~iii) The beyond use date is supported by Stability Studies, and

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

…

Committee Action: The committee asked board staff to research the impact to patients who need more than one dose and look for alternatives.

- **Proposed Change to CCR Section 1735.6(e), regarding the venting requirements for hazardous drug compounding.**

The board's current regulations require hazardous compounding (among other requirements) must be completed in an externally vented, physically separated room and that each PEC in the room shall also be externally vented. [Note: This is one of two provisions where the board has established the authority for a pharmacy to secure a temporary waiver to complete construction necessary to comply.] Board staff received questions about the venting requirements and was recently advised that the board's application of the requirement (which allows a single venting system for both the PEC and the room) is consistent with OSHPD's. Specifically, OSHPD advised board staff that there is nothing in the code or USP that prevents a

designer from venting the room through the hood and noted that the key is to ensure that the design would not violate the hood's listing requirements to be able to maintain its ISO-5 environment.

Committee Discussion
The committee was advised that board staff received information that the board's requirements should be placed in the Building Standards Code.

Committee Action: Board staff will be working with legal counsel to determine if such a change is necessary and if so, the best strategy for implementation.

- **Proposed Change to CCR Section 1751.4(d) regarding decontamination requirements and cleaning frequency.**

In response to questions submitted previously, it was suggested that the board consider detailing contamination requirements as well as reconsider the frequency of cleaning of some surfaces and areas.

Committee Discussion
The committee considered proposed language that that could be used to update such requirements.

…

(d) Cleaning shall be done using a germicidal detergent ~~and sterile water.~~ The use of a sporicidal agent is required to be used at least monthly. When hazardous drugs are being compounded, decontamination with an inactivating agent shall take place before each cleaning. Any dilution of the germicidal detergent, sporicidal agent, or inactivating agent shall only be done with sterile water.

(1) All ISO Class 5 surfaces, work table surfaces, carts, counters, and the cleanroom floor shall be cleaned at least every 48 hours and at minimum must be cleaned each day prior to compounding.~~at least daily.~~ After each cleaning, disinfection using a suitable sterile agent shall occur on all ISO Class 5 surfaces, work table surfaces, carts, and counters.

(2) Walls, ceilings, storage, shelving, tables, stools, and all other items in the ISO Class 7 or ISO Class 8 environment, and the segregated sterile compounding areas shall be cleaned at least monthly.

(3) Cleaning shall also occur after any unanticipated event that could increase the risk of contamination.

(4) All cleaning materials, such as wipers, sponges, and mops, shall be non-shedding and dedicated to use in the cleanroom, or ante-area, and segregated sterile compounding areas and shall not be removed from these areas except for disposal.

…

Committee Action: The committee directed board staff to conduct more research to present to the committee, at a future meeting.

- **Proposed Change to CCR Section 1751.7(e)(1) regarding alternative testing methods and end product testing requirements**

The committee has previously considered whether a rapid microbial test method may be appropriate to consider. Such testing, when used and applied appropriately can provide test results much more quickly than current testing requirements which could address some concerns raised about delays in therapy.

Committee Discussion

The committee considered language that would allow for alternative testing methods and provided below.

> …(e)(1) Batch-produced sterile drug preparations compounded from one or more non-sterile ingredients, except as provided in paragraph (2), shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens. Sterility testing shall be USP chapter 71 compliant unless a validated rapid microbial method (RMM) test is performed and pyrogens testing shall confirm acceptable levels of pyrogens per USP chapter 85 limits, before dispensing. Validation studies (method suitability) for each formulation using a RMM test shall be kept in a readily retrievable form at the licensed location. 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. Exempt from pyrogen testing are topical ophthalmic and inhalation preparations.
> …

Also related to this section, the committee has previously considered if the board should expand its current exception for end product testing of non-sterile to sterile batch preparations. Given that pharmacies need to provide compounded preparations when a drug is in short supply, a limited exception for such instances may be appropriate. The committee considered the below language that could be used to create such an exception.

> …
> (2) The following non-sterile-to-sterile batch drug preparations do not require end product testing for sterility and pyrogens:
> (A) Preparations for self-administered ophthalmic drops in a quantity sufficient for administration to a single patient for 30 days or less pursuant to a prescription.
> (B) Preparations for self-administered inhalation in a quantity sufficient for
>
> administration to a single patient for 5 days or less pursuant to a prescription.
>
> (C) Preparations noted as "Currently in Shortage" on the FDA website for a single patient on a one-time basis for 21 days or less pursuant to a prescription. The pharmacy shall retain a copy of the documentation of the shortage and the specific medical need as part of the pharmacy record.
> …

Committee Action: In response to public comment regarding irrigation solutions, the committee directed board staff to research if irrigation solutions require pyrogen testing and

report back to the committee its finding.

Attachment 6 includes a copy of each of the above regulation sections showing the full regulation text for each section, a paper entitled, "*Strength and Stability Testing for Compounded Preparations,"* and the PowerPoint presentation provided to the committee.

h. Status Report on Waivers Issued for Compounding Construction Compliance Delays Pursuant to California Code of Regulations, Title 16, Sections 1735.6 and 1751.4

Relevant Law

Title 16 of California Code of Regulations (CCR) section 1735.6 (f) states that where compliance with California's compounding regulations requires physical construction or alteration to a facility or physical environment, the board may grant a waiver for a period of time to permit the required physical changes. There is a related provision in CCR section 1751.4 which provides the same allowances for sterile compounding facilities.

Overview of Process

An application for any waiver must be made in writing, identify the provisions requiring physical construction or alteration, and provide a timeline for any such changes. The board is able to grant the waiver for a specified period when, in its discretion, good cause is demonstrated for the waiver.

Initial review of the waiver is performed by staff led by the executive officer, who approves or denies the waiver request. Approval or denial of a waiver is provided to facilities in writing. If a waiver is denied by the executive officer, there is an appeal process that will be reviewed by two board members, currently Board Members Schaad and Law.

The goal of the construction waiver process is to secure full compliance at the earliest possible time.

Facilities that have been denied a waiver have been made aware that there is an appeal process. Such waiver appeals go to the subcommittee of Mr. Schaad and Mr. Law. There have been no appeals made since July 1, 2017.

Committee Discussion

The committee noted that the waiver review process is ongoing as pharmacies continue to seek extensions or modifications (often due to construction delays) in their facilities to comply with <USP> 800. During the November 2017 Board Meeting, the recent delay in USP <800> to December 1, 2019, was discussed at which time the board granted authority to the executive officer to grant waivers through November 30, 2019.

The board's continued monitoring of progress is consistent with USP, which is "…encouraging early adoption and implementation of Chapter <800> to help ensure a safe environment and protection of healthcare practitioners and others when handling hazardous drugs."

The committee was advised that since the waiver process began, 415 waivers have been approved. Board staff continues to receive a relatively low number of new requests. However, as implementation of the waivers transitions to a monitoring phase, board staff is now undertaking

review of status reports that are documenting progress of an entity to achieving compliance.

i. Enforcement Statistics

Enforcement statistics for the first six months of FY 2017/18 are provided in **Attachment 7**.

The board received 1306 complaints and has closed 1459 investigations. The board has issued 103 Letters of Admonishment, 1,035 Citations and referred 185 cases to the Office of the Attorney General. The board has secured three interim suspension orders, been granted six penal code 23 suspensions, and issued one cease and desist. Further, the board has revoked 54 licenses, accepted the disciplinary surrender of 28 licenses, and imposed other levels of discipline against 75 licensees.

j. Future Committee Meeting Dates

Below are the committee dates for 2018.

- March 28, 2018
- June 7, 2018
- September 5, 2018
- December 13, 2018

Attachment 1

Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Office of Compliance at 301-796-3100 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, or drugtrackandtrace@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

November 2017
Procedural

Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

November 2017
Procedural

TABLE OF CONTENTS

I. INTRODUCTION 4

II. BACKGROUND 5

A. Drug Supply Chain Security Act 5

B. Scope of This Guidance 7

III. INTERPRETATION OF SECTION 582(a)(5)(A) OF THE DSCSA 7

IV. GRANDFATHERING POLICY 7

A. Grandfathering Exemption from Certain Transaction-Related Requirements of Section 582 8

1. Scope of Grandfathering Exemption 8

2. Trading Partner Requirements under the Grandfathering Exemption 8

B. Saleable Returned Packages and Homogenous Cases of Product 11

V. DISTINCTIONS BETWEEN THE GRANDFATHERING POLICY AND THE COMPLIANCE POLICY FOR PRODUCT IDENTIFIER REQUIREMENTS UNDER THE DSCSA 12

Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public.[2] You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance addresses product distribution security provisions in section 582 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360eee). Section 582 was added by the Drug Supply Chain Security Act (DSCSA) (Title II of Public Law 113-54) and facilitates the tracing of products through the pharmaceutical distribution supply chain by requiring trading partners[3] (manufacturers, repackagers, wholesale distributors, and dispensers) to exchange transaction information, transaction history, and a transaction statement (product tracing information) when engaging in transactions involving certain prescription drug products. In addition, section 582 requires manufacturers and repackagers to start affixing or imprinting a product identifier to each package[4] and homogenous case[5] of product no later than November 27, 2017 (for manufacturers) and November 27, 2018 (for repackagers).[6]

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

[2] This sentence does not apply to the discussion regarding the circumstances under which packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582 of the FD&C Act shall be exempted from the requirements of section 582.

[3] For this guidance, *trading partner* is defined as described in section 581(23)(A) of the FD&C Act (21 U.S.C. 30eee(23)(A)). Although third-party logistics providers are also considered trading partners under section 581(23)(B) (21 U.S.C. 30eee(23)(B)) of the FD&C Act, they are not subject to the same product tracing requirements of section 582.

[4] *Package* is defined in section 581(11) of the FD&C Act.

[5] *Homogeneous case* is defined in section 581(7) of the FD&C Act. The terms "homogeneous" and "homogenous" are used interchangeably throughout the DSCSA. FDA has chosen to use only the term "homogenous" throughout this guidance.

[6] See section 582(b)(2)(A) and 582(e)(2)(A)(i) of the FD&C Act. See also FDA's draft guidance, *Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy* (explaining, among other things, that FDA does not intend to take action against manufacturers who do not affix or imprint a product identifier to each package and homogenous case of products intended to be introduced in a transaction into commerce before November 26, 2018).

We are issuing this guidance to help trading partners understand their compliance obligations under section 582 for packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582. This guidance, which is required by section 582(a)(5)(A) of the DSCSA, specifies whether and under what circumstances such packages and homogenous cases of product shall be exempted, as grandfathered, from certain requirements of section 582. It also briefly discusses the distinctions between the grandfathering policy provisions of this guidance with the draft guidance, *Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy*.[7]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

An exception to that framework derives from section 582(a)(5)(A) of the FD&C Act, wherein Congress granted authorization to FDA to issue guidance specifying whether and under what circumstances packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582 shall be exempted from the requirements of section 582. Accordingly, insofar as this guidance specifies such circumstances, this document is not subject to the usual restriction in FDA's good guidance practice regulations that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d). Therefore, when finalized, the portion of this guidance that specifies the circumstances under which packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582 shall be exempted from the requirements of section 582 will have binding effect, as indicated by the use of the words *must*, *shall*, or *required*.

II. BACKGROUND

A. Drug Supply Chain Security Act

The DSCSA (Title II of Public Law 113-54) was signed into law on November 27, 2013. Section 202 of the DSCSA added section 582 to the FD&C Act, which established product tracing requirements for manufacturers, repackagers, wholesale distributors, and dispensers of most prescription drugs in a finished dosage form for administration to a patient without

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or FDA Biologics guidance web page at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

substantial further manufacturing (products).[8] The DSCSA phases in its new requirements over a period of 10 years.

A critical component of the product tracing scheme outlined in the DSCSA is the product identifier.[9] Section 582 requires that each package and homogenous case of product in the pharmaceutical distribution supply chain bear a product identifier that is encoded with the product's standardized numerical identifier, lot number, and expiration date by specific dates. Under the statute, manufacturers are required to begin affixing or imprinting (adding) a product identifier to each package and homogenous case of a product intended to be introduced into commerce no later than November 27, 2017.[10] Repackagers are required to do the same no later than November 27, 2018.[11]

Sections 582(c)(2), (d)(2), and (e)(2)(A)(iii) of the DSCSA restrict trading partners' ability to engage in transactions involving packages and homogenous cases of product that are not labeled with a product identifier after specific dates. Beginning November 27, 2018, repackagers may not receive or transfer ownership of a package or homogenous case of a product that is not encoded with a product identifier.[12] Similar restrictions go into effect for wholesale distributors and dispensers on November 27, 2019, and November 27, 2020, respectively.[13]

Section 582(a)(5)(A) gives FDA the authority to exempt packages and homogenous cases of product without a product identifier from the product tracing requirements discussed above. We are required to issue guidance that specifies whether and under what circumstances we will exercise this authority. Only packages and homogenous cases of product that are "in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of [section 582]" are eligible for an exemption under section 582(a)(5)(A).

The draft guidance *Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy* (Product Identifier Compliance Policy or compliance policy) explains that FDA does not intend to take action against manufacturers who do not add a product identifier to each package and homogenous case of product intended to be introduced in a transaction into commerce before November 27, 2018. This represents a 1-year delay in enforcement of section 582(b)(2)(A) of the FD&C Act. The Product Identifier Compliance Policy also explains that FDA does not intend to take action against manufacturers and other trading partners who transact such product or verify it for investigatory purposes or saleable returns without using the product identifier. The grandfathering policy in this guidance should be read in conjunction with the Product Identifier Compliance Policy, which is currently a draft guidance, but which the agency plans to finalize after considering comments received.

[8] Certain prescription drugs are excluded from the product tracing requirements of section 582. See section 581(13) of the FD&C Act for the definition of the term *product*.

[9] *Product identifier* is defined in section 581(14) of the FD&C Act.

[10] See section 582(b)(2)(A) of the FD&C Act. See also FDA's draft guidance, *Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy*.

[11] See section 582(e)(2)(A)(i) of the FD&C Act.

[12] See section 582(e)(2)(A)(iii) of the FD&C Act.

[13] See sections 582(c)(2), (d)(2) of the FD&C Act.

B. Scope of This Guidance

This guidance specifies the circumstances under which packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582, including saleable returned packages and homogenous cases of product, shall be exempted, as grandfathered, from certain requirements of section 582. This guidance does not address products or transactions for which a waiver, exception, or exemption has been granted under section 582(a)(3) of the DSCSA from the requirement to bear a product identifier on packages and homogenous cases. FDA intends to address waivers, exceptions, and exemptions under section 582(a)(3) in a separate guidance.

III. INTERPRETATION OF SECTION 582(a)(5)(A) OF THE DSCSA

Under section 582(a)(5)(A), packages and homogenous cases of product that are not labeled with a product identifier are eligible to be exempted from the requirements of section 582 if they are "in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of this section [(i.e., section 582)]." For the purposes of this guidance, a package or homogenous case of product is "in the pharmaceutical distribution supply chain" if it was packaged by the product's manufacturer before November 27, 2018. We interpret "the effective date of the requirements of this section" as referring to the date set forth in section 582(e)(2)(A)(i) of the DSCSA regarding when repackagers must begin adding product identifiers to packages and homogenous cases of product (i.e., no later than November 27, 2018).

Consequently, a package or homogenous case of product that is not labeled with a product identifier is eligible for an exemption under section 582(a)(5)(A) as described in this guidance only if the product's manufacturer packaged the product before November 27, 2018.

IV. GRANDFATHERING POLICY[14]

FDA has determined that there are circumstances under which it would be appropriate to exempt packages and homogenous cases of product meeting the conditions of section 582(a)(5)(A) of the FD&C Act (i.e., the packages and homogenous cases of product that are not labeled with a product identifier and are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582) from certain requirements of section 582. Those circumstances, and the statutory requirements from which packages and homogenous cases of product without a product identifier shall be exempted, as grandfathered, are set forth below. Our policy for saleable returned packages and homogenous cases of product meeting the conditions of section 582(a)(5)(A) is also described below.

[14] Insofar as section IV of this guidance specifies the circumstances under which packages and homogenous cases of product that are not labeled with a product identifier and that are in the pharmaceutical distribution supply chain at the time of the effective date of the requirements of section 582 of the FD&C Act shall be exempted from the requirements of section 582, it will have binding effect, once finalized.

A. Grandfathering Exemption[15] from Certain Transaction-Related Requirements of Section 582

1. Scope of Grandfathering Exemption

A package or homogenous case of product that is not labeled with a product identifier shall be exempted from certain requirements in section 582 (i.e., grandfathered) where there is documentation that it was packaged by a manufacturer before November 27, 2018. For example, if a package or homogenous case of product not labeled with a product identifier is accompanied by transaction information or a transaction history that includes a sale before November 27, 2018, that trading partner can reasonably conclude the product was packaged by a manufacturer before that date.

If the transaction information or transaction history does not include a sale before November 27, 2018, and absent other indicia that a product may be suspect or illegitimate, the transaction statement is one indication that the product was in the pharmaceutical distribution supply chain before that date.[16] Furthermore, manufacturers retain packaging date information in the ordinary course of business and as a part of batch recordkeeping, and they should provide the packaging date to subsequent trading partners if they request it.

2. Trading Partner Requirements under the Grandfathering Exemption

The specific requirements of section 582 from which a grandfathered product is exempted are set forth below. To assist trading partners in understanding how the grandfathering exemption applies to their activities, the requirements for trading partners are addressed separately below.

- Manufacturer Requirements

  Manufacturers are exempted from two requirements of section 582 in situations where there is documentation that the product involved in the transaction was in the pharmaceutical distribution supply chain before November 27, 2018.

  - First, in those circumstances, manufacturers investigating suspect product without a product identifier to determine whether that product is illegitimate are exempted from that part of section 582(b)(4)(A)(i)(II) which requires that they verify product at the package level using the product identifier beginning November 27, 2017; specifically, manufacturers shall not be required to verify the product at the package level using the product identifier. However, a manufacturer must still validate any applicable transaction history and transaction information in its possession and otherwise investigate the product

[15] As used in this guidance, the term *grandfathering exemption* refers to an exemption from the requirements of section 582 that is established by this guidance under the authority of section 582(a)(5)(A) of the FD&C Act.

[16] Per section 581(27)(d) of the FD&C Act, the transaction statement indicates that an owner did not knowingly ship a suspect or illegitimate product.

to determine if it is illegitimate in accordance with section 582(b)(4)(A)(i)(II); the exemption does not extend to these requirements.

- Second, in those circumstances, manufacturers are exempted from that part of section 582(b)(4)(C) of the DSCSA which, beginning November 27, 2017, requires that upon request from an authorized trading partner in possession or control of a product that believes is from the manufacturer, such manufacturer verifies[17] a product at the package level using the product identifier. However, a manufacturer must still follow all other steps as described in 582(b)(4)(C).

Manufacturers must comply with all other applicable requirements of section 582 when engaging in transactions pursuant to this exemption.

- Wholesale Distributor Requirements

Wholesale distributors are exempted from two requirements of section 582 in situations where there is documentation that the product involved in the transaction was in the pharmaceutical distribution supply chain before November 27, 2018.

- First, in those circumstances, wholesale distributors are exempted from section 582(c)(2), which requires that they engage in transactions involving only product encoded with a product identifier beginning November 27, 2019.

- Second, in those circumstances, wholesale distributors are exempted from that part of section 582(c)(4)(A)(i)(II) of the DSCSA which requires that they undertake certain activities to determine whether a product is illegitimate. Specifically, wholesale distributors shall not be required to verify the product at the package level using the product identifier beginning November 27, 2019. However, wholesale distributors must still validate any applicable transaction history and transaction information in their possession and otherwise investigate the suspect product to determine if it is illegitimate. The exemption does not extend to these requirements of section 582(c)(4)(A)(i)(II).

Wholesale distributors must comply with all other applicable requirements of section 582 when engaging in transactions pursuant to this exemption.

- Dispenser Requirements

Dispensers are exempted from two requirements of section 582 in situations where there is documentation that the product involved in the transaction was in the pharmaceutical distribution supply chain before November 27, 2018.

[17] *Verify* is defined in section 581(28) of the FD&C Act.

- First, in those circumstances, dispensers are exempted from section 582(d)(2) of the DSCSA, which requires that they engage in transactions involving only product encoded with a product identifier beginning November 27, 2020.

- Second, in those circumstances, dispensers are exempted from section 582(d)(4)(A)(ii)(II), which requires that they verify the product identifier of a portion of packages beginning November 27, 2020, as part of an investigation conducted to determine whether a product is illegitimate. However, dispensers must still verify the lot number of a suspect product as described in section 582(d)(4)(A)(ii)(I), validate any applicable transaction history and transaction information in their possession as described in section 582(d)(4)(A)(ii)(III), and otherwise investigate the product to determine if it is illegitimate as required by section 582(d)(4)(A)(ii)(IV). The exemption does not extend to these requirements of section 582(d)(4)(A)(ii) of the DSCSA.

Dispensers must comply with all other applicable requirements of section 582 when engaging in transactions pursuant to this exemption.

- Repackager Requirements

  FDA has also determined that the grandfathering exemption applies to certain repackager activities in situations where there is documentation that the product involved in the transaction was in the pharmaceutical distribution supply chain before November 27, 2018.

  - First, in those circumstances, repackagers are partially exempted from the requirement of section 582(e)(2)(A)(iii) of the DSCSA to only engage in transactions of product encoded with a product identifier beginning November 27, 2018; specifically, repackagers may ***accept*** ownership of packages or homogenous cases of product without a product identifier after November 27, 2018. However, if a repackager wishes to ***transfer*** ownership of a package or homogenous case of product without a product identifier on or after November 27, 2018, it must, in accordance with section 582(e)(2)(A)(i), first add a product identifier to the package or homogenous case of product.

  - Second, in those circumstances, repackagers investigating suspect product without a product identifier to determine whether that product is illegitimate are also exempted from that part of section 582(e)(4)(A)(i)(II) which requires that they verify product at the package level using the product identifier beginning November 27, 2018; specifically, repackagers shall not be required to verify the product at the package level using the product identifier. However, a repackager must still validate any applicable transaction history and transaction information in its possession and otherwise investigate the product to determine if it is illegitimate in accordance with section 582(e)(4)(A)(i)(II); the exemption does not extend to these requirements.

- Third, if a repackager initially repackaged and sold product without a product identifier before November 27, 2018, it is exempted from that part of section 582(e)(4)(C) of the DSCSA which, beginning November 27, 2018, requires that upon request from an authorized trading partner in possession or control of a product it believes is from the repackager, such repackager verifies the product using the product identifier. However, a repackager must still follow all other steps as described in 582(e)(4)(C).

Repackagers must comply with all other applicable requirements of section 582 when engaging in transactions pursuant to this exemption.

Trading partners may engage in transactions involving products exempted as grandfathered per the conditions of the grandfathering policy until product expiry, regardless of when the transaction occurs. Although there is no sunset date for the grandfathering exemption, FDA expects there to be relatively few, if any, of these packages and homogenous cases of product without a product identifier in the pharmaceutical distribution supply chain by November 27, 2023.[18]

The FDA guidance *Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification* notes that a package missing product tracing information is a scenario that could significantly increase the risk of a suspect product entering the drug supply chain.[19] As product identifier requirements are implemented over time, trading partners should be diligent when engaging in a transaction of a package or homogenous case of product without a product identifier to ensure it is subject to the grandfathering policy, other type of exemption, or a compliance policy.

FDA emphasizes that trading partners must comply with all other applicable requirements of section 582 when engaging in transactions covered by the exemption established by this guidance. For example, a wholesale distributor that transfers ownership of a package or homogenous case of product without a product identifier after November 27, 2019 that is subject to the grandfathering exemption must provide the subsequent owner with the product's transaction information, transaction history, and transaction statement prior to, or at the time of, the transaction.

B. Saleable Returned Packages and Homogenous Cases of Product

Section 582 addresses trading partners' ability to accept and redistribute product that is returned to them in saleable condition. Manufacturers, wholesale distributors, and repackagers are required under sections 582(b)(4)(E), (c)(4)(D), and (e)(4)(E), respectively, to verify the product identifier of a saleable returned package or sealed homogenous case of product that is intended for further distribution. This requirement goes into effect on November 27, 2017 (per the

[18] We note that the enhanced drug distribution security provisions of section 582(g) go into effect on November 27, 2023.

[19] See guidance for industry at https://www.fda.gov/downloads/drugs/guidances/ucm400470.pdf.

statute) for manufacturers, November 27, 2018, for repackagers, and November 27, 2019, for wholesale distributors. [20]

For returns[21] of saleable packages and homogeneous cases of product without product identifiers that were in the pharmaceutical distribution supply chain before November 27, 2018, manufacturers, wholesale distributors, and repackagers are exempted from the requirements of sections 582(b)(4)(E), (c)(4)(D), and (e)(4)(E), respectively, to verify the product identifier of a saleable returned package or sealed homogenous case of product that is intended for further distribution. Manufacturers are exempted from the requirements of 582(b)(2)(A) to add product identifiers before redistributing such product. Repackagers are exempted from the requirements of 582(e)(2)(A)(i) and (e)(2)(A)(iii) to add product identifiers before redistributing such product if they initially repackaged and sold the product without a product identifier before November 27, 2018. Trading partners must comply with all other applicable requirements of section 582 when engaging in returns. For example, wholesale distributors must still meet the requirements of section 582(c)(1)(B)(i)(II) and only accept returned product from a dispenser or repackager beginning November 27, 2019, if they can associate the returned product with the transaction information and transaction statement for that product.

V. DISTINCTIONS BETWEEN THE GRANDFATHERING POLICY AND THE COMPLIANCE POLICY FOR PRODUCT IDENTIFIER REQUIREMENTS UNDER THE DSCSA

The grandfathering and compliance policies have different legal statuses and apply in different scenarios. Under the grandfathering policy, eligible packages and homogenous cases of product are exempted, as grandfathered, from certain DSCSA requirements. The Product Identifier Compliance Policy, by contrast, describes FDA's intention not to take action against certain trading partners in certain circumstances; the DSCSA requirements remain in effect, but the Agency intends to exercise discretion in how it enforces the law.

[20] See also FDA's draft guidance, *Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy*.

[21] *Return* is defined in section 581(17) of the FD&C Act.

Attachment 2

California's Controlled Substance Utilization Review and Evaluation System

CURES 2.0

Survey of California Physicians' and Pharmacists' Experience with and Attitudes about CURES 2.0

September 2017

California's Controlled Substance Utilization Review and Evaluation System (CURES 2.0)

Survey of California Physicians' and Pharmacists' Experience with and Attitudes about CURES 2.0

September 2017

This survey was funded by cooperative agreement 2015-PM-BX-K001, awarded to the California Department of Justice by the United States Bureau of Justice Assistance and by cooperative agreement 1U17CE002747, awarded to the California Department of Public Health by the Centers for Disease Control and Prevention. This report is solely the responsibility of the authors and does not necessarily reflect official views of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the United States Department of Justice.

The authors gratefully acknowledge the advice, cooperation and in-kind support provided by staff from the California State Board of Pharmacy, the Medical Board of California, and the Osteopathic Medical Board of California, without which this survey would not have been possible.

Authors

Stephen G. Henry, MD
John Pugliese, PhD
Melissa Gosdin, PhD
Andrew J. Crawford, PhD
Garen J. Wintemute, MD, MPH

EXECUTIVE SUMMARY

In 2013, California enacted a new law that provided dedicated funding for California's Controlled Substance Utilization, Review and Evaluation System (CURES), authorized an update and expansion of the CURES database and functionality, and mandated CURES registration for pharmacists and controlled substance prescribers. As part of a comprehensive evaluation of these updates (collectively known as "CURES 2.0"), a statewide, representative survey of California physicians and pharmacists was conducted to assess attitudes and beliefs about CURES and controlled substance use, and to identify areas for further improvement of CURES.

The survey was conducted with cooperation from the California State Board of Pharmacy, the Medical Board of California, and the Osteopathic Medical Board of California. The overall survey response rate was 24% (n = 1904). Comparison of aggregate data on responders and non-responders indicated that responders appear to be representative of California physicians and pharmacists.

Response patterns were broadly similar for pharmacists and physicians. Compared to physicians, pharmacists generally expressed more positive attitudes about CURES, were more likely to register for and use CURES, were more concerned about prescription drug abuse, and expressed a greater sense of professional obligation to use CURES. Pharmacists reported near perfect compliance with mandatory CURES registration (which took effect a few months prior to survey deployment), compared to approximately 82% compliance among DEA-licensed physicians. An additional 12% of physicians reported that they planned to register within the next 3 months. Physicians most frequently cited the time required to register and lack of importance as reasons for not registering; technical problems with CURES were rarely cited as a reason for not registering.

Thirty-one percent of physicians and 20% of pharmacists reported a recent decrease in the number of controlled substances they prescribed and dispensed, respectively. Survey data indicated that access to data from CURES, increased professional awareness of controlled substance risks and benefits, and new clinical guidelines all played major roles in decreasing prescribing and dispensing.

Twenty-eight percent of physicians indicated that they check CURES for least 50% of the patients to whom they prescribe controlled substances. Thirty-six percent of pharmacists indicated that they check CURES for at least 50% of the controlled substance prescriptions they dispense. Sixty percent of physicians and 80% of pharmacists agreed that CURES was helpful. Thirty-two percent of physicians and 59% of pharmacists agreed that CURES was easy to use. Among physicians and prescribers who had used both CURES 1.0 and CURES 2.0, more than 90% rated CURES 2.0 as the same or better than CURES 1.0 across all categories. Forty-seven percent of physicians and 40% of pharmacists reported a need for additional training on how to

use CURES. The most commonly identified needs for additional training related to the new advanced features of CURES 2.0, such as peer-to-peer messaging.

A substantial majority of physicians (81%) and pharmacists (91%) felt that their peers should check CURES when prescribing or dispensing a controlled substance, respectively. Nineteen percent of physicians and 36% of pharmacists felt that their peers ought to be using CURES 100% of the time when prescribing or dispensing controlled substances. In contrast, only 23% of physicians felt that physicians should be required to check CURES when prescribing. The corresponding value for pharmacists was 39%, indicating that nearly two-fifths of pharmacists supported mandatory CURES use for pharmacists. Over two-thirds of pharmacists (69%) agreed that checking CURES was considered standard of care, compared to 40% of physicians.

When asked to give open-ended suggestions or comments, many physicians and pharmacists felt that CURES was not relevant to their practice, particularly those who did not practice in California. Some physicians who rarely prescribed controlled substances and pharmacists who worked in hospital settings also felt that CURES was not relevant to their practice. Finally, several pharmacists recommended improving the accuracy and timeliness of CURES data, including adding data from federal pharmacies in California.

INTRODUCTION AND BACKGROUND

Prescription Drug Monitoring Programs (PDMPs) are considered an important, but under used, tool for combating the ongoing epidemic of prescription opioid abuse and overdose.[1,2] Preliminary evidence suggests that PDMP use may be associated with changes in prescribing behaviors;[3-5] however, important knowledge gaps remain around PDMPs. Each state has a separate PDMP, so the administration, technical details, strengths, and weakness of PDMPs vary widely across states. Thus, to a large extent, the strengths, weaknesses, and effectiveness of PDMPs must be evaluated on a state-by-state basis, because suggestions for improving PDMPs in one state may not be applicable to PDMPs in other states.

On the other hand, all PDMPs share the same general characteristics and so findings related to general PDMP attributes (e.g., ease of registration and use, data accuracy and timeliness) do likely generalize across states. In addition, social and professional norms (i.e., physicians' and pharmacists' beliefs and attitudes about PDMPs) are also likely to be an important determinant of PDMP use and effectiveness, but these concepts have so far been relatively unexplored. Most prior research on barriers to PDMP use has focused on state-specific technical and logistical barriers (e.g., website design, registration processes, etc).[6-9]

California has the nation's oldest prescription drug monitoring program. CURES was established in 1939. An electronic interface that prescribers and pharmacists could search in real time was implemented in 2009, but the CURES program was de-funded in 2011 due to state budget cuts. In September 2013, California enacted a new law to update CURES. This law (SB-809) provided a dedicated funding source for CURES. It also required CURES to streamline the registration process and mandated registration for dispensers and DEA-licensed prescribers. The bill did not specifically define all of the features that needed to be part of the CURES upgrade. Nevertheless, as part of the upgrade, CURES personnel added the following new features: streamlined electronic registration process, automatic alerts for certain high risk prescribing practices, ability to send peer-to-peer messages within CURES, ability to flag patient-provider agreements in CURES, and ability for CURES users to identify delegates who can initiate CURES patient reports. The bundle of upgrades authorized by SB-809 is collectively referred to as "CURES 2.0." The current CURES home page can be accessed at the following web address: https://oag.ca.gov/cures.

To evaluate the impacts of CURES 2.0, a representative, statewide survey of California physicians and pharmacists was conducted by University of California, Davis researchers in collaboration with the California Department of Public Health. The survey focused on physicians and pharmacists because these two professions comprise over 80% of all CURES users and because they represent the two primary categories of CURES users, prescribers and dispensers. Surveys were completed between August 2016 and January 2017. Data collection started after California implemented mandatory CURES registration (July 1, 2016), in order to ensure that all

respondents had a chance to register for CURES prior to the survey. The primary survey goals were as follows:

- To assess attitudes and beliefs about controlled substance misuse and abuse among California physicians and pharmacists
- To assess compliance with mandatory CURES registration
- To evaluate the impact of changes made as part of CURES 2.0
- To evaluate beliefs, attitudes, and social and professional norms related to using CURES
- To elicit suggestions and identify priority areas for further improvement of CURES

This report provides a detailed account of the survey methodology and a descriptive account of survey results. More detailed analysis of predictors of intent to use CURES and of the responses to an open-ended survey question will be published separately. The intended audience for this report includes the California Departments of Justice and Public Health, California state licensing and regulatory boards, California physicians and pharmacists, as well as researchers and public health officials in other states.

FUNDING AND ACKNOWLDGEMENTS

This survey was funded by the Harold Rogers Prescription Drug Monitoring Program (BJA cooperative agreement 2015-PM-BX-K001 awarded to the California Department of Justice) and the Prevention for States program (CDC cooperative agreement 1U17CE002747 awarded to the California Department of Public Health). Neither funding agency had any input into the design or conduct of this survey, or into the analysis of results. The final decision about what to publish in this report rested solely with the listed report authors.

The authors gratefully acknowledge the advice, cooperation and in-kind support provided by staff from the California State Board of Pharmacy, the Medical Board of California, and the Osteopathic Medical Board of California, without which this survey would not have been possible.

METHODS

Survey development

This survey was developed and conducted by the University of California Davis in collaboration with the California Department of Public Health, and with cooperation from the California State Board of Pharmacy, the Medical Board of California (MBC), and the Osteopathic Medical Board of California (OMBC).

Survey questions assessed the following topics: demographics and prescribing / dispensing practice patterns, concern about prescription drug misuse and abuse, beliefs about CURES effectiveness, CURES registration status, barriers to CURES registration and use, beliefs about professional norms, social norms, and moral obligations regarding CURES, questions about

specific features of CURES 2.0, need for additional training on how to use CURES, and comparing CURES 2.0 versus CURES 1.0. Survey questions were informed in part by reviewing previously published PDMP surveys.[6-9] Questions for allopathic and osteopathic physicians were identical; questions for pharmacists were very similar to questions for physicians, but asked about dispensing or managing rather than prescribing controlled substances. In order to reduce respondent fatigue, skip logic was used so that, to the extent possible, prescribers only answered questions relevant to their practice. For example, physicians who reported not having a DEA license (and so were not eligible to register for CURES) did not answer questions about CURES, and physicians who reported not being registered for CURES did not answer questions about how often they checked CURES. An open-ended question asking "Is there anything else you would like to tell us about CURES? (e.g., problems, recommendations)" was also included. The survey was web-based and was hosted by Qualtrics (Provo, UT), an online survey program. The complete physician and pharmacist surveys are shown in Appendix A and B, respectively.

Survey questions were reviewed by the study team and approved by the 3 regulatory boards. Community physicians and pharmacists not related to the study pilot tested the survey to identify any ambiguous questions and technical problems with the web interface. This project was reviewed by the University of California Davis Institutional Review Board and deemed to be program evaluation rather than human subjects research.

Sampling strategy

The survey sample was all pharmacists and allopathic physicians with licenses expiring on November 30, 2016 and all osteopathic physicians with licenses expiring on December 31, 2016. Licenses in California must be renewed every 2 years and expire at the end of the licensee's birth month; for osteopathic physicians, licenses must be renewed every 2 years and expire 6 times a year based on licensee birth month. Therefore, the sample comprised a quasi-random sample of one-twenty-fourth of all California pharmacists (n = 1626) and allopathic physicians (n = 5701) and one-twelfth of all California osteopathic physicians (n = 577).

Initial survey invitations were mailed from each regulatory board between August and October, 2016 and were included in the same envelope as the licensee's license renewal paperwork. One or two additional reminders were sent by mail from the survey team; an additional reminder letter was mailed from each regulatory board using envelopes showing that board's return address. Allopathic physicians also received several email reminders. The OMBC and the State Board of Pharmacy do not maintain licensee email addresses and so could not send out email reminders. All survey materials included the logos of both the University of California Davis and the applicable regulatory board. A detailed timeline of the survey reminder schedule for each survey is shown in Appendix C. All surveys were closed on January 31, 2017. Licensees were advised that participation was voluntary and that their individual responses would not be shared with the regulatory boards. All surveys were completed on the web. Respondents could access the survey by typing in a short web address, scanning a QR code on their cell phone, or clicking on a survey link on the appropriate regulatory board's web page. Licensees were required to type

in their license number before starting the survey. This approach prevented licensees from taking the survey multiple times, restricted respondents to licensees in the sample, and allowed us to keep track of respondents in order to avoid sending reminders to licensees who had already completed the survey.

Statistical analysis

All surveys opened with 2 items assessing respondents' concern about prescription drug misuse and abuse. Because physicians without a DEA license were screened out after these 2 items, physicians who completed these 2 survey items were considered responders for purposes of calculating overall survey response rate. To assess for response bias, the demographic and training characteristics of responders and non-responders were compared using aggregate data obtained from each regulatory board. Descriptive statistics (means and standard deviations for continuous measures, proportions for ordinal and Likert-type items) were calculated for each survey item. Responses from allopathic and osteopathic physicians were combined for all analyses; differences between allopathic and osteopathic physicians were not investigated.

Path analysis

A subset of items was also used to conduct a *path analysis* to identify factors associated with physicians' and pharmacists' intent to use CURES during the next 3 months. Path analysis is a statistical method for modeling and evaluating causal associations between variables.[10] Full details of this analysis will be published elsewhere, and so are not repeated in this report.

Qualitative analysis

Responses to the open-ended survey question were analyzed using content analysis followed by thematic analysis. For the content analysis, two investigators independently reviewed responses to identify content categories that emerged from the data. Investigators met weekly to discuss provisional categories, refine definitions, and discuss challenging cases. Codes were developed and reviewed jointly to ensure coding consistency while minimizing investigator bias. Disagreements were resolved by discussion, resulting in a final list of 18 codes. Both investigators independently coded responses using the final list of codes and compared results until they could apply codes reliably with high levels of agreement on a 5% sample of all open-ended responses. The remaining responses were each coded by one investigator; both investigators reviewed all comments where coding was considered ambiguous. The prevalence of each content category was assessed separately for physicians and pharmacists; the final list of codes was identical for both groups of respondents. Open-ended responses varied in length from a few words to a few paragraphs; therefore, coding categories were exhaustive but not mutually exclusive. For example, if a single response mentioned three different categories, that response was assigned to all three categories.

For the thematic analysis, investigators reviewed responses for each code to identify categories and themes that occurred within the responses. Crosscutting categories and themes were identified and discussed. Based on this analysis, codes were collapsed into larger themes.

RESULTS AND DISCUSSION

Response rate and sample representativeness

The survey received 1904 responses, for an overall response rate of 24%. As shown in Table 1, the response rate for pharmacists was substantially higher than rates for physicians. Detailed comparison of survey responders versus non-responders is shown in Table 2. Overall, characteristics for responders and non-responders were similar. Compared to non-responders, responders were older and more likely to be white or Asian / Pacific Islander. Physician responders were more likely to report psychiatry or emergency medicine as their primary specialty and to have a California address of record. Pharmacist responders were more likely to have a BS degree than a PharmD degree; this difference likely reflects the age difference between responders and non-responders, because PharmD became the required entry-level pharmacist degree in 2003.

Table 1. Survey response rates

Item	Pharmacists	MBC	OMBC	All physicians	Total
Responses	498	1289	117	1406	1904
Invitees[a]	1626	5701	577	6278	7904
Response rate (%)	30.6	22.6	20.3	22.4	24.1

[a]Pharmacy and MBC samples included licensees with out of state addresses. OMBC sample included only licensees with California addresses.

A major strength of this survey was collaboration with and support from the State Board of Pharmacy, OMBC, and MBC. Cooperation from these boards made it possible to survey a representative, statewide sample of physicians and pharmacists, to achieve a higher response rate than prior web-based surveys of prescription drug monitoring programs,[8,11] and to compare characteristics of responders and non-responders to assess sample representativeness and possibility of response bias. As shown in Table 2, physician responders were slightly more likely to report specialties that commonly prescribe controlled substances (e.g., emergency medicine, psychiatry, internal medicine, family medicine, and anesthesiology). However, responders and non-responders were otherwise similar, suggesting that the sample is likely to be representative of California pharmacists and physicians despite a response rate that is lower than traditional paper surveys delivered by U.S. mail.

Table 2. Comparison of responder and non-responder characteristics.

	Physicians					Pharmacists[f]			
	Responders		Non-Responders			Responders		Non-Responders	
Item Response	n = 1406		n = 4872			n = 497		n = 1119	
Gender (n, %)[a]					Gender (n, %)				
Male	908	64.6	3152	64.7	Male	207	41.7	439	39.2
Female	498	35.4	1719	35.3	Female	290	58.4	680	60.8
Mean age, Years (SD)[b]	56.7	(13.0)	52.7	(14.1)	Mean age, Years (SD)	48.9	(13.6)	44.8	(13.8)
Foreign medical graduate (n,%)[c]	289	22.4	1065	24.1					
Race and ethnicity (n, %)[d]					Degree type (n, %)[g]				
White	672	47.8	1843	37.8	PharmD	332	66.8	868	77.6
Black	40	2.8	126	2.6	BS	165	33.2	251	22.4
Asian/Pacific Islander	389	27.7	1571	32.2					
Hispanic	40	2.8	226	4.6	Pharmacy school (n, %)				
Other	16	1.1	26	0.5	Foreign school	61	12.3	89	8.0
Decline to state	198	14.1	764	15.7	US school	436	87.7	1030	92.1
Missing	51	3.6	316	6.5	California school	251	50.5	644	57.6
Primary specialty (n, %)[e]									
Internal medicine	186	13.2	589	12.1					
Family medicine	175	12.4	503	10.3					
Psychiatry	116	8.3	250	5.1					
Emergency medicine	93	6.6	185	3.8					
Anesthesiology	78	5.5	228	4.7					
OBGYN	55	3.9	207	4.2					
Pediatrics	84	6.0	295	6.1					
Pain medicine	10	0.7	23	0.5					
Radiology	53	3.8	241	4.9					
Current license	1390	98.9	4450	91.3					
California address[c]	1123	87.1	3419	77.5	California address	444	89.2	974	86.4

[a]1 missing value; [b]weighted average of osteopathic and allopathic physician data; [c] Reported for allopathic physicians only (1,289 responders; 4,412 non-responders); [d] Categories not mutually exclusive; [e] Categories are mutually exclusive; only results for the most common specialty categories are shown; [f] Data missing for 10 pharmacists; [g] PharmD became the required entry-level degree in 2003.

Respondent characteristics

All California pharmacists were required to register for CURES by July 1, 2016. According to California's mandatory CURES registration law (SB-809), only physicians authorized to prescribe controlled substances (i.e., physicians who are licensed in California and who have a DEA license assigned to a California address) are required to register for CURES. Of the physicians surveyed, 91% (n = 1275) reported having a DEA license to prescribe controlled substances, and 78% (n = 995) of physicians with a DEA license reported currently prescribing controlled substances in their practice. Physicians who self-reported not having a DEA license did not answer any further survey questions, because they are not eligible to register for or use CURES. The survey did not prompt physicians to specify whether their DEA license was assigned to an address in California. Thus, it is not possible to determine exactly how many physician respondents had DEA licenses associated with a California address and so were required to register for CURES under SB-809.

Analysis of answers to the open-ended survey question indicated that a large proportion of the 22% of physicians who reported not prescribing controlled substances were retired or not in active clinical practice. Nineteen percent of all physician respondents commented that that they felt CURES was not relevant to their practice, and about half of these responses indicated that this lack of relevance was due to the physician being retired or working outside of California.

Table 3 shows respondent demographics (excluding physicians who reported not having a DEA license to prescribe controlled substances). Physician respondents were predominantly male and white; pharmacist respondents were predominantly female. Pharmacists were 47% Asian and 42% white. Physicians were slightly older than pharmacists.

Table 3. Respondent demographics

	Physicians n = 1275[a]		Pharmacists n = 482	
Item Response	n	%	n	%
Gender				
Male	734	63.9	193	43.3
Female	407	35.4	251	56.3
Other	8	0.7	2	0.4
Did not respond	126		36	
Ethnicity				
Not Hispanic or Latino	1034	93.0	421	97.7
Hispanic or Latino	78	7.0	10	2.3
Did not respond	163		51	
Race and Ethnicity				
American Indian or Alaskan Native	6	0.5	4	0.9
Asian	272	24.6	206	47.1
Black or African American	34	3.1	9	2.1
Hawaiian or Pacific Islander	14	1.3	5	1.1
White	694	62.7	184	42.1
Other	86	7.8	29	6.6
Did not respond	169		45	
	Mean	SD	Mean	SD
Respondent age (years)	55	12.9	49	13.4
Did not respond (n)	152		45	
Years in practice	23	13.2	21	13.7
Did not respond (n)	139		37	

[a]Physicians who reported having a DEA license

Table 4 shows physician-reported specialty and pharmacist-reported practice location. The most common physician specialties were adult primary care (i.e., internal medicine and family medicine) and surgical specialties. The most common pharmacist practice location was chain pharmacy (31%), followed by hospital (26%). Nine percent of pharmacists reported not being involved in patient care. Twelve percent of pharmacists noted in the open-ended survey question that CURES was not relevant to their practice, and many of these specified that CURES was not relevant to their practice because they only dispensed controlled substances in the hospital setting.

Table 4. Practice specialties and dispensing sites of survey respondents

	Physicians n = 1275[a]		Pharmacists n = 482	
Item Response	n	%	n	%
Specialty				
Anesthesiology and pain medicine	81	7.2		
Emergency medicine	98	8.7		
Pediatrics	94	8.3		
Adult primary care	454	40.1		
Psychiatry	110	9.7		
Surgical specialty	166	14.7		
Other	128	11.3		
Did not respond	144			
Dispensing Site				
Chain pharmacy			137	30.8
Hospital			116	26.1
Independent pharmacy			67	15.1
Mass merchandiser			3	0.7
Supermarket			21	4.7
Other patient care practice			60	13.5
Other non-patient care			41	9.2
Did not respond			37	

[a]Demographic counts available for physicians who reported having a DEA license

Prescribing and dispensing practices

The survey included several items designed to gauge how often respondents prescribed or dispensed controlled substances. Based on respondents' description of their clinical practice patterns, physicians who reported prescribing any controlled substances were estimated to prescribe to a mean of 55 patients per month (median=35, interquartile range 22-65). Pharmacists were estimated to dispense or manage a mean of 760 controlled substance prescriptions per month (median=522, IQR 196-1044).

Respondents were also asked about changes in their prescribing and dispensing practices over the past 3 months. As shown in Table 5, 31% of physicians and 20% of pharmacists reported prescribing / dispensing fewer controlled substances, respectively. Very few respondents indicated that they had prescribed / dispensed more controlled substances over the past 3 months.

Table 5. How have your prescribing / dispensing practices changed in the last 3 months?

	Physicians n = 1275[a]		Pharmacists n = 482	
Item Response	n	%	n	%
Prescribe (dispense) far fewer controlled substances	137	11.6	24	5.4
Prescribe (dispense) fewer controlled substances	231	19.6	65	14.7
No change	800	68.0	321	72.5
Prescribe (dispense) more controlled substances	8	0.7	31	7.0
Prescribe (dispense) far more controlled substances	0	0.0	2	0.5
Did not respond	99		39	

[a]Physicians who reported having a DEA license.

Respondents who reported any change in practice were then asked about the reasons for this change (Table 6). For physicians, increased professional awareness of risks and benefits was by far the most commonly cited reason for changes in prescribing, and was endorsed by 65% of physicians who reported a recent change in their prescribing practices. Other common reasons cited by physicians were new clinical guidelines (47%) and increased patient awareness of risks and benefits (37%). The majority of pharmacists (55%) also cited increased professional awareness. For pharmacists, information from CURES was the most common reason endorsed for changes in their dispensing practices (63%); only 25% of physicians endorsed this factor. Other commonly cited reasons pharmacists endorsed for changing dispensing habits were increased professional awareness of risks and benefits (55%) and new clinical guidelines (35%). Among physicians who endorsed "other" reasons, most cited either increased concern about opioid risks or working in a setting that did not involve controlled substance prescribing. *These results suggest that access to CURES has a major effect on pharmacist dispensing practices, and that increased professional awareness of risks and benefits plays a major role in decreased prescribing /dispensing for both physicians and pharmacists.*

Table 6. What factors led you to change your prescribing / dispensing practices [Check all that apply]?

	Physicians n = 376[a]		Pharmacists n = 122[a]	
Item Response	n	%	n	%
Change in practice location or patient mix	90	24.1	36	28.8
Increased professional awareness of risks, benefits, and other solutions	243	65.2	67	54.9
New clinical guidelines and recommendations	175	46.9	43	35.2
CURES providing greater access to patient prescription drug history	94	25.2	77	63.1
Increased patient awareness of risks and benefits	136	36.5	38	31.1
Medico-legal ramifications	103	27.6	14	11.5
Other	55	14.8	14	11.5

[a]Respondents who reported a change in their prescribing or dispensing habits were eligible to answer this question.

Attitudes about use, misuse, and abuse of controlled substances

The first two survey items assessed respondents' attitudes about prescription drug misuse and abuse. Table 7 shows that 87% of physicians and 93% of pharmacists reported being at least moderately concerned about prescription drug misuse and abuse in California; 44% of physicians and 62% of pharmacists were extremely concerned about prescription drug misuse and abuse in California. Overall, respondents were slightly less concerned about prescription drug misuse in their local community compared to the state overall, and pharmacists were substantially more concerned about prescription drug misuse and abuse than physicians.

Table 7. How concerned are you about prescription drug misuse and abuse among patients in:

	Physicians n = 1401[a]				Pharmacists n = 482[a]			
	California		Practice Community		California		Practice Community	
Item Response	n	%	n	%	n	%	n	%
Not concerned at all	42	3.0	65	4.7	2	0.4	9	1.9
Slightly concerned	137	9.8	230	16.5	34	7.1	60	12.6
Moderately concerned	603	43.4	570	41.0	148	30.8	147	30.9
Extremely concerned	609	43.8	525	37.8	296	61.7	260	54.6
Did not respond	10		11		2		6	

[a]All respondents were eligible to answer these items, including physicians who reported that they did not have a DEA license.

The survey also included items about the perceived benefits and risks of controlled substances in California (Figures 1 and 2). Physicians and pharmacists provided similar estimates about perceived benefits and risks for California overall. Based on the responses shown in Figures 1 and 2, the mean estimate for both physicians and pharmacists was that about one-third of patients taking controlled substances in California misused or abused them, whereas fewer than 60% of patients taking controlled substances in California benefited from them

Figure 1. Percent of California patients perceived to misuse or abuse controlled substance medications

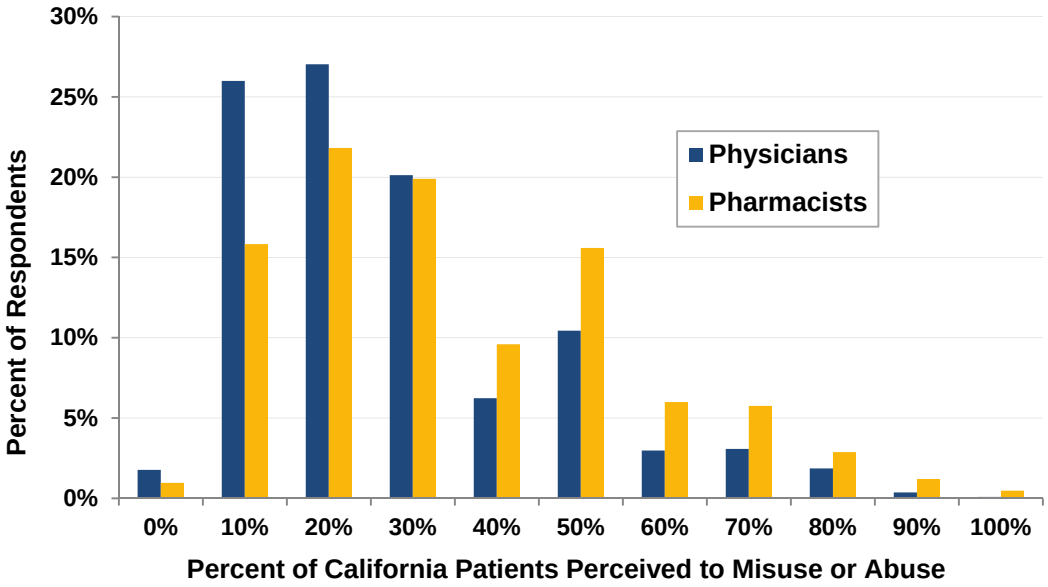
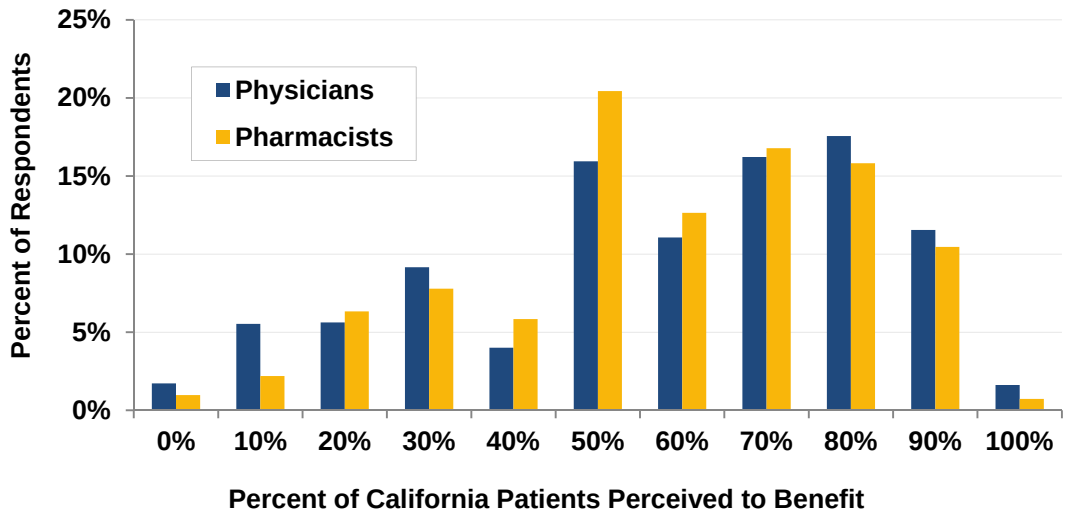


Figure 2. Percent of California patients perceived to benefit from controlled substance medications



Respondents were then asked these same questions specifically about their own patients. Both physicians and pharmacists estimated that the rate of misuse and abuse was substantially lower among their patients compared to all California patients (Figures 3 and 4). This difference may indicate that respondents think their own patients have lower risk of misuse or abuse, or that respondents consider themselves to have safer or more cautious prescribing habits than typical physicians and pharmacists in California.

Figure 3. Physicians: What percent of your own patients (compared with California patients) taking controlled substance medications do you feel misuse or abuse them?

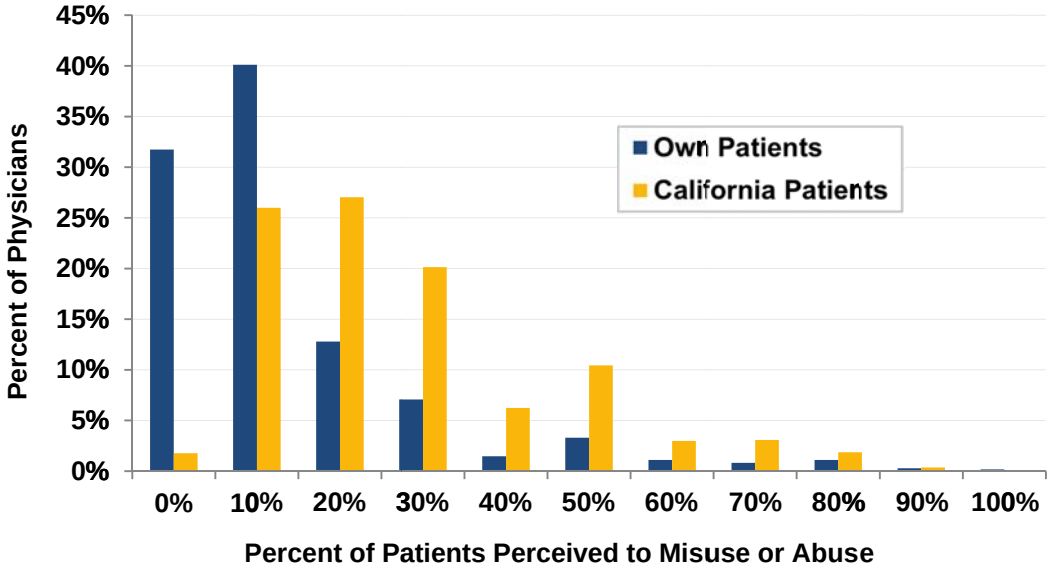
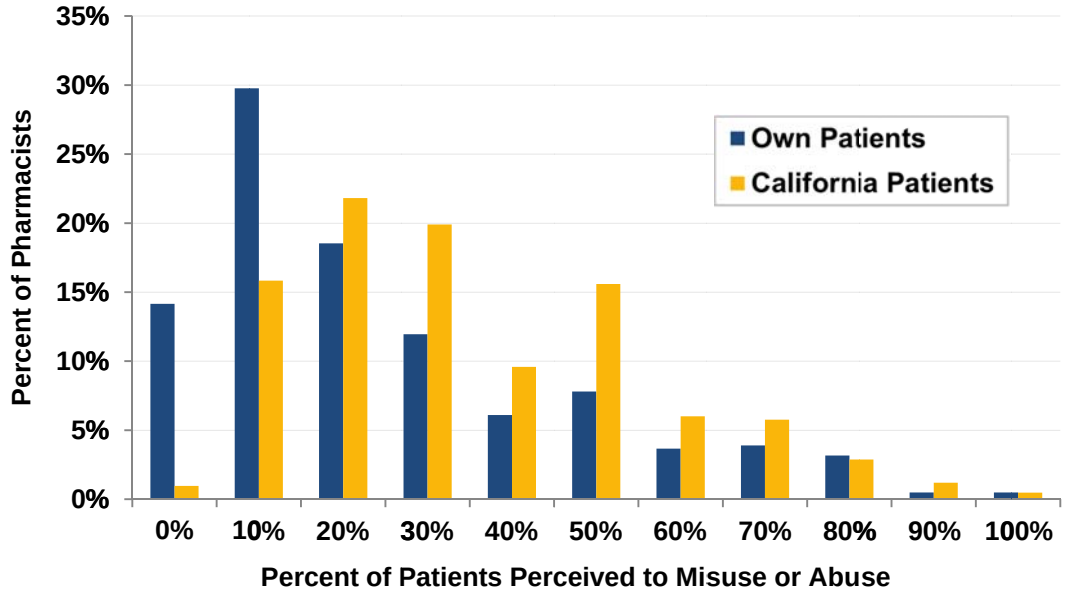
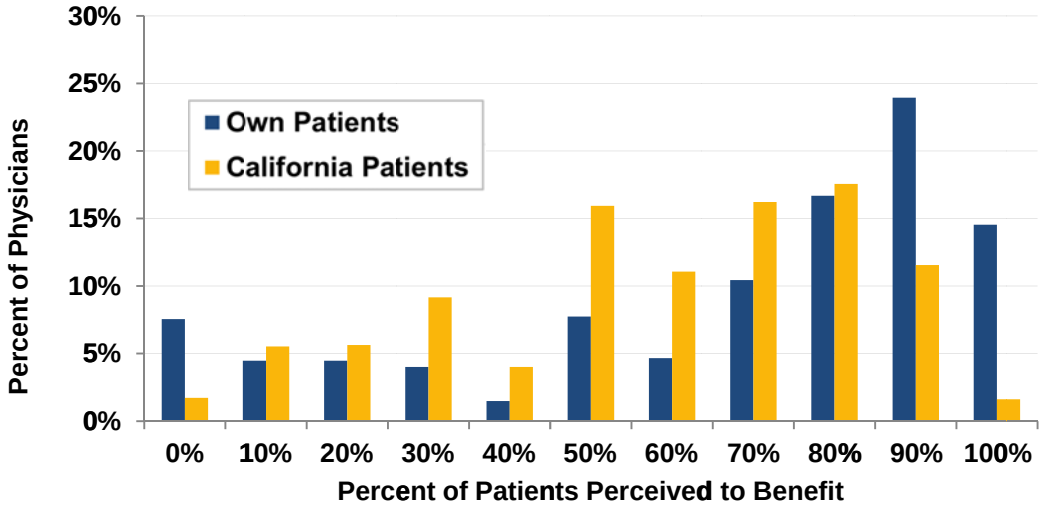


Figure 4. Pharmacists: What percent of your own patients (compared with California patients) taking controlled substance medications do you feel misuse or abuse them?



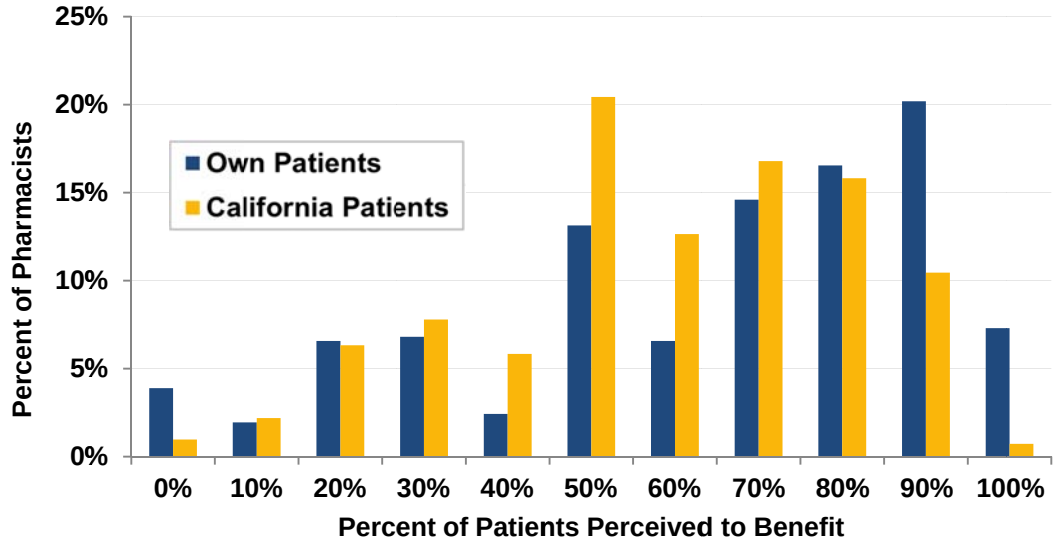
When asked about patient benefit, physicians estimated that a higher proportion of their patients benefited from controlled substances compared to the state average (Figure 5).

Figure 5. Physicians: What percent of your own patients (compared with California patients) taking controlled substance medications do you feel benefit from them?



In contrast, pharmacists estimated that a lower proportion of their patients benefited compared to the state average (Figure 6). This difference between pharmacists and physicians may be due to the fact that physicians have more detailed clinical information on their patients (compared to pharmacists) or that physicians are more inclined to presume that prescriptions they write are helping their patients.

Figure 6. Pharmacists: What percent of your own patients (compared with California patients) taking controlled substance medications do you feel benefit from them?



Awareness of CURES and CURES registration requirement

Tables 8 and 9 show rates of awareness of CURES and CURES registration status, respectively. Nearly all pharmacists and 92% of physicians reported that they had heard of CURES. Among respondents who were required to register for CURES, 82% of physicians and 96% of pharmacists reported that they were either registered or in the process of registering for CURES. Only 18 pharmacists were not registered or in the process of registering, and 16 of these reported that they were likely or very likely to register for CURES in the next 3 months. Of the 231 physicians who were not registered, 70% reported that they were likely or very likely to register for CURES in the next 3 months. *These results indicate that pharmacists have near perfect compliance with mandatory CURES registration. In contrast, only about 82% of DEA-licensed physicians reported compliance with mandatory CURES registration*, though 94% of physicians were either registered or indicated that they were likely to register in the next 3 months.

Table 8. Have you heard of CURES?

	Physicians n = 1275[a]		Pharmacists n = 482	
Heard of CURES?	n	%	n	%
Yes	1156	92.0	464	98.5
No	101	8.0	7	1.5
Did not respond	18		11	

[a]Physicians who reported having a DEA license.

Table 9. Are you registered for CURES?

	Physicians n = 1275[a]		Pharmacists n = 482	
CURES Registration	n	%	n	%
Yes	988	78.7	445	94.7
No	128	10.2	11	2.3
Registration in process	37	2.9	7	1.5
Do not know	103	8.2	7	1.5
Did not respond	19		12	

[a]Physicians who reported having a DEA license.

Tables 10 and 11 show additional information for respondents who had not yet registered for CURES, or who did not know their registration status. Among non-registered physicians, the majority (71%) were not aware that CURES registration was mandatory for DEA-licensed physicians. Separately, 71% of non-registered physicians reported that they were likely to register for CURES in the next 3 months. Among DEA-licensed physicians who were not registered and who reported being unlikely or very unlikely to register for CURES in the next 3

months, nearly half had addresses outside of California (46%; n = 31 of 68). Many physicians with addresses outside California likely also have DEA licenses with non-California addresses, and so are not covered by the mandatory CURES registration requirement.

Table 10. Are you aware that registering for CURES is mandatory for…?

	Physicians[a] n = 231		Pharmacists[a] n = 18	
CURES Registration	n	%	n	%
Yes	65	28.8	8	52.9
No	161	71.2	9	47.1
Did not respond	5		1	

[a]Respondents who reported they had not registered, or did not know if they were registered, were eligible to answer this item.

Table 11. How likely are you to register for CURES within the following month?

	Physicians[a] n = 231		Pharmacists[a] n = 18	
Item Response	n	%	n	%
Extremely unlikely	35	15.5	1	6.3
Unlikely	33	14.6	1	6.3
Likely	76	33.6	5	31.3
Extremely likely	82	36.3	9	56.3
Did not respond	5		2	

[a]Respondents who reported they had not registered, or did not know if they were registered, were eligible to answer this item.

Past and future CURES use

Table 12 shows how long respondents reported having used CURES. Based on the timing of survey administration, those who had been using CURES for 7 months or more likely registered at least a few months prior to implementation of mandatory registration on July 1, 2016. Overall, pharmacists reported having used CURES for longer than physicians. Over half (54%) of pharmacists reported using CURES for more than a year, and 70% reported using CURES for 7 months or more. In contrast, only 33% of physicians reported using CURES for more than a year, and 49% of physicians reported using CURES for 7 months or more. Forty percent of physicians indicated they had been using CURES for 6 months or less, suggesting that physicians were more likely to register at or near the mandatory registration deadline. *These results indicate that pharmacists have been using CURES longer than physicians and were more likely to have registered for CURES before mandatory registration went into effect.*

Table 12. How long have you been using CURES?

	Physicians[a] n = 988		Pharmacists[a] n = 445	
Item Response	n	%	n	%
Less than 3 months	287	29.4	70	15.8
4 to 6 months	210	21.5	61	13.7
7 months to 1 year	158	16.2	75	16.9
More than 1 year	321	32.9	238	53.6
Did not respond	12		1	

[a]Respondents who reported they had registered were eligible to answer this item.

Table 13 indicates respondents' expected likelihood of using CURES at least once in the next 3 months. Overall, pharmacists were much more likely than physicians to report planned use of CURES in the next 3 months. Some of this difference may be due to physicians' and pharmacists' different roles regarding controlled substances.

Table 13. How likely are you to use CURES at least once in the next 3 months?

	Physicians[a] n = 1025		Pharmacists[a] n = 452	
Item Response	n	%[b]	n	%
Extremely unlikely	233	23.1	93	20.7
Unlikely	238	23.6	76	16.9
Likely	240	23.8	75	16.7
Extremely likely	296	29.4	205	45.7
Did not respond	18		3	

[a]Respondents who reported they had registered, or were in process, were eligible to answer this item.

Barriers to CURES registration and use

Table 14 describes barriers to registration among physicians and pharmacists who were not already registered for CURES. Most physicians reported that they knew how to register for CURES; however, 29% indicated that they had more important things to do than registering for CURES and only 19% reported that the registration process takes little time, indicating *that lack of importance and time required for registration were the most commonly reported barriers to registration for physicians.* In contrast, only 13% of physicians reported encountering technical problems when trying to register. Given the small number of pharmacists not registered for CURES, it is difficult to draw meaningful conclusions about barriers to registration among pharmacists.

Table 14. Please indicate the extent to which you agree with the following:

	Physicians[a] n = 231		Pharmacists[a] n = 18	
Item Response	n	%[b]	n	%[b]
I have other problems that are more important than registering for CURES	65	29.4	7	43.8
I know how to go about registering for CURES	123	55.1	7	43.8
Every time I try to register for CURES, something goes wrong	29	13.2	6	37.6
Registering for CURES takes little time	41	18.7	4	35.1
I don't have access to a computer or the internet where I practice	10	4.4	2	12.5

[a]Respondents who reported they had not registered, or did not know if they were registered, were eligible to answer this item.
[b]Percent of respondents indicating they 'somewhat agree' or 'strongly agree' with item.

For respondents who reported being registered for CURES, the survey included several items related to the logistics of accessing and checking CURES. Table 15 shows results for items related to accessing CURES. Overall, physicians reported more difficulty accessing CURES than did pharmacists. For example, 43% of physicians rated registering for CURES as "difficult" or "very difficult" compared to 32% of pharmacists. Other than CURES registration, pharmacist and physicians indicated that remembering security questions was the most common barrier to accessing CURES, with 31% of physicians and 29% of pharmacists indicating that remembering passwords was difficult or very difficult. In the open-ended question, 7% of all physician respondents and 5% of all pharmacist respondents commented on barriers to accessing CURES, such as difficulties with registration and the time required to access CURES.

Table 15. How difficult are the following in CURES?

	Physicians n = 1025[a]		Pharmacists n = 452[a]	
Item Response	n	%[b]	n	%[b]
Registering for CURES	427	42.8	145	32.3
Logging in to CURES	275	28.3	55	12.53
Resetting your password	291	30.4	105	23.92
Remembering security questions	301	31.4	128	28.96

[a]Respondents who reported they had registered, or were in process, were eligible to answer this item.
[b]Percent of respondents indicating item was 'difficult' or 'very difficult'.

Table 16 shows results of items designed to assess non-logistical barriers to using CURES. One quarter (25%) of pharmacists and nearly one-third (32%) of physicians agreed or strongly agreed that CURES was not relevant to their practice. Pharmacists who were practicing in a hospital, a non-clinical setting, or some "other patient care practice" (see Table 4 above) were more likely to agree or strongly agree that CURES was not relevant to their practice than pharmacists working in retail settings (i.e., chain, supermarket, independent or mass merchandiser). Compared to pharmacists, physicians were more likely to agree that CURES was not easy to use, and to agree that they did not know how to use CURES. Very few physicians (9%) and pharmacists (2%) agreed that CURES is not helpful.

Table 16. Please indicate the extent to which you agree with the following:

	Physicians n = 988[a]		Pharmacists n = 445[a]	
Item Response	n	%[b]	n	%[b]
CURES is helpful	594	60.1	356	80.0
CURES is not relevant to my practice	302	30.6	108	24.2
CURES is easy to use	320	32.4	264	59.3
I don't know how to use CURES	194	19.7	31	6.9
CURES is checked by someone else in the office	107	10.8	60	13.5
I have limited or no access to CURES while I practice	112	11.3	45	10.1

[a]Respondents who reported they had registered for CURES were eligible to answer this item.
[b]Percent of respondents indicating they 'agree' or 'strongly agree' with item.

Patterns of CURES use

Table 17 shows frequency of CURES use reported by respondents. Pharmacists reported using CURES more often than physicians. Only 30% reported that they had never used CURES during the past 3 months, and 48% indicated that they used CURES at least daily. In comparison, 44% of physicians reported that they never used CURES, and only 14% reported using CURES at least

daily. These results are consistent with the general finding that pharmacists are more likely to register and use CURES than are physicians.

Table 17. On a typical day when you prescribe (dispense or manage) medications, how many times do you use CURES to look up a patient's controlled substance medication history?

	Physicians n = 1025[a]		Pharmacists n = 452[a]	
Item Response	n	%	n	%
Never	431	44.5	129	29.6
Less than once a day	398	41.1	98	22.5
1-2 times a day	104	10.7	120	27.5
3-5 times a day	24	2.5	36	8.3
6+ times a day	11	1.1	53	12.2
Did not respond	57		16	

[a]Respondents who reported they had registered for CURES, or that their registration was in process, were eligible to answer this item.

The survey included several items asking respondents the percentage of time they checked CURES when prescribing or dispensing a controlled substance, for those who report checking CURES at least once in the last 3 months. Figure 7 shows these results graphically for physicians and pharmacists. For physicians, 28% indicated that they check CURES for least 50% of the *patients* to whom they prescribe controlled substances. For pharmacists, 36% indicated that they check CURES for at least 50% of the controlled substance *prescriptions* they dispense or manage. Although the question did not distinguish between short-term and long-term opioid use, the pattern of CURES use reported by physicians is likely below what would be observed when CURES use becomes mandatory for prescribers in 2018.

Figure 7. When a controlled substance was prescribed, for what percentage of patient visits (physicians) or prescription fills (pharmacists) did you review CURES information (last 3 months)?

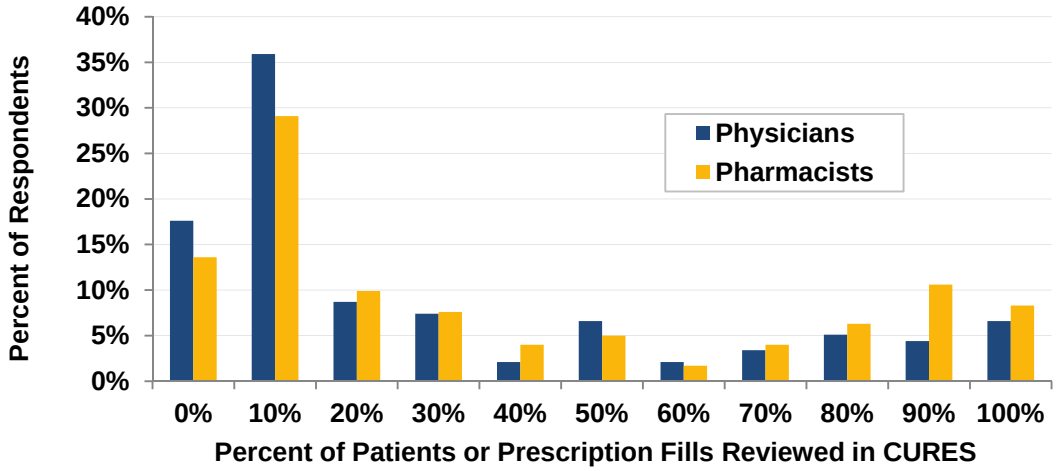
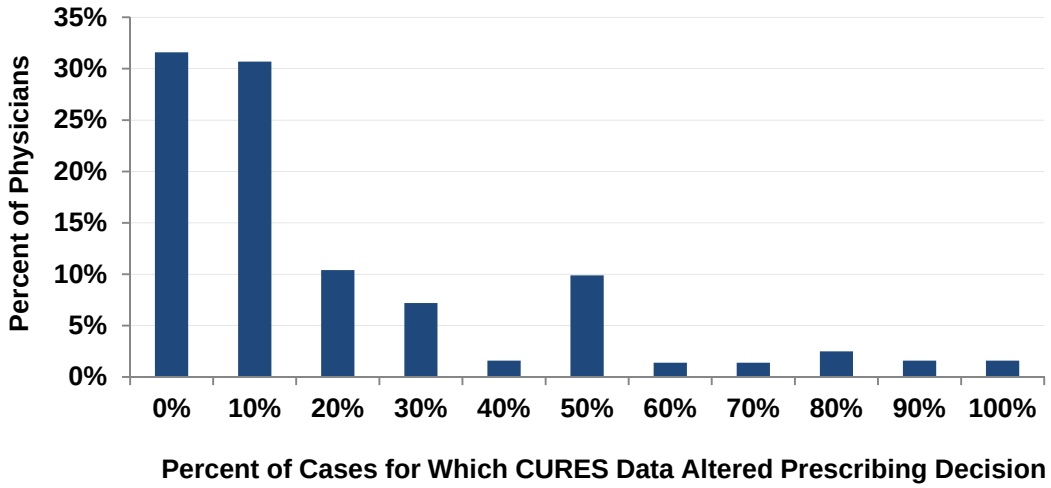


Figure 8 shows physician responses to items asking them to indicate the proportion of time that checking CURES altered their prescribing decision.

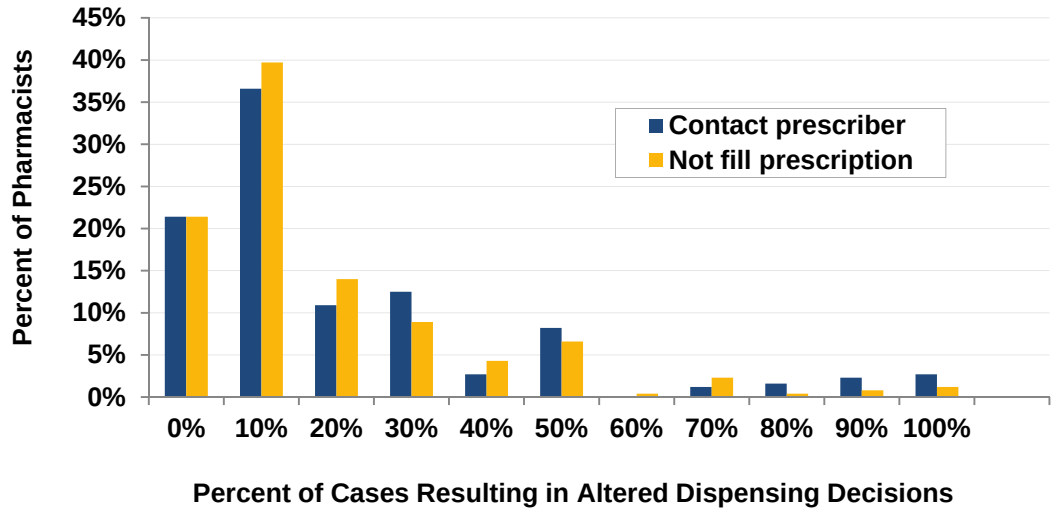
Figure 8. What percent of the time did the information you obtained from CURES alter your prescribing decision (during the past 3 months)?



Overall, results suggest that checking CURES regularly but infrequently caused physicians to change their prescribing decisions. Two-thirds (68%) of physicians reported changing a prescribing decision at least once during the past 3 months based on information they obtained from CURES; however, 63% of physicians reported that checking CURES only affected their prescribing decision in 10% or fewer of the times when they checked CURES. On the other hand, 18% indicated that information obtained from CURES affected their prescribing decision at least 50% of the time that they checked CURES. Of note, these responses do not account for how often physicians checked CURES. In the open-ended response item at the end of the survey, 4% of physicians indicated that CURES should be checked based on physician or pharmacist judgement about the patient. Thus, some physicians likely checked CURES only when they did not know a patient or when they suspected prescription drug misuse or observed unusual patient behavior. It is likely that physicians who reported changing prescribing decisions 50% or more of the time did not check CURES for every patient to whom they prescribed controlled substances, and only checked CURES when they already had a high suspicion for prescription drug misuse.

Figure 9 shows analogous survey results for pharmacists, who were asked to estimate the proportion of time that checking CURES caused them to either contact the prescriber for more information, or to refuse to dispense a controlled substance.

Figure 9. Percent of cases for which pharmacists reviewed patient information in CURES (past 3 months) and altered dispensing decisions.



Response patterns were qualitatively similar to physician responses; 86% and 79% of pharmacists reported that checking CURES caused them to contact the prescriber or refuse to dispense a prescription, respectively, at least once in the prior 3 months. On the other hand, 42% of physicians and 61% of pharmacists reported that checking CURES caused them to contact the prescriber or refuse to dispense, respectively, in 10% or fewer of the times when they checked CURES. As with the physicians, these responses do not account for how often pharmacists checked CURES, so pharmacists who reported contacting the prescriber in most of the cases likely checked CURES only when they had a high suspicion for prescription drug misuse.

Attitudes about the usefulness of CURES

Table 18 lists the reasons that respondents cited for checking CURES. More than three-quarters of physicians and pharmacists endorsed checking CURES prior to prescribing or dispensing a controlled substance in order to look for "doctor shopping." Many respondents also reported checking CURES in order to monitor patients on controlled substances or to improve their communication with patients. Respondents who answered "other" were given the opportunity to type in additional reasons. Many respondents used this open-ended response to note that they do not practice in California or that they work only in inpatient settings. Other reasons provided by respondents included checking on new patients who request controlled substances, evaluating the status of supposedly missing or unfilled prescriptions, helping patients who cannot remember their medications, and to review the fill dates of prior prescriptions.

Table 18. What are your reasons for checking CURES? [Check all that apply]

	Physicians n = 988[a]		Pharmacists n = 445[a]	
Item Response	n	%	n	%
To check on patients prior to dispensing or managing a controlled substance	418	78.0	277	89.4
To look for evidence of "drug seeking"	465	86.9	257	82.9
To monitor patients on controlled substances	365	68.1	246	79.4
To improve my communication with patients regarding controlled substances	258	48.1	187	60.3
Other	35	3.5	28	9.0

[a]Respondents who reported they had registered for CURES were eligible to answer this item.

The survey included multiple items related to respondents' attitudes and beliefs about CURES. Table 19 shows items about the usefulness of CURES for various functions. Overall, pharmacists were more likely to report that CURES was useful or very useful than were physicians. Nearly 90% of pharmacy respondents indicated that CURES was useful or very useful for informing clinical decisions, for identifying "doctor shopping" or "pharmacy shopping," and for identifying patients who misuse or abuse prescriptions drugs. Physician responses in these categories ranged from 62% to 76%. A majority of pharmacists indicated that CURES was useful or very useful for helping manage patients with pain and for building trust with patients. In comparison, 46% of physicians felt that CURES was useful or very useful for helping them to manage patients with pain, and 37% felt that CURES was useful or very useful for helping them to build trust with patients. In the open-ended item at the end of the survey, 7% of all physician respondents and 4% of all pharmacist respondents noted that CURES was a useful or valuable tool. In contrast, 2% of physician respondents and 0.4% of pharmacist respondents used the open-ended item to convey skepticism that CURES was useful for curbing prescription drug abuse.

Table 19. How useful to you is CURES for the following:

	Physicians n = 1025[a]		Pharmacists n = 452[a]	
Item Response	n	%[b]	n	%[b]
Helping manage patients with pain	412	45.5	271	64.5
Helping build trust with patients	333	36.7	243	58.0
Informing decisions to prescribe, dispense, or manage controlled substances	556	61.6	363	86.4
Identifying patients filling prescriptions from multiple doctors and/or pharmacies	685	75.5	374	88.6
Identifying patients who misuse or abuse controlled prescription drugs	672	74.1	370	87.7

[a]Respondents who reported they had registered for CURES, or that their registration was in process, were eligible to answer this item.
[b]Percent of respondents indicating they 'useful' or 'very useful' with item.

Feedback on CURES 2.0

An important survey goal was to get feedback about changes made as part of CURES 2.0, in order to identify what is working well and to identify areas for further improvement. Respondents who reported having used the prior version of CURES were asked to compare CURES 2.0 to the prior version. *As shown in Table 20, more than 90% of respondents rated CURES 2.0 as the same or better across all categories.* For overall ease of use, 43% of physicians and 47% of pharmacists rated CURES 2.0 as an improvement over the prior system. For patient activity reports, 36% of physicians and 52% of pharmacists reported that CURES 2.0 was an improvement over the prior system.

Table 20. Compared to the old website, how would you rate the CURES website on the following characteristics:

	Physicians[a] n = 276						Pharmacists[a] n = 216					
Item Response	Worse		About the same		Better		Worse		About the same		Better	
	n	%	n	%	n	%	n	%	n	%	n	%
Overall ease of use	25	9.1	132	47.8	119	43.1	12	5.6	102	47.2	102	47.2
Login process	16	5.8	163	58.8	98	35.4	8	3.7	125	57.6	84	38.7
Patient activity reports	27	9.8	151	54.7	98	35.5	10	4.6	94	43.3	113	52.1
Help desk support	19	7.3	181	69.1	62	23.7	11	5.2	141	66.8	59	28.0

[a]Respondents who reported they had used the previous version of CURES were eligible to answer this item.

Respondents were also asked about several specific features that were new to CURES 2.0: the ability to send secure peer to peer messages within CURES, the ability to designate delegates to access CURES on one's behalf, automatic alerts for high risk patients, and the ability to flag patients with whom a physician has signed a controlled substance agreement ("compact"). As shown in Table 21, most respondents had never heard of these new features. Only 3% of pharmacists reported having used each of these new features at least once. Similarly, very few physicians reported having used the messaging function (2%), the ability to flag controlled substance agreements (3%), the delegate function (5%), or the automatic alerts (5%) at least once.

Table 21. Are you aware of the following new features in CURES?

	Physicians n = 988[a]		Pharmacists n = 452[a]	
Item Response	n	%[b]	n	%[b]
Sending secure peer-to-peer messages about specific patients	755	77.7	308	70.6
Giving delegates the ability to access to CURES on your behalf	665	68.5	331	76.3
Automatic alerts for high risk patients	721	74.3	319	73.3
The ability to flag patients who have patient-provider agreements	671	69.1	Not Applicable	

[a]Respondents who reported they had registered for CURES were eligible to answer this item.
[b]Percent of respondents indicating they never heard of the feature.

When asked whether they felt they needed additional training or education about CURES, 47% of physicians and 40% of pharmacists responded affirmatively. The most commonly identified need for additional training related to the new advanced features of CURES 2.0. As shown in Table 22, physicians most commonly indicated needing additional training or education about flagging patients with controlled substance agreements (63%), sending secure messages (54%), and running patient activity reports (57%). Pharmacists most commonly indicated needing additional training about how automatic reports are generated (68%), sending secure messages (76%), and using the delegate feature (55%).

Table 22. What would you like additional training on? [Check all that apply]

	Physicians n = 949[a]		Pharmacists n = 205[a]	
Item Response	n	%[b]	n	%[b]
Registering for CURES	158	24.7	29	13.2
CURES passwords and security questions	134	20.9	33	15.0
Running patient activity reports	362	56.6	108	49.1
Identifying and using CURES delegates from my account	301	47.0	121	55.0
Sending secure messages	345	53.9	167	75.9
How automatic reports are generated	317	49.5	149	67.7
Flagging patients who have patient-provider agreements	400	62.5	Not Applicable	
Other topics	58	9.1	15	6.8

[a]Respondents who indicated a need for additional training or education about CURES (or skipped the item) were eligible to answer this item.
[b]Percent of respondents identifying the topic as needed.

Professional attitudes and beliefs related to CURES

Respondents who reported being registered for CURES had similar responses related to social norms, or respondents' beliefs about their colleagues' use of CURES. Both physicians (Figure 10) and pharmacists (Figure 11) tended to think that the proportion of their colleagues using CURES at least weekly was lower than the proportion of their colleagues who *ought* to be using CURES weekly. In other words, respondents felt that some of their colleagues who should be using CURES regularly were not doing so.

Figure 10. Physicians: What percentage of your colleagues do you feel are (or ought to be) using CURES at least weekly?

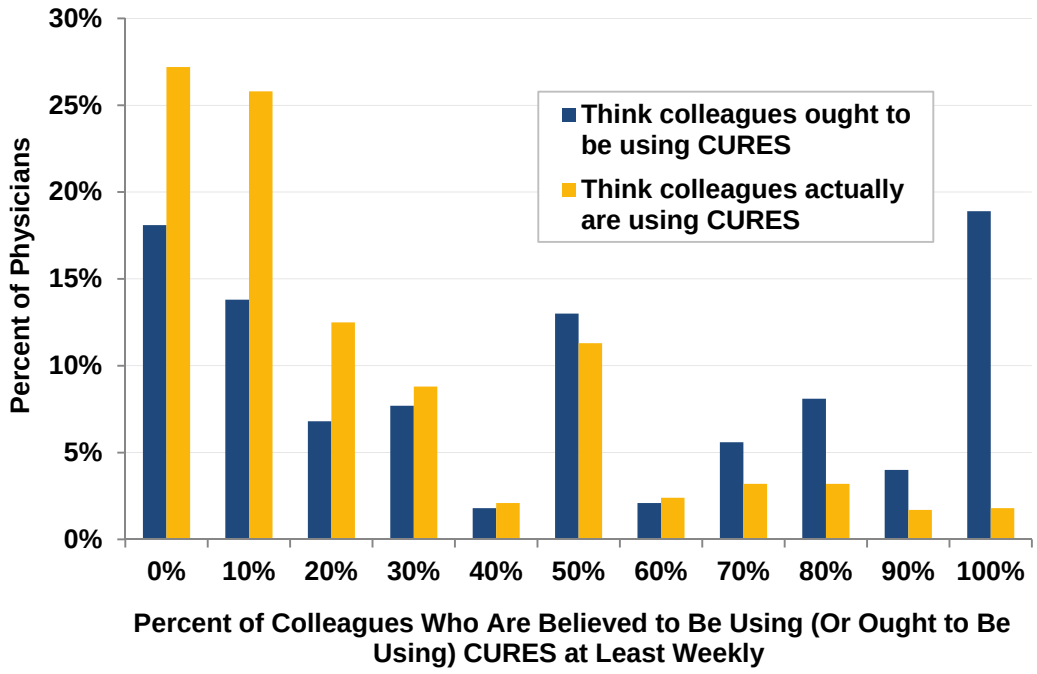


Figure 11. Pharmacists: What percentage of your colleagues do you feel are (or ought to be) using CURES at least weekly

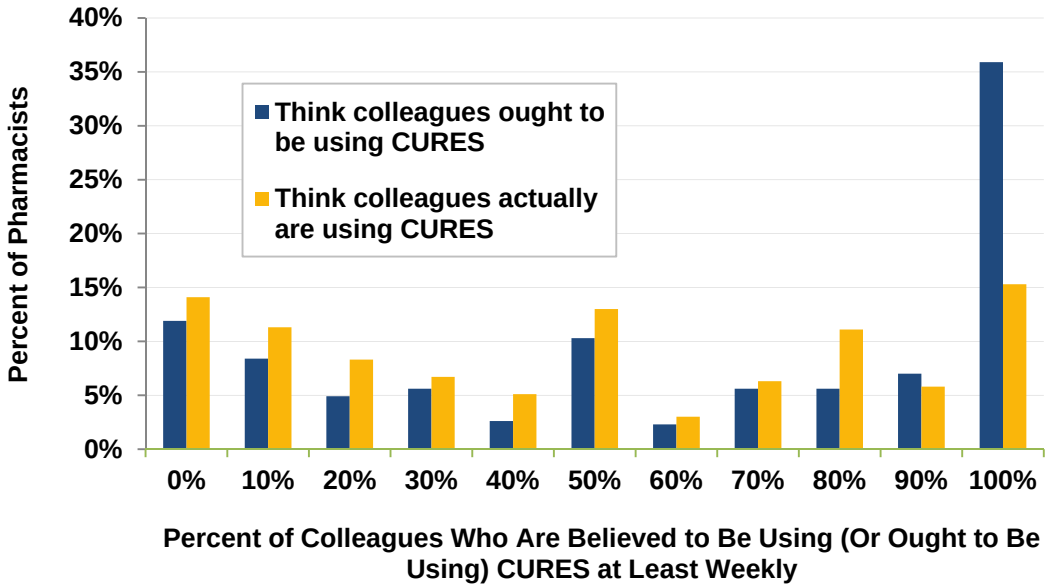


Table 23 summarizes information from Figures 8 and 9 and shows that, on average, pharmacists' estimates of the proportion of their colleagues *using* CURES were higher than physicians' estimates (means = 49% and 24%, respectively). Similarly, pharmacists had higher estimates than physicians for proportion of their colleagues who *ought* to be using CURES (means = 62% and 47%, respectively). As shown in Figures 8 and 9, 19% of physicians and 36% of pharmacists felt that their colleagues ought to be using CURES 100% of the time when prescribing or dispensing controlled substances.

Table 23. What percent of your colleagues do you feel… ?

	Physicians n =1275[a]		Pharmacists n = 482[b]	
	Mean	SD	Mean	SD
Item Response	%	%	%	%
Use CURES at least weekly	23.8	25.9	48.9	35.3
Ought to be using CURES at least weekly	46.5	37.3	61.6	38.1

[a]Of 1275 total DEA-licensed physicians eligible to answer this question, question 1 (n = 1100) and question 2 (n = 1088).
[b]Of 482 total pharmacists, question 1 (n = 432) and question 2 (n = 429).

The questions in Table 24 relate to beliefs about CURES use and regulation. *A substantial majority of physicians (81%) and pharmacists (91%) agreed that their colleagues should check CURES when prescribing or dispensing a controlled substance, respectively. In contrast, only 23% of physicians felt that physicians should be required to check CURES when prescribing. The corresponding value for pharmacists was 39%, indicating that about two-fifths of pharmacists supported mandatory CURES use*

for their colleagues. The survey did not directly ask pharmacists about requirements for physicians (or vice versa). In the open-ended question, 3% of pharmacists commented that prescribers should use CURES more often.

Table 24. Should physicians / pharmacists…

	Physicians n = 1275[a]		Pharmacists n = 482[a]	
Item Response	n	%[b]	n	%[b]
Check CURES when prescribing / dispensing a controlled substance?	728	80.6	367	91.3
Be *required* to check CURES when prescribing / dispensing a controlled substance	218	22.6	152	39.2

[a]Total DEA-licensed physicians and pharmacists eligible to answer.
[b]Percent of respondents who answered "yes" to this item

While the survey was being administered, California passed a new law that, when implemented, will require physicians (and other prescribers) to use CURES when prescribing controlled substances (SB-482). Some survey reminders to physicians mentioned this new law in order to increase physician survey response rates. To evaluate whether passage of the new law (or the survey reminders mentioning the new law) affected results, we analyzed survey responses to the items in Table 24 based on the date that physician respondents took their survey. Seventy-six percent of physicians who took the survey before the Governor signed SB-482 agreed that physicians should check CURES prior to prescribing a controlled substance, compared to 83% of physicians who took the survey after the Governor signed SB-482. Only 19% of physicians who took the survey before the new law was signed agreed that physicians should be required to check CURES prior to prescribing a controlled substance, compared to 25% of physicians who took the survey after the new law was signed. Thus, we found no evidence of a "backlash" by physicians in response to SB-482. In contrast, physicians who took the survey after the new law was signed were more likely to agree that physicians should be required to check CURES before prescribing controlled substances.

Table 25 shows results for survey items relating to respondents' professional and moral obligations to use CURES. Pharmacists indicated greater obligations to use CURES than did physicians, though a majority of physicians did agree that they had a professional responsibility to check CURES and that checking CURES when prescribing controlled substances is the right thing to do. *Over two-thirds of pharmacists (69%) agreed that checking CURES was considered standard of care, compared to 40% of physicians.* In contrast relatively few respondents agreed with negatively worded items on this topic.

Table 25. Please indicate the extent to which you agree with the following…[a]

Item Response	Physicians n = 1275[a]		Pharmacists n =482[a]	
	n	%[b]	n	%[b]
I have a professional responsibility to check CURES when prescribing /dispensing controlled substances	623	52.6	353	77.6
Checking CURES when prescribing / dispensing controlled substances is the right thing to do	710	60.0	368	80.7
Using CURES when prescribing / dispensing controlled substances is considered standard of care	446	37.9	310	68.7
Prescribing / dispensing controlled substances without checking CURES would be morally wrong	190	16.2	142	31.5
Checking CURES when prescribing /dispensing controlled substances is NOT a necessary part of my job	290	24.7	59	13.1

[a]Physicians who reported having a DEA license (valid denominator n per item ranged from 1171-1184) and pharmacist respondents (valid denominator n per item ranged from 451-456) were eligible to answer this item.
[b]Percent of respondents indicating they "agree" or "strongly agree" with item.

Content analysis of responses to the open-ended survey question

Table 26 shows results of the content analysis performed on a single open-ended survey question, "Is there anything else you would like to tell us about CURES (e.g., problems, recommendations)?" Sixty-three percent (n = 597 of 1275) of DEA-licensed physicians and 56% (n = 270 of 482) of pharmacists provided responses to the question. Thus, responses were received from approximately half (49%, n=867 of 1757) of all survey respondents who were eligible to answer the open-ended question.

For both physicians and pharmacists, the most common response category was "relevance," indicating that respondents felt that CURES was not relevant to their practice. Many of the comments in this category indicated that the respondent was retired or no longer working in California. However, many other respondents indicated that they felt CURES was not relevant to them because they rarely prescribed controlled substances or because the respondents were confident that none of their patients were "doctor shopping" or misusing controlled substances. Several physicians commented that they only checked CURES for new patients. After "relevance," the second most common category for pharmacists was "data." Thirty-four pharmacists (7% of all pharmacist respondents) complained about the quality and accuracy of CURES data, with several indicating that they felt CURES data accuracy should be improved and/or that the time lag between dispensing prescriptions and data showing up in CURES reports was too long. This category of responses also included comments about the lack of Veterans Health Administration or out of state prescriptions in CURES. Pharmacists typically dispense many more controlled substances than physicians, which likely explains why pharmacists were more attuned to the need for improved CURES data quality than were

physicians. For physicians, the second most common categories included difficulty accessing (7%) or using (8%) CURES, along with positive statements indicating that CURES had value or was useful to physicians (7%). Comments about difficulty using CURES most often related to the amount of time needed to access CURES and run patient reports while working in clinic.

Table 26. Definitions and frequency of content codes derived from the open-ended survey question[a]

Code	Definition	Physicians n =1275[b]		Pharmacists n =482	
		n	%	n	%
Access	Problems with registration, login, password or security questions, help desk, customer service	85	6.7	27	5.4
Difficulty	Difficulty using CURES, including time consuming, website not user friendly, difficult to generate reports,	99	7.8	14	2.8
Regulation	Loss of physician autonomy, micromanaging patient care, social control by state/ medical board / DOJ, red tape	39	3.1	5	1.0
Relevance	CURES not relevant to respondent due to various reasons, including out of state, retired, specialty, practice patterns, or patient population	240	18.8	61	12.1
Data	Limitations related to CURES data, including timeliness of data, absence of out of state prescriptions, other data quality problems	32	2.5	34	6.8
Laws	Comments about whether CURES should or should not be legally required, either laws for mandatory CURES registration or mandatory CURES use	47	3.7	8	1.6
Value	Positive statements about CURES indicating that it is valuable, helpful, or useful in some way	87	6.8	22	4.4
Skepticism	Statements that CURES is not effective or not useful for curbing drug abuse	19	1.5	2	0.4
Training	Statements about needing training or help to use CURES or better use CURES	21	1.6	8	1.6
Misinform	Statements that are factually incorrect	2	0.2	1	0.2
Suggestion	Concrete suggestions for making CURES better not covered in other categories	51	4.0	31	6.2
Care	Comments that CURES impacts quality of care or patient care	27	2.1	2	0.4
Pharmacist	Comments about how pharmacists should use CURES (physicians only)	11	0.9	0	n/a
Prescriber	Comments about how prescribers / physicians should use CURES (pharmacists only)	0	n/a	16	3.2
Judgment	Comments that using CURES should be based on physician/pharmacist judgment	55	4.3	5	1.0
Aware	Comments that person is not aware of CURES or doesn't know how to use it	21	1.6	3	0.6
Cost	Cost of CURES license fee; productivity costs that mention money	3	0.2	4	0.8
Misc	Any response that does not fit in any of the above categories	58	4.5	46	9.1
None	Respondent left question blank	671	52.6	270	53.7

[a]Responses could be counted in multiple categories.
[b]Physicians who reported having a DEA license were eligible to answer this question

Qualitative analysis of responses to the open-ended survey question

Forty-nine percent (n=867) of sample respondents (n=1757) answered the open-ended question, "Is there anything else you would like to tell us about CURES? (e.g., problems, recommendations)." A qualitative analysis of responses revealed four major themes illustrating attitudes and perceptions of CURES among physicians and pharmacists: (1) cost of using CURES (2) interference with professionalism (3) shifting responsibility and (4) benefits and future direction of CURES. These four major themes are explained in detail in the sections below. Overall, responses from physicians and pharmacists were similar with some exceptions. Pharmacists expressed more positive perceptions of CURES, but were more likely than physicians to report limitations including timeliness and accuracy of data as well as lack of inclusion of data from federal pharmacies in California, such as Veterans Health Administration pharmacies. The qualitative analysis also collected general and specific recommendations that respondents gave for increasing the use and utility of CURES among California physicians and pharmacists.

Cost of using CURES

Costs of using CURES comprise the time required to routinely access and enter patient information as well as the actual monetary cost associated with registration. Both groups of participants expressed that using CURES requires a significant amount of time which reduces the quality of the patient/customer interaction and thus negatively impacts the quality of care provided. A few physicians also expressed a decreased willingness to prescribe opioids due perceived barriers.

> *"…checking CURES has to fit efficiently into a busy primary care workflow, or else providers will burn out and choose not to prescribe opioids to anyone, even if indicated. The decision to prescribe opioids to patients is already a challenging process."* (Physician)

> *"I strongly disagree that pharmacists be required legally to check CURES before dispensing because it is a legal burden. Pharmacists should be encouraged and fully trained without a fee to use CURES, but not required."* (Pharmacist)

> *"CURES is a great resource, but too much CURES will interfere with clinical care. Time should be spent with the patient, not with the database."* (Physician)

Interference with professionalism

While physicians were slightly more likely to express lack of autonomy, professional judgement, and relevance as reasons for not mandating the use of CURES, pharmacists also shared concerns about relevance; some pharmacists who worked in hospital settings indicated that CURES was not relevant to their daily work. Many physicians reported that CURES was irrelevant to their

practice for a variety of reasons including: prescribing patterns, trust and established relationship with patients, medical specialty, pharmacy practice location, and the fact that they use professional judgement. Physicians who rarely, if ever, prescribe controlled substances believed that they should be exempt from using CURES along with pharmacists who work outside of retail settings.

> "*I work in an inpatient setting. CURES, for the most part, is irrelevant to my practice. Perhaps I need further training on how it applies to my work*." (Pharmacist)

> "*An astute physician knows when to check with CURES or prior colleagues treating his patients…*" (Physician)

> "*As it is I generally only use it CURES when someone is demonstrating drug seeking behavior.*" (Physician)

Shifting responsibility

Perceptions of who should be responsible for consulting CURES were contingent on one's role in health care. Many physicians hold pharmacists accountable for using CURES because pharmacists dispense medications. At the same time, some pharmacists shifted responsibility to physicians, noting that physicians have the prescription writing privileges and so have greater responsibility for preventing prescription drug misuse.

> *"I think all prescribers of controlled substances should be required to check CURES before they write prescriptions. The sole responsibility of should not be with pharmacists."* (Pharmacist)

> "*Pharmacists should check on all patients and send notice to us [physicians*]." (Physician)

> "*Unless MDs are forced to buy in you are making me the policeman…unless there are consequences for the MD by the Medical Association nothing will ever change."* (Pharmacist)

> *"Pharmacy involvement should be greater in monitoring patients that reflect misuse."* (Physician)

Benefits of CURES and future directions

While both groups reported various concerns regarding CURES, they also expressed many benefits and suggestions for improving the process. An appreciation for the underlying philosophy of CURES was evident in the open-ended responses.

> *"CURES is a wonderful contribution to help identify patients who are 'doctor shopping' for opioids (Physician).*

> *"CURES is very helpful in ensuring honesty from patients in the patient-pharmacist relationship." (Pharmacist)*

A variety of recommendations was suggested by both physicians and pharmacists and includes: increased training and advertisement around CURES, data updates in real time, and expansion to include out-of-state patient information. Some of these recommendations (e.g., the ability to save commonly-used patient searches) actually already exist in CURES 2.0, while others (e.g., including out-of-state prescriptions and decreasing data lag time) would require new state legislation.

> *"*CURES *should be part of a network like insurance DUR system, so without logging in pharmacists get prompted about prescriptions filled at other places."* (Pharmacist)

> *"Great program. Needs to be promoted more along with further training. Would be good if there were an incentive for less than conscience physicians to use the program."* (Physician)

> *"Some of the chains [pharmacies] have firewalls when it comes to resetting passwords and when trying to reset on a mobile device it does not work. Fixing this problem would be very helpful."* (Pharmacist)

General recommendations made in open-ended responses

- Offer incentives to encourage physicians and pharmacists to use CURES
- Promote CURES to increase awareness and visibility
- Provide additional CURES training
- Improve usability of CURES (including use on mobile devices)

Specific recommendations made in open-ended responses:

- Provide access to out-of-state prescription information
- Store patient names in memory bank to save time on repeat patient searches
- Alert pharmacists when patients get prescriptions filled at other pharmacies
- Update data in real time (currently CURES has a 1-week submission lag time).
- Track and report over-prescribers
- Link registered aliases and legal name changes
- Track identify theft and fraud in conjunction with prescriptions drugs

REFERENCES

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA*. Apr 19 2016;315(15):1624-1645.
2. Prescription drug monitoring programs: Evidence-based practices to optimize prescriber use. 2016; http://www.pewtrusts.org/~/media/assets/2016/12/prescription_drug_monitoring_programs.pdf.
3. Wen H, Schackman BR, Aden B, Bao Y. States With Prescription Drug Monitoring Mandates Saw A Reduction In Opioids Prescribed To Medicaid Enrollees. *Health Aff (Millwood)*. Apr 01 2017;36(4):733-741.
4. Patrick SW, Fry CE, Jones TF, Buntin MB. Implementation Of Prescription Drug Monitoring Programs Associated With Reductions In Opioid-Related Death Rates. *Health Aff (Millwood)*. Jul 01 2016;35(7):1324-1332.
5. Moyo P, Simoni-Wastila L, Griffin BA, et al. Impact of prescription drug monitoring programs (pdmps) on opioid utilization among medicare beneficiaries in 10 u.s. States. *Addiction*. May 12 2017.
6. Wixson SE, Blumenschein K, Goodin AJ, Talbert J, Freeman PR. Prescription drug monitoring program utilization in Kentucky community pharmacies. *Pharmacy practice*. Apr-Jun 2015;13(2):540.
7. Poon SJ, Greenwood-Ericksen MB, Gish RE, et al. Usability of the Massachusetts Prescription Drug Monitoring Program in the Emergency Department: A Mixed Methods Study. *Acad Emerg Med*. Jan 25 2016.
8. Norwood CW, Wright ER. Promoting consistent use of prescription drug monitoring programs (PDMP) in outpatient pharmacies: Removing administrative barriers and increasing awareness of Rx drug abuse. *Research in social & administrative pharmacy : RSAP*. Aug 7 2015.
9. Rutkow L, Turner L, Lucas E, Hwang C, Alexander GC. Most primary care physicians are aware of prescription drug monitoring programs, but many find the data difficult to access. *Health Aff (Millwood)*. Mar 1 2015;34(3):484-492.
10. Kline RB. *Principles and practice of structural equation modeling*. 3rd ed. New York: Guilford Press; 2011.
11. Gershman JA, Gershman JA, Fass AD, Popovici I. Evaluation of Florida physicians' knowledge and attitudes toward accessing the state prescription drug monitoring program as a prescribing tool. *Pain Med*. Dec 2014;15(12):2013-2019.

Appendix A CURES MBC survey

Q52 How concerned are you about prescription drug misuse and abuse among:

	Not concerned at all (0)	Slightly concerned (1)	Moderately concerned (2)	Extremely concerned (3)
Patients in California (1)	❍	❍	❍	❍
Patients in the community where you practice (2)	❍	❍	❍	❍

Q2 Do you currently have a DEA license to prescribe controlled substances?
- ❍ Yes (1)
- ❍ No (0)

If No Is Selected, Then Skip To End of Survey

Q4 Do you currently prescribe controlled substances in your practice?
- ❍ Yes (1)
- ❍ No (0)

Q8 Now we would like you to think about the last 3 months.

Q9 On average, how many days a week do you see patients?

Q10 On average, how many patients do you see per day?

Display This Question:
If Do you currently prescribe controlled substances in your practice? Yes Is Selected

Q11 On average, for how many of the patients that you see per day do you prescribe a controlled substance?

Q5 Now we'd like to ask you some questions about California's Controlled Substance Utilization Review and Evaluation System (CURES). CURES is California's online, computer-based system for monitoring the prescribing of all Schedule II, III and IV controlled substances dispensed in California. Have you heard of CURES?
- ❍ Yes (1)
- ❍ No (0)

Q7 Are you registered for CURES?
- ❍ Yes (1)
- ❍ No (2)
- ❍ Registration in process (3)
- ❍ Do not know (4)

Q12 Are you aware that registering for CURES is mandatory for DEA-licensed physicians?
- ❍ Yes (1)
- ❍ No (0)

Q13 How likely are you to register for CURES within the following month?
- ❍ Extremely unlikely (1)
- ❍ Unlikely (2)
- ❍ Likely (3)
- ❍ Extremely likely (4)

Q14 Please indicate the extent to which you agree with the following:

	Strongly disagree (1)	Somewhat disagree (2)	Neither agree nor disagree (3)	Somewhat agree (4)	Strongly agree (5)
I have other problems that are more important than registering for CURES. (2)	❍	❍	❍	❍	❍
I know how to go about registering for CURES. (3)	❍	❍	❍	❍	❍
Every time I try to register for CURES, something goes wrong. (5)	❍	❍	❍	❍	❍
Registering for CURES takes little time. (4)	❍	❍	❍	❍	❍
I don't have access to a computer or the internet where I practice. (6)	❍	❍	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q34 How long have you been using CURES?
- ❍ Less than 3 months (1)
- ❍ 4 to 6 months (2)
- ❍ 7 months to 1 year (3)
- ❍ More than 1 year (4)

Q17 How likely are you to use CURES at least once in the next 3 months?
- ❍ Extremely unlikely (1)
- ❍ Unlikely (2)
- ❍ Likely (3)
- ❍ Extremely likely (4)

Q15 How difficult are the following in CURES?

	Very difficult (5)	Difficult (4)	Average (3)	Easy (2)	Very easy (1)
Registering for CURES (1)	❍	❍	❍	❍	❍
Logging in to CURES (2)	❍	❍	❍	❍	❍
Resetting your password (3)	❍	❍	❍	❍	❍
Remembering security questions (4)	❍	❍	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q16 Now we would like you to think about the last 3 months.On a typical day when you see patients, how many times do you use CURES to look up a patient's controlled substance medication history?
- ❍ Never (1)
- ❍ Less than once a day (5)
- ❍ 1-2 times a day (2)
- ❍ 3-5 times a day (3)
- ❍ 6+ times a day (4)

Q18 Please indicate the extent to which you agree with the following:

	Strongly disagree (1)	Disagree (2)	Neither agree nor disagree (3)	Agree (4)	Strongly Agree (5)
CURES is helpful (2)	❍	❍	❍	❍	❍
CURES is not relevant to my practice (3)	❍	❍	❍	❍	❍
CURES is easy to use (4)	❍	❍	❍	❍	❍
I don't know how to use CURES (5)	❍	❍	❍	❍	❍
CURES is checked by someone else in the office (6)	❍	❍	❍	❍	❍
I have limited or no access to CURES while I practice (7)	❍	❍	❍	❍	❍

Display This Question:
If We would like you to think about the last 3 months. On a typical day when you see patients, how m... Never Is Not Selected
And Are you registered for CURES? Yes Is Selected

Q19 What are your reasons for checking CURES? [Check all that apply]
- ❑ To check on patients prior to prescribing a controlled substance. (1)
- ❑ To look for evidence of “drug seeking.” (5)
- ❑ To monitor patients on controlled substances. (2)
- ❑ To improve my communication with patients regarding controlled substances. (7)
- ❑ Other (6) _____

Display This Question:
If We would like you to think about the last 3 months. On a typical day when you see patients, how m... Never Is Not Selected
And Are you registered for CURES? Yes Is Selected

Q20 Thinking about the past 3 months, for what percentage of patient visits that resulted in a prescription for controlled substances did you review CURES information?
- ❍ 0% (0)
- ❍ 10% (1)
- ❍ 20% (2)
- ❍ 30% (3)
- ❍ 40% (4)
- ❍ 50% (5)
- ❍ 60% (6)
- ❍ 70% (7)
- ❍ 80% (8)
- ❍ 90% (9)
- ❍ 100% (10)

Display This Question:
If Thinking about the past 3 months, for what percentage of patient visits that resulted in a prescr... 0% Is Not Selected
And We would like you to think about the last 3 months. On a typical day when you see patients, how m... Never Is Not Selected
And Are you registered for CURES? Yes Is Selected

Q21 Consider the patient visits for which you have reviewed CURES in the past 3 month period. For what percent of these cases did the information you obtained from CURES alter your prescribing decision?
- ❍ 0% (0)
- ❍ 10% (1)
- ❍ 20% (2)
- ❍ 30% (3)
- ❍ 40% (4)
- ❍ 50% (5)
- ❍ 60% (6)
- ❍ 70% (7)
- ❍ 80% (8)
- ❍ 90% (9)
- ❍ 100% (10)

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q28 How useful to you is CURES for the following:

	Very Useful (4)	Useful (3)	A little useful (2)	Not useful at all (1)
Helping manage patients with pain (1)	❍	❍	❍	❍
Helping build trust with patients (2)	❍	❍	❍	❍
Informing decisions to prescribe controlled substances. (4)	❍	❍	❍	❍
Identifying patients filling prescriptions from multiple doctors and/or pharmacies (5)	❍	❍	❍	❍
Identifying patients who misuse or abuse controlled prescription drugs (6)	❍	❍	❍	❍

Q27 Are you aware of the following new features in CURES?

	Never heard of it (0)	Heard of it, but never use it (1)	Used it at least once (2)
Sending secure peer-to-peer messages about specific patients (2)	❍	❍	❍
Giving delegates the ability to access to CURES on your behalf (4)	❍	❍	❍
The ability to flag patients who have patient-provider agreements (3)	❍	❍	❍
Automatic alerts for high risk patients (5)	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q31 Did you use the previous version of CURES in your practice?

❍ Yes (1)
❍ No (0)

Display This Question:
If Did you use the previous version of CURES in your practice? Yes Is Selected
And Are you registered for CURES? Yes Is Selected

Q32 Compared to the old website, how would you rate the new CURES website on the following characteristics?

	Much worse (-2)	Somewhat worse (-1)	About the same (0)	Somewhat better (1)	Much better (2)
Overall ease of use (1)	❍	❍	❍	❍	❍
Login process (2)	❍	❍	❍	❍	❍
Patient Activity Reports (3)	❍	❍	❍	❍	❍
Help Desk support (4)	❍	❍	❍	❍	❍

Q29 Do you feel that you need additional training or education about CURES?
- ❍ Yes (1)
- ❍ No (0)
- ❍ Don't know (2)

Display This Question:
If Do you feel that you need additional training or education about CURES? Yes Is Selected
Or Do you feel that you need additional training or education about CURES? Don't know Is Selected

Q30 What would you like additional training on? [Check all that apply]
- ❑ Registering for CURES (1)
- ❑ CURES passwords and security questions (2)
- ❑ Running patient activity reports (3)
- ❑ Identifying and using CURES delegates from my account (4)
- ❑ Sending secure messages (5)
- ❑ How automatic reports are generated (6)
- ❑ Flagging patients who have patient-provider agreements (7)
- ❑ Other topics (8) _____

Q33 Now we would like to ask you some general questions about monitoring patient's controlled substance medications using systems such as CURES.

Q54 Should physicians check CURES prior to writing a prescription for a controlled substance?
- ❍ Yes (1)
- ❍ No (0)
- ❍ Don't know (2)

Q55 Should physicians be required to check CURES prior to writing a prescription for a controlled substance?
- ❍ Yes (1)
- ❍ No (0)
- ❍ Don't know (2)

Q56 What percentage of your colleagues do you think use CURES at least weekly?
- ❍ 0% (1)
- ❍ 10% (2)
- ❍ 20% (3)
- ❍ 30% (4)
- ❍ 40% (5)
- ❍ 50% (6)
- ❍ 60% (7)
- ❍ 70% (8)
- ❍ 80% (9)
- ❍ 90% (10)
- ❍ 100% (11)

Q57 What percentage of your colleagues do you feel ought to be using CURES at least weekly?
- ❍ 0% (1)
- ❍ 10% (2)
- ❍ 20% (3)
- ❍ 30% (4)
- ❍ 40% (5)
- ❍ 50% (6)
- ❍ 60% (7)
- ❍ 70% (8)
- ❍ 80% (9)
- ❍ 90% (10)
- ❍ 100% (11)

Q35 I have a professional responsibility to check CURES when prescribing controlled substances.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q36 Checking CURES when prescribing controlled substances is the right thing to do.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q37 Using CURES when prescribing controlled substances is considered standard of care.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q38 Prescribing controlled substances without checking CURES would be morally wrong.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q39 Checking CURES when prescribing controlled substances is NOT a necessary part of my job.
- ❍ Strongly agree (1)
- ❍ Agree (2)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (4)
- ❍ Strongly disagree (5)

Q40 Now we would like to ask you some questions regarding your prescribing practices more generally.

Q41 How have your prescribing practices changed in the last 3 months?
- ❍ I prescribe FAR FEWER controlled substances (-2)
- ❍ I prescribe FEWER controlled substances (-1)
- ❍ No change (0)
- ❍ I prescribe MORE controlled substances (1)
- ❍ I prescribe FAR MORE controlled substances (2)

If No change Is Selected, Then Skip To End of Block

Q42 What factors led you to change your prescribing practices? [Check all that apply]
- ❑ Change in practice location or patient mix (1)
- ❑ Increased professional awareness of risks, benefits, and other solutions (3)
- ❑ New clinical guidelines and recommendations (4)
- ❑ CURES providing greater access to patient prescription drug history (6)
- ❑ Increased patient awareness of risks and benefits (7)
- ❑ Medico-legal ramifications (8)
- ❑ Other reason (10) _____

Q44 What percent of patients in California taking controlled substance medications do you feel:

	0% (1)	10% (2)	20% (3)	30% (4)	40% (5)	50% (6)	60% (7)	70% (8)	80% (9)	90% (10)	100% (11)
Misuse/Abuse them (1)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Benefit from them (2)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q43 What percent of your patients taking controlled substance medications do you feel:

	0% (1)	10% (2)	20% (3)	30% (4)	40% (5)	50% (6)	60% (7)	70% (8)	80% (9)	90% (10)	100% (11)
Misuse/Abuse them (1)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Benefit from them (2)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q45 Is there anything else you would like to tell us about CURES? (e.g., problems, recommendations)

Q46 Which gender do you identify with?
- ❍ Male (0)
- ❍ Female (1)
- ❍ Other (2) _____

Q47 Please indicate your age in years:

Q51 Please indicate whether you consider yourself
- ❍ Hispanic or Latino (1)
- ❍ Not Hispanic or Latino (2)

Q48 Which one of the following groups do you most identify with?
- ❍ American Indian or Alaskan Native (1)
- ❍ Asian (2)
- ❍ Black or African American (3)
- ❍ Native Hawaiian or Other Pacific Islander (4)
- ❍ White (5)
- ❍ Other (please specify) (6) _____

Q49 How long have you been practicing in years:

Q50 Please choose the specialty that best describes your current practice:

- ❍ Allergy and Immunology (24)
- ❍ Anesthesiology (1)
- ❍ Colon and Rectal Surgery (2)
- ❍ Dermatology (3)
- ❍ Emergency Medicine (4)
- ❍ Family Medicine (5)
- ❍ Internal Medicine (general) (6)
- ❍ Internal Medicine (subspecialty) (7)
- ❍ Medical Genetics (25)
- ❍ Neurology (8)
- ❍ Neurosurgery (26)
- ❍ Nuclear Medicine (27)
- ❍ Obstetrics and Gynecology (9)
- ❍ Ophthalmology (10)
- ❍ Orthopaedic Surgery (17)
- ❍ Otolaryngology (28)
- ❍ Pathology (29)
- ❍ Pain Medicine (11)
- ❍ Pediatrics (general) (12)
- ❍ Pediatrics (subspecialty) (30)
- ❍ Physical Medicine and Rehabilitation (31)
- ❍ Plastic Surgery (14)
- ❍ Preventive Medicine (32)
- ❍ Psychiatry (15)
- ❍ Radiology (13)
- ❍ Surgery (general) (34)
- ❍ Surgery (subspecialty) (35)
- ❍ Thoracic and Cardiac Surgery (33)
- ❍ Urology (16)

Q51 As part of the effort to understand prescribing practice and CURES usage, some of your colleagues have volunteered to participate in a follow up survey. May we contact you in the future regarding your prescribing practices and usage of CURES?

- ❍ Yes (1)
- ❍ No (0)

If No Is Selected, Then Skip To End of Survey

Q58 Thank you for your participation. Please provide your email address so we may contact you at a later date.

Appendix B CURES pharmacist survey

Q52 How concerned are you about prescription drug misuse and abuse among:

	Not concerned at all (0)	Slightly concerned (1)	Moderately concerned (2)	Extremely concerned (3)
Patients in California (1)	❍	❍	❍	❍
Patients in the community where you practice (2)	❍	❍	❍	❍

Q8 Now we would like you to think about the last 3 months.

Q9 On average, how many days a week do you dispense or manage medications?

Q10 On average, how many prescriptions do you dispense or manage per day?

Q11 On average, how many controlled substance substance prescriptions do you dispense or manage per day?

Q5 Now we'd like to ask you some questions about California's Controlled Substance Utilization Review and Evaluation System (CURES). CURES is California's online, computer-based system for monitoring the dispensing of all Schedule II, III and IV controlled substances dispensed in California. Have you heard of CURES?

❍ Yes (1)
❍ No (0)

Q7 Are you registered for CURES?

❍ Yes (1)
❍ No (2)
❍ Registration is in process (3)
❍ Don't know (4)

Q12 Are you aware that registering for CURES is mandatory for pharmacists?

❍ Yes (1)
❍ No (0)

Q13 How likely are you to register for CURES within the following month?

❍ Extremely unlikely (1)
❍ Unlikely (2)
❍ Likely (3)
❍ Extremely likely (4)

Q14 Please indicate the extent to which you agree with the following:

	Strongly disagree (1)	Somewhat disagree (2)	Neither agree nor disagree (3)	Somewhat agree (4)	Strongly agree (5)
I have other problems that are more important than registering for CURES. (2)	❍	❍	❍	❍	❍
I know how to go about registering for CURES. (3)	❍	❍	❍	❍	❍
Every time I try to register for CURES, something goes wrong. (5)	❍	❍	❍	❍	❍
Registering for CURES takes little time. (4)	❍	❍	❍	❍	❍
I don't have access to a computer or the internet where I practice. (6)	❍	❍	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q34 How long have you been using CURES?

- ❍ Less than 3 months (1)
- ❍ 4 to 6 months (2)
- ❍ 7 months to 1 year (3)
- ❍ More than 1 year (4)

Q17 How likely are you to use CURES at least once in the next 3 months?

- ❍ Extremely unlikely (1)
- ❍ Unlikely (2)
- ❍ Likely (3)
- ❍ Extremely likely (4)

Q15 How difficult are the following in CURES?

	Very difficult (5)	Difficult (4)	Average (3)	Easy (2)	Very easy (1)
Registering for CURES (1)	❍	❍	❍	❍	❍
Logging in to CURES (2)	❍	❍	❍	❍	❍
Resetting your password (3)	❍	❍	❍	❍	❍
Remembering security questions (4)	❍	❍	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q16 Now we would like you to think about the last 3 months.On a typical day when you dispense or manage medications, how many times do you use CURES to look up a patient's controlled substance medication history?

- ❍ Never (1)
- ❍ Less than once a day (5)
- ❍ 1-5 times a day (2)
- ❍ 6-9 times a day (3)
- ❍ 10+ times a day (4)

Q18 Please indicate the extent to which you agree with the following:

	Strongly disagree (1)	Disagree (2)	Neither agree nor disagree (3)	Agree (4)	Strongly Agree (5)
CURES is helpful (2)	❍	❍	❍	❍	❍
CURES is not relevant to my practice (3)	❍	❍	❍	❍	❍
CURES is easy to use (4)	❍	❍	❍	❍	❍
I don't know how to use CURES (5)	❍	❍	❍	❍	❍
CURES is checked by someone else in the office (6)	❍	❍	❍	❍	❍
I have limited or no access to CURES while I practice (7)	❍	❍	❍	❍	❍

Display This Question:
If On a typical day when you dispense or manage medications, how many times do you use CURES to look... Never Is Not Selected
And Are you registered for CURES? Yes Is Selected

Q19 What are your reasons for checking CURES? [Check all that apply]

- ❑ To check on patients prior to dispensing or managing a controlled substance. (1)
- ❑ To look for evidence of “drug seeking.” (5)
- ❑ To monitor patients on controlled substances. (2)
- ❑ To improve my communication with patients regarding controlled substances. (7)
- ❑ Other (6) _____

Display This Question:
If On a typical day when you dispense or manage medications, how many times do you use CURES to look... Never Is Not Selected
And Are you registered for CURES? Yes Is Selected

Q20 Thinking about the past 3 months, for what percentage of controlled substance fills did you review CURES information?

- ❍ 0% (6)
- ❍ 10% (7)
- ❍ 20% (8)
- ❍ 30% (9)
- ❍ 40% (10)
- ❍ 50% (11)
- ❍ 60% (12)
- ❍ 70% (13)
- ❍ 80% (14)
- ❍ 90% (15)
- ❍ 100% (16)

Display This Question:
If On a typical day when you dispense or manage medications, how many times do you use CURES to look... Never Is Not Selected
And Thinking about the past 3 months, for what percentage of controlled substance fills did you revie... 0% Is Not Selected
And Are you registered for CURES? Yes Is Selected

Q21 Consider the prescriptions for which you have reviewed CURES in the past 3 month period. For what percent of these prescriptions did the information you obtained from CURES prompt you to...

	0% (1)	10% (2)	20% (3)	30% (4)	40% (5)	50% (6)	60% (7)	70% (8)	80% (9)	90% (10)	100% (11)
contact the prescriber for more information? (2)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
not to fill the prescription? (3)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q28 How useful to you is CURES for the following

	Very Useful (4)	Useful (3)	A little useful (2)	Not useful at all (1)
Helping manage patients with pain (1)	❍	❍	❍	❍
Helping build trust with patients (2)	❍	❍	❍	❍
Informing decisions to dispense or manage controlled substances (4)	❍	❍	❍	❍
Identifying patients filling prescriptions from multiple doctors and/or pharmacies (8)	❍	❍	❍	❍
Identifying patients who misuse or abuse controlled prescription drugs (6)	❍	❍	❍	❍

Q27 Are you aware of the following new features in CURES?

	Never heard of it (0)	Heard of it, but never use it (1)	Used it at least once (2)
Sending secure peer-to-peer messages about specific patients (2)	❍	❍	❍
Giving delegates the ability to access CURES on your behalf (4)	❍	❍	❍
Automatic alerts for high-risk patients (5)	❍	❍	❍

Display This Question:
If Are you registered for CURES? Yes Is Selected

Q31 Did you use the previous version of CURES in your practice?
- ❍ Yes (1)
- ❍ No (0)

Display This Question:
If Did you use the previous version of CURES in your practice? Yes Is Selected
And Are you registered for CURES? Yes Is Selected

Q32 Compared to the old website, how would you rate the new CURES website on the following characteristics?

	Much worse (-2)	Somewhat worse (-1)	About the same (0)	Somewhat better (1)	Much better (2)
Overall ease of use (1)	❍	❍	❍	❍	❍
Login process (2)	❍	❍	❍	❍	❍
Patient Activity Reports (3)	❍	❍	❍	❍	❍
Help Desk support (4)	❍	❍	❍	❍	❍

Q29 Do you feel that you need additional training or education about CURES?
- ❍ Yes (1)
- ❍ No (0)
- ❍ Don't know (2)

Display This Question:
If Do you feel that you need additional training or education about CURES? Yes Is Selected
Or Do you feel that you need additional training or education about CURES? Don't know Is Selected

Q30 What would you like additional training on? [Check all that apply]
- ❑ Registering for CURES (1)
- ❑ CURES passwords and security questions (2)
- ❑ Running patient activity reports (3)
- ❑ Identifying and using CURES delegates from my account (4)
- ❑ Sending secure messages (5)
- ❑ How automatic reports are generated (6)
- ❑ Other topics (8) _____

Q33 Now we would like to ask you some general questions about monitoring patient's controlled substance medications using systems such as CURES.

Q51 Should pharmacists check CURES prior to dispensing or managing a controlled substance?
- ❍ Yes (1)
- ❍ No (0)
- ❍ Don't know (2)

Q52 Should pharmacists be required to check CURES prior to dispensing or managing a controlled substance?
- ❍ Yes (1)
- ❍ No (0)
- ❍ Don't know (2)

Q54 What percentage of your colleagues do you think use CURES at least weekly?
- ❍ 0% (1)
- ❍ 10% (2)
- ❍ 20% (3)
- ❍ 30% (4)
- ❍ 40% (5)
- ❍ 50% (6)
- ❍ 60% (7)
- ❍ 70% (8)
- ❍ 80% (9)
- ❍ 90% (10)
- ❍ 100% (11)

Q56 What percentage of your colleagues do you feel ought to be using CURES at least weekly?
- ❍ 0% (1)
- ❍ 10% (2)
- ❍ 20% (3)
- ❍ 30% (4)
- ❍ 40% (5)
- ❍ 50% (6)
- ❍ 60% (7)
- ❍ 70% (8)
- ❍ 80% (9)
- ❍ 90% (10)
- ❍ 100% (11)

Q35 I have a professional responsibility to check CURES when dispensing or managing controlled substances.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q36 Checking CURES when dispensing or managing controlled substances is the right thing to do.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q37 Using CURES when dispensing or managing controlled substances is considered standard of care.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q38 Dispensing or managing controlled substances without checking CURES would be morally wrong.
- ❍ Strongly agree (5)
- ❍ Agree (4)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (2)
- ❍ Strongly disagree (1)

Q39 Checking CURES when dispensing or managing controlled substances is NOT a necessary part of my job.
- ❍ Strongly agree (1)
- ❍ Agree (2)
- ❍ Neither agree nor disagree (3)
- ❍ Disagree (4)
- ❍ Strongly disagree (5)

Q40 Now we would like to ask you some questions regarding your dispensing and managing practices more generally.

Q41 How have your dispensing or managing practices changed in the last 3 months?
- ❍ I dispense/manage FAR FEWER controlled substances (-2)
- ❍ I dispense/manage FEWER controlled substances (-1)
- ❍ No change (0)
- ❍ I dispense/manage MORE controlled substances (1)
- ❍ I dispense/manage FAR MORE controlled substances (2)

If No change Is Selected, Then Skip To End of Block

Q42 What factors led you to change your prescribing practices? [Check all that apply]
- ❑ Change in practice location or patient mix (1)
- ❑ New professional standards and protocols where I practice (2)
- ❑ Increased professional awareness of risks, benefits, and other solutions (3)
- ❑ New clinical guidelines and recommendations (4)
- ❑ Increased law enforcement activity (5)
- ❑ CURES providing greater access to patient prescription drug history (6)
- ❑ Increased patient awareness of risks and benefits (7)
- ❑ Medico-legal ramifications (8)
- ❑ Other reason (10) _____

Q43 What percent of patients in California taking controlled substance medications do you feel:

	0% (1)	10% (2)	20% (3)	30% (4)	40% (5)	50% (6)	60% (7)	70% (8)	80% (9)	90% (10)	100% (11)
Misuse/Abuse them (1)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Benefit from them (2)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q44 What percent of your patients taking controlled substance medications do you feel:

	0% (1)	10% (2)	20% (3)	30% (12)	40% (13)	50% (14)	60% (15)	70% (16)	80% (17)	90% (18)	100% (19)
Misuse/Abuse them (1)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Benefit from them (2)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

Q45 Is there anything else you would like to tell us about CURES? (e.g. problems, recommendations)

Q46 Which gender do you identify with?
- Male (0)
- Female (1)
- Other (2) _____

Q47 Please indicate your age in years:

Q50 Please indicate whether you consider yourself
- Hispanic or Latino (1)
- Not Hispanic or Latino (2)

Q48 Which one of the following groups do you most identify with?
- American Indian or Alaskan Native (1)
- Asian (2)
- Black or African American (3)
- Native Hawaiian or Other Pacific Islander (4)
- White (5)
- Other (please specify) (6) _____

Q49 How long have you been practicing in years:

Q50 Please identify the choice that best describes your primary practice site?
- Independent pharmacy (1)
- Chain pharmacy (2)
- Hospital (3)
- Supermarket (4)
- Mass merchandiser (5)
- Other patient care practice (6)
- Other (non patient care) (7)

Q51 As part of the effort to understand clinical practice and CURES usage, some of your colleagues have volunteered to participate in a follow up survey. May we contact you in the future regarding your clinical practice and usage of CURES?
- Yes (1)
- No (0)

If No Is Selected, Then Skip To End of Survey

Q57 Thank you for your participation. Please provide your email address so we may contact you at a later date.

Appendix C. Timeline of survey deployment and reminders

	Medical Board	Pharmacy Board[a]	Osteopathic Board[a]
Initial fliers mailed	8/10/2016	9/6/2016	10/6/2016
Email #1 sent	8/23/2016	--	--
Post card #1 mailed	8/27/2016	9/26/2016	--
SB-482 signed[b]	9/27/2016		
Tri-fold reminder #1	--	--	10/19/2016
Email #2 sent	10/18/2016	--	--
Reminder letter mailed from Board of Pharmacy	--	10/12/2016**	--
Postcard #2 mailed	--	--	12/5/2016
Email #3 sent	11/9/2016	--	--
Email #4 sent	11/16/2016	--	--
Email #5 sent	11/30/2016	--	--
Reminder letter mailed from MBC	11/21/2016	--	--
Reminder letter mailed from OMBC	--	--	12/19/2016
Survey closed	1/31/2017	1/31/2017	1/31/2017

[a]Email reminders were not possible for Pharmacy Board and OMBC.

[b]SB-482, a state law mandating eventual CURES use by prescribers, was signed during the survey period. Some physician reminders sent out after this date mentioned SB-482 in order to encourage participation.

Attachment 3

Subscriber Alert

California Health and Safety Code section 11162.1 contains 14 elements that must appear on California Security Forms, the forms used to prescribe controlled substances in California. These elements were first enacted in 2003 when the triplicate prescription form was discontinued. The law also requires that California Security Forms must be printed by CA Department of Justice licensed printers. In 2006, the law was amended again to make several changes that took effect in January 2007. Finally legislation enacted in 2011 required that the California Security Forms in use must be fully compliant with all requirements of the Health and Safety Code by July 1, 2012.*

Here is a link to the required elements in the Health and Safety Code (go to page 357):
http://www.pharmacy.ca.gov/laws_regs/lawbook.pdf

In recent years, the board has continued to identify noncompliant California Security Forms in use that have been filled by California pharmacies, in violation of the Health and Safety Code requirements. The board's response upon identification of noncompliant forms having been used to dispense controlled drugs is to educate the licensee, and to cite and fine the pharmacy/pharmacists involved. Typically the licensing board for the prescriber is advised as well.

Recently some pharmacies have begun to refuse to fill prescriptions written on noncompliant forms where item 11162.1(a)(10) is not fully compliant with the required elements. One of these elements is " Check boxes shall be printed on the form so that the prescriber may indicate the number of refills ordered." There are also additional elements missing on some forms, including lack of a watermark on the reverse of the form.

The board recently has received complaints from patients or prescribers whose patients have been denied medication from the pharmacy because of the noncompliant forms.

Interim Solutions

- *Prescribers and dispensers need to become familiar with the 14 required elements of the security prescription forms.*
- *Prescribers with noncompliant forms should reorder compliant forms from a DOJ-licensed security printer.*
- *Prescribers with noncompliant forms should consider using e-prescribing for controlled substances.*

Additionally:

1. *Schedule III -V controlled substances may be filled (and refilled) if the pharmacist treats the prescription as an oral prescription and verifies orally with the prescriber*

the number of any refills ordered with notations on the security form.

2. *California law provides that Schedule II drugs cannot generally be orally prescribed, nor can they be refilled using a California Security Prescription. However, when there is no alternative except to prescribe a Schedule II controlled medication using a noncompliant California Security Form to allow patients to receive their pain medications timely, prescribers and dispensers should communicate about why a noncompliant California Security Form is being used on a temporary basis.*

**Please note this exception to the security forms requirements: controlled substances prescriptions written for patients with a terminal illness may be written on ordinary prescription forms pursuant to section*
11159.2 of the Health &Safety Code – here is a link (see page 352):
http://www.pharmacy.ca.gov/laws_regs/lawbook.pdf

Attachment 4

Title 16. Board of Pharmacy

Changes made to the current regulation language are shown by strikethrough for deleted language and underline for added language. Additionally, [Brackets] indicates language that is not being amended.

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

1735.2. Compounding Limitations and Requirements; Self-Assessment.

[…..]

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

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

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

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

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

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

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

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

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

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

(ii) the dosage form and its components,

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

(iv) the container in which it is packaged,

(v) the expected storage conditions, and

(vi) the intended duration of therapy.

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

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

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

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

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

[…..]

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

Compounding
16 CCR §§ 1735.1, 1735.2, 1735.6, 1751.1, and 1751.4

Title 16. Board of Pharmacy

Changes made to the current regulation language are shown by strikethrough for deleted language and underline for added language. Additionally, [Brackets] indicate language that is not being amended.

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

1735.1. Compounding Definitions.

[…..]

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

(d) “Bulk drug substance” means any substance that, when used in the preparation of a compounded drug preparation, processing, or packaging of a drug, is an active ingredient or a finished dosage form of the drug, but the term does not include any intermediate used in the synthesis of such substances.

(e) “Cleanroom or clean area or buffer area” means a room or area with HEPA-filtered air that provides ISO Class 7 or better air quality where the primary engineering control (PEC) is physically located.

(1) For nonhazardous compounding a positive pressure differential of 0.02- to 0.05-inch water column relative to all adjacent spaces is required.

(2) For hazardous compounding at least 30 air changes per hour of HEPA-filtered supply air and a negative pressure of between 0.01 to 0.03 inches of water column relative to all adjacent spaces is required.

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

[…..]

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

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

1735.2. Compounding Limitations and Requirements; Self-Assessment.

[…..]

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

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

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

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

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

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

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

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

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

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

(ii) the dosage form and its components,

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

(iv) the container in which it is packaged,

(v) the expected storage conditions, and

(vi) the intended duration of therapy.

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

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

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

(B) The chemical stability of any one ingredient in the sterile compounded drug preparation,
(C) The chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and
(D) The beyond use date assigned for sterility in section 1751.8.

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

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

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

[…..]

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

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

1735.6. Compounding Facilities and Equipment.

[…..]

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

(1) Minimum of 30 air changes per hour except that 12 air changes per hour are acceptable for segregated compounding areas with a BSC or CACI when products are assigned a BUD of 12 hrs or less or when non sterile products are compounded; and

(2) Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors); and

(3) Each ~~PEC~~ BSC in the room shall also be externally vented except that a BSC used only for nonsterile compounding may also use a redundant-HEPA filter in series; and

(4) All surfaces within the room shall be smooth, seamless, impervious, and non-shedding.

(f) Where compliance with the January 1, 2017 amendments to Article 4.5 or Article 7, requires physical construction or alteration to a facility or physical environment, the board or its designee may grant a waiver of such compliance for a period of time to permit such physical change(s). Application for any waiver shall be made by the licensee in writing, and the request shall identify the provision(s) requiring physical construction or alteration, and the timeline for any such change(s). The board or its designee may grant the waiver when, in its discretion, good cause is demonstrated for such waiver.

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code.

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

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

1751.1. Sterile Compounding Recordkeeping Requirements.

(a) In addition to the records required by section 1735.3, any pharmacy engaged in any compounding of sterile drug preparations shall maintain the following records, which must be readily retrievable, within the pharmacy:
  (1) Documents evidencing training and competency evaluations of employees in sterile drug preparation policies and procedures.
  (2) Results of hand hygiene and garbing assessments with integrated gloved fingertip testing.
  (3) Results of assessments of personnel for aseptic techniques including results of media-fill tests and gloved fingertip testing performed in association with media-fill tests.
  (4) Results of viable air and surface sampling.
  (5) Biannual ~~V~~ video of smoke studies in all ISO Class 5 certified spaces.
  (6) Documents indicating daily documentation of room, refrigerator, and freezer temperatures appropriate for sterile compounded drug preparations consistent with the temperatures listed in section 1735.1 for:
    (A) Controlled room temperature.
    (B) Controlled cold temperature.
    (C) Controlled freezer temperature.

[…..]

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

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

1751.4. Facility and Equipment Standards for Sterile Compounding.

[…..]

(k) The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which includes a room temperature of ~~20-~~24 degrees Celsius (~~68-~~75 degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.
(l) A licensee may request a waiver of these provisions as provided in section 1735.6(f).

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.

Attachment 5

Frequently Asked Questions - Board Compounding Regulations

Question: Can an electronic monitoring system be used to comply with the daily monitoring requirements established to maintain refrigerator and freezer temperatures?

Answer: Yes, if it fulfills all requirements. For example, if the electronic monitoring system collects and maintains temperature readings for the refrigerator and freezer, and could create a report documenting the temperature, and that report is available and can be provided upon request.

Question: What is "sterility?"

Answer: The definition of this term will ultimately be determined by professional standard of practice in the context where it is used. As guidance, however, USP <1211> (*Sterilization and Sterility Assurance of Compendial Articles*) provides a general description of the concepts and principles involved in the quality control of articles that must be sterile. The introduction to Chapter <1211> notes that any modifications of, or variations in, sterility test procedures from those described under *Sterility Tests* <71> should be validated. For additional information on sterility, refer to these and other relevant chapters of USP.

Question: What is "stability?"

Answer: The definition of this term will ultimately be determined by professional standard of practice in the context where it is used. As guidance, however, USP <1150> (*Pharmaceutical Stability*) indicates that the term "stability" refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. For additional information on stability, refer to this and other relevant chapters of USP.

Question: How is "identical" applied in CCR, title 16, section 1735.2(i)(4)?

Answer: A pharmacist must use his or her professional judgment to determine if the drugs or compounded drug preparations tested and studied are identical in ingredients, specific and essential compounding steps, quality reviews, and packaging as the finished drug or compounded drug preparation. For example, a drug or preparation from different manufacturers may be considered identical if the pharmacist determines that the formulation components, amounts, and parameters (such as pH and dilution) are the same. Preparations may have the same formulations, however, if the parameters (such as pH and dilution) differ, the pharmacist may not be able to consider the preparations to be identical. Where a pharmacist exercises such judgment, the standard of practice in the industry may require that documentation be maintained to support the conclusion reached.

Question: What is the minimum testing frequency required to comply with the quality assurance plan requirements established in CCR, title 16, Section 1735.8?

Answer: The board's regulation requires testing a minimum of two specified compounded drug preparations. A pharmacist, using his or her professional judgment, should determine the appropriate testing schedule and frequency for the pharmacy.

Attachment 6

Possible Amendments to compounding regulations as specified below in red ink

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) "Ante-area" means an area with ISO Class 8 or better air quality where personnel hand hygiene and garbing procedures, staging of components, and other high-particulate-generating activities are performed, that is adjacent to the area designated for sterile compounding. It is a transition area that begins the systematic reduction of particles, prevents large fluctuations in air temperature and pressures in the cleanroom, and maintains air flows from clean to dirty areas. ISO Class 7 or better air quality is required for ante-areas providing air to a negative pressure room.

(b) "Beyond use date" means the date, or date and time, after which administration of a compounded drug preparation shall not begin, the preparation shall not be dispensed, and the preparation shall not be stored (other than for quarantine purposes).

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

(d) "Bulk drug substance" means any substance that, when used in the preparation of a compounded drug preparation, processing, or packaging of a drug, is an active ingredient or a finished dosage form of the drug, but the term does not include any intermediate used in the synthesis of such substances.

(e) "Cleanroom or clean area or buffer area" means a room or area with HEPA-filtered air that provides ISO Class 7 or better air quality where the primary engineering control (PEC) is physically located.

(1) For nonhazardous compounding a positive pressure differential of 0.02- to 0.05-inch water column relative to all adjacent spaces is required.

(2) For hazardous compounding at least 30 air changes per hour of HEPA-filtered supply air and

a negative pressure of between 0.01 to 0.03 inches of water column relative to all adjacent spaces is required.

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

(g) “Compounding Aseptic Isolator (CAI)” means a form of isolator specifically designed for non-hazardous compounding of pharmaceutical ingredients or preparations while bathed with unidirectional HEPA-filtered air. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Air within the CAI shall not be recirculated nor turbulent.

(h) “Controlled cold temperature” means 2 degrees to 8 degrees C (35 degrees to 46 degrees F).

(i) “Controlled freezer temperature” means -25 degrees to -10 degrees C (-13 degrees to 14 degrees F) or at a range otherwise specified by the pharmaceutical manufacturer(s) for that product.

(j) “Controlled room temperature” means 20 degrees to 25 degrees C (68 degrees to 77 degrees F).

(k) “Copy or essentially a copy” of a commercially available drug product includes 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.

(l) "Daily" means occurring every day the pharmacy is operating, except when daily monitoring of refrigerator and freezer temperature are required, then daily means every 24 hours.

(m) "Displacement airflow method" means a concept which utilizes a low pressure differential, high airflow principle to maintain segregation from the adjacent ante-area by means of specific pressure differentials. This principle of displacement airflow shall require an air velocity of 40 ft per minute or more, from floor to ceiling and wall to wall, from the clean area across the line of demarcation into the ante-area. The displacement concept may not be used to maintain clean area requirements for sterile compounds which originate from any ingredient that was at any time non-sterile, regardless of intervening sterilization of the ingredient, or for hazardous compounds.

(n) "Dosage unit" means a quantity sufficient for one administration to one patient.

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

(p) "First air" means the air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.

(q) "Gloved fingertip sampling" means a process whereby compounding personnel lightly press each fingertip and thumb of each hand onto appropriate growth media, which are then incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms.

(r) Until December 1, 2019, "~~H~~hazardous" means all anti-neoplastic agents identified by the National Institute for Occupational Safety and Health (NIOSH) as meeting the criteria for a hazardous drug and any other drugs, compounds, or materials identified as hazardous by the pharmacist-in-charge. Effective December 1, 2019, "hazardous" means any drug identify by NIOSH and that exhibit as at least one of the following six criteria:

(1) Carcinogenicity

(2) Teratogencitiy of developmental toxicity

(3) Reproductive toxicity in humans

(4) Organ toxicity in low doses in human or animals

(5) Genotoxicity

(6) New drugs that mimic existing hazardous drugs in structure or toxicity.

(s) “Integrity” means retention of potency until the beyond use date provided on the label, so long as the preparation is stored and handled according to the label directions.

(t) “Lot” means one or more compounded drug preparation(s) prepared during one uninterrupted continuous cycle of compounding from one or more common active ingredient(s).

(u) “Media-fill test” means a test used to measure the efficacy of compounding personnel in aseptic techniques whereby compounding procedures are mimicked using a growth-based media and then the resulting preparation is evaluated for sterility. The media-fill test must mimic the most complex compounding procedures performed by the pharmacy.

(v) “Non-sterile-to-sterile batch” means any compounded drug preparation containing two (2) or more dosage units with any ingredient that was at any time non-sterile, regardless of intervening sterilization of that ingredient.

(w) “Parenteral” means a preparation of drugs administered in a manner other than through the digestive tract. It does not include topical, sublingual, rectal or buccal routes of administration.

(x) “Personal protective equipment” means clothing or devices that protect the employee from exposure to compounding ingredients and/or potential toxins and minimize the contamination of compounded preparations. These include shoe covers, head and facial hair covers, face masks, gowns, and gloves.

(y) “Potency” means active ingredient strength within +/- 10% (or the range specified in USP37-NF32, 37th Revision, Through 2nd Supplement Effective December 1, 2014) of the labeled amount. Sterile injectable products compounded solely from commercially manufactured sterile pharmaceutical products in a health care facility licensed under section 1250 of the Health and Safety Code are exempt from this definition. For those exempt, the range shall be calculated and defined in the master formula.

(z) “Preparation” means a drug or nutrient compounded in a licensed pharmacy; the preparation may or may not be sterile.

(aa) "Prescriber's office" or "prescriber office" means an office or suite of offices in which a prescriber regularly sees patients for outpatient diagnosis and treatment. This definition does not include any hospital, pharmacy, or other facility, whether or not separately licensed, that may be affiliated with, adjacent to, or co-owned by, the prescriber’s practice environment.

(ab) “Primary Engineering Control (PEC)” means a device that provides an ISO Class 5 or better environment through the use of non-turbulent, unidirectional HEPA-filtered first air for compounding sterile preparations. Examples of PEC devices include, but are not limited to, laminar airflow workbenches, biological safety cabinets, sterile compounding automated robots, compounding aseptic isolators, and compounding aseptic containment isolators.

(ac) “Process validation” means demonstrating that when a process is repeated within specified limits, the process will consistently produce preparations complying with predetermined requirements. If any aspect of the process is changed, the process would need to be revalidated.

(ad) “Product” means a commercially manufactured drug or nutrient evaluated for safety and efficacy by the FDA.

(ae) “Quality” means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, the absence of active ingredients other than those listed on the label, and the absence of inactive ingredients other than those listed on the master formula document.

(af) “Segregated sterile compounding area” means a designated space for sterile-to-sterile compounding where a PEC is located within either a demarcated area (at least three foot perimeter) or in a separate room. Such area or room shall not contain and shall be void of activities and materials that are extraneous to sterile compounding. The segregated sterile compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors, in a location with high traffic flow, or in a location that is adjacent to construction sites, warehouses, or food preparation. The segregated sterile compounding area shall not have a sink, other than an emergency eye-washing station, located within three feet of a PEC. The segregated sterile compounding area shall be restricted to preparation of sterile-to-sterile compounded preparations.

(1) The BUD of a sterile drug preparation made in a segregated sterile compounding area is limited to 12 hours or less as defined by section 1751.8(d).

(2) When the PEC in the segregated sterile compounding area is a CAI or a CACI and the documentation provided by the manufacturer shows it meets the requirements listed in section 1751.4(f)(1)-(3), the assigned BUD shall comply with section 1751.8(a-b) or (d).

(ag) “Strength” means amount of active ingredient per unit of a compounded drug preparation.

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 preparation 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 preparation either orally or in writing. Where approval is given orally, that approval shall be noted on the prescription prior to compounding.

(b) A pharmacy may prepare and store a limited quantity of a compounded drug preparation in advance of receipt of a patient-specific prescription where and solely in such quantity as is necessary to ensure continuity of care for an identified population of patients of the pharmacy based on a documented history of prescriptions for that patient population.

(c) A "reasonable quantity" that may be furnished to a prescriber for office use by the prescriber as authorized by Business and Professions Code section 4052, subdivision (a)(1), means that amount of compounded drug preparation that:

(1) Is ordered by the prescriber or the prescriber's agent using a purchase order or other documentation received by the pharmacy prior to furnishing that lists the number of patients seen or to be seen in the prescriber's office for whom the drug is needed or anticipated, and the quantity for each patient that is sufficient for office administration; and

(2) Is delivered to the prescriber's office and signed for by the prescriber or the prescriber's agent; and

(3) Is sufficient for administration or application to patients solely in the prescriber's office, or for furnishing of not more than a 120-hour supply for veterinary medical practices, solely to the prescriber's own veterinary patients seen as part of regular treatment in the prescriber's office, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing; and

(4) That the pharmacist has a credible basis for concluding it is a reasonable quantity for office use considering the intended use of the compounded medication and the nature of the

prescriber's practice; and

(5) With regard to any individual prescriber to whom the pharmacy furnishes, and with regard to all prescribers to whom the pharmacy furnishes, is an amount which the pharmacy is capable of compounding in compliance with pharmaceutical standards for integrity, potency, quality and strength of the compounded drug preparation; and

(6) Does not exceed an amount the pharmacy can reasonably and safely compound.

(d) No pharmacy or pharmacist shall compound a drug preparation that:

(1) Is classified by the FDA as demonstrably difficult to compound;

(2) Appears on an FDA list of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective; or

(3) Is a copy or essentially a copy of one or more commercially available drug products, unless that drug product appears on an ASHP (American Society of Health-System Pharmacists) or FDA list of drugs that are in short supply at the time of compounding and at the time of dispense, and the compounding of that drug preparation is justified by a specific, documented medical need made known to the pharmacist prior to compounding. The pharmacy shall retain a copy of the documentation of the shortage and the specific medical need in the pharmacy records for three years from the date of receipt of the documentation.

(e) A drug preparation shall not be compounded until the pharmacy has first prepared a written master formula document that includes at least the following elements:

(1) Active ingredients to be used.

(2) Equipment to be used.

(3) The maximum allowable beyond use date for the preparation, and the rationale or reference source justifying its determination.

(4) Inactive ingredients to be used.

(5) Specific and essential compounding steps used to prepare the drug.

(6) Quality reviews required at each step in preparation of the drug.

(7) Post-compounding process or procedures required, if any.

(8) Instructions for storage and handling of the compounded drug preparation.

(f) Where a pharmacy does not routinely compound a particular drug preparation, the master formula record for that preparation may be recorded on the prescription document itself.

(g) The pharmacist performing or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug preparation until the beyond use date indicated on the label, so long as label instructions for storage and handling are followed after the preparation is dispensed.

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

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

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

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

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

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

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

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

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

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

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

(ii) the dosage form and its components,

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

(iv) the container in which it is packaged,

(v) the expected storage conditions, and

(vi) the intended duration of therapy.

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

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

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

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

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

(D) The beyond use date assigned for sterility in section 1751.8~~.~~, or

(~~3~~E) ~~Extension of a beyond use date is only allowable when supported by the following:~~ A beyond use date established by a pharmacist using his or her professional judgement after conducting research and analysis and preparing documentation. The pharmacist's documentation must demonstrate that:

(~~A~~ i) The beyond use date is supported by a USP <671> compliant Method Suitability Test,

(~~B~~ii) The beyond use date is supported by a USP <1191> Container Closure Integrity Test, ~~and~~

(~~C~~iii) The beyond use date is supported by Stability Studies, and

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

(~~5~~3) Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.

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

(k) Prior to allowing any drug product preparation 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.) as required by Section 1715 of Title 16, Division 17, of the California Code of Regulations. 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 compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of each odd-numbered year, within 30 days of the start date of a new pharmacist-in-charge or change of location, 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.

(l) Packages of ingredients, both active and inactive, that lack a supplier's expiration date are subject to the following limitations:

(1) such ingredients cannot be used for any non-sterile compounded drug preparation more than three (3) years after the date of receipt by the pharmacy.

(2) such ingredients cannot be used for any sterile compounded drug preparation more than one (1) year after the date of receipt by the pharmacy.

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 § 1751.4 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.4. Facility and Equipment Standards for Sterile Compounding.

(a) No sterile drug preparation 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 drug preparations.

(b) During the compounding of sterile drug preparations, access to the areas designated for

compounding must be limited to those individuals who are properly attired.

(c) All equipment used in the areas designated for compounding must be made of a material that can be easily cleaned and disinfected.

(d) Cleaning shall be done using a germicidal detergent ~~and sterile water~~. The use of a sporicidal agent is required to be used at least monthly. When hazardous drugs are being compounded decontamination with an inactivating agent shall take place before each cleaning. Any dilution of the germicidal detergent, sporicidal agent, or inactivating agent shall only be done with sterile water.

(1) All ISO Class 5 surfaces, work table surfaces, carts, counters, and the cleanroom floor shall be cleaned at least every 48 hours and at minimum must be cleaned each day prior to compounding.~~at least daily~~. After each cleaning, disinfection using a suitable sterile agent shall occur on all ISO Class 5 surfaces, work table surfaces, carts, and counters.

(2) Walls, ceilings, storage, shelving, tables, stools, and all other items in the ISO Class 7 or ISO Class 8 environment, and the segregated sterile compounding areas shall be cleaned at least monthly.

(3) Cleaning shall also occur after any unanticipated event that could increase the risk of contamination.

(4) All cleaning materials, such as wipers, sponges, and mops, shall be non-shedding and dedicated to use in the cleanroom, or ante-area, and segregated sterile compounding areas and shall not be removed from these areas except for disposal.

(e) Disinfection, using a suitable sterile agent, shall also occur on all surfaces in the ISO Class 5 PEC frequently, including:

(1) At the beginning of each shift;

(2) At least every 30 minutes when compounding involving human staff is occurring or before each lot;

(3) After each spill; and

(4) When surface contamination is known or suspected.

(f) Pharmacies preparing sterile compounded preparations require the use of a PEC that provides ISO Class 5 air or better air quality. Certification and testing of primary and secondary engineering controls shall be performed no less than every six months and whenever the device or area designated for compounding is relocated, altered or a service to the facility is performed

that would impact the device or area. Certification must be completed by a qualified technician who is familiar with certification methods and procedures in accordance with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015), which is hereby incorporated by reference. Certification records must be retained for at least 3 years. Unidirectional compounding aseptic isolators or compounding aseptic containment isolators may be used outside of an ISO Class 7 cleanroom if the isolator is certified to meet the following criteria:

(1) Particle counts sampled approximately 6-12 inches upstream of the critical exposure site shall maintain ISO Class 5 levels during compounding operations.

(2) Not more than 3520 particles (0.5 um and larger) per cubic meter shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing transfer.

(3) Recovery time to achieve ISO Class 5 air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.

Compounding aseptic isolators that do not meet the requirements as outlined in this subdivision or are not located within an ISO Class 7 cleanroom may only be used to compound preparations that meet the criteria specified in accordance with subdivision (d) of Section 1751.8 of Title 16, Division 17, of the California Code of Regulations.

(g) Pharmacies preparing sterile hazardous agents shall do so in accordance with Section 505.5.1 of Title 24, Chapter 5, of the California Code of Regulations, requiring a negative pressure PEC. Additionally, each PEC used to compound hazardous agents shall be externally vented. The negative pressure PEC must be certified every six months by a qualified technician who is familiar with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015), which is hereby incorporated by reference. Any drug preparation that is compounded in a PEC where hazardous drugs are prepared must be labeled as hazardous, regardless of whether the drug ingredients are considered hazardous.

(1) During the hazardous drug compounding that is performed in a compounding aseptic containment isolator, full hand hygiene and garbing must occur. Garbing shall include hair cover, facemask, beard cover (if applicable), polypropylene or low shedding gown that closes in the back, shoe covers, and two pairs of sterile ASTM D6978-05 standard gloves.

(h) If a compounding aseptic isolator is certified by the manufacturer to maintain ISO Class 5 air quality during dynamic operation conditions during compounding as well as during the transfer of ingredients into and out of the compounding aseptic isolator, then it may be placed into a non-ISO classified room. Individuals that use compounding aseptic isolators in this manner must ensure appropriate garbing, which consists of donning sterile gloves over the isolator gloves immediately before non-hazardous compounding. These sterile gloves must be changed by each individual whenever continuous compounding is ceased and before compounding starts again.

(i) Compounding aseptic isolator and compounding aseptic containment isolator used in the compounding of sterile drug preparations shall use non-turbulent unidirectional air flow patterns. A smoke patterned test shall be used to determine air flow patterns.

(j) Viable surface sampling shall be done at least every six months for all sterile-to-sterile compounding and quarterly for all non-sterile-to-sterile compounding. Viable air sampling shall be done by volumetric air sampling procedures which test a sufficient volume of air (400 to 1,000 liters) at each location and shall be done at least once every six months. Viable surface and viable air sampling shall be performed by a qualified individual 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. Viable surface sampling is to be performed under dynamic conditions of actual compounding. When the environmental monitoring action levels are exceeded, the pharmacy shall identify the CFUs at least to the genus level in addition to conducting an investigation pursuant to its policies and procedures. Remediation shall include, at minimum, an immediate investigation of cleaning and compounding operations and facility management.

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

(l) A licensee may request a waiver of these provisions as provided in section 1735.6(f).

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

1751.7. Sterile Compounding Quality Assurance and Process Validation.

(a) Any pharmacy engaged in compounding sterile drug preparations 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 that it meets required specifications. The quality assurance program shall include at least the following:

(1) Procedures for cleaning and sanitization of the sterile preparation area.

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

(3) Documentation justifying the chosen beyond use dates for compounded sterile drug preparations.

(b)(1) The pharmacy and each individual involved in the compounding of sterile drug preparations must successfully demonstrate competency on aseptic technique and aseptic area practices before being allowed to prepare sterile drug preparations. The validation process 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 the types of manipulations, products and batch sizes the individual is expected to prepare and include a media-fill test. The validation process shall be as complicated as the most complex manipulations performed by staff and contain the same amount or greater amount of volume transferred during the compounding process. The same personnel, procedures, equipment, and materials must be used in the testing. Media used must have demonstrated the ability to support and promote growth. Completed medium samples must be incubated in a manner consistent with the manufacturer's recommendations. If microbial growth is detected, then each individual's sterile preparation process must be evaluated, corrective action taken and documented, and the validation process repeated.

(2) Each individual's competency must be revalidated at least every twelve months for sterile to sterile compounding and at least every six months for individuals compounding sterile

preparations from non-sterile ingredients.

(3) The pharmacy's validation process on aseptic technique and aseptic area practices must be revalidated whenever:

(A) the quality assurance program yields an unacceptable result,

(B) there is any change in the compounding process, the Primary Engineering Control (PEC), or the compounding environment. For purposes of this subsection, a change includes, but is not limited to, when the PEC is moved, repaired or replaced, when the facility is modified in a manner that affects airflow or traffic patterns, or when improper aseptic techniques are observed.

(4) The pharmacy must document the validation and revalidation process.

(c) All sterile compounding personnel must successfully complete an initial competency evaluation. In addition, immediately following the initial hand hygiene and garbing procedure, each individual who may be required to do so in practice must successfully complete a gloved fingertip (all fingers on both hands) sampling procedure (zero colony forming units for both hands) at least three times before initially being allowed to compound sterile drug preparations.

(d) Re-evaluation of garbing and gloving competency shall occur at least every 12 months for personnel compounding products made from sterile ingredients and at least every six months for personnel compounding products from non-sterile ingredients.

(e)(1) Batch-produced sterile drug preparations compounded from one or more non-sterile ingredients, except as provided in paragraph (2), shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens. Sterility testing shall be USP chapter 71 compliant unless a validated rapid microbial method (RMM) test is performed and pyrogens testing shall confirm acceptable levels of pyrogens per USP chapter 85 limits, before dispensing. Validation studies (method suitability) for each formulation using a RMM test shall be kept in a readily retrievable form at the licensed location. 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. Exempt from pyrogen testing are topical ophthalmic and inhalation preparations.

(2) The following non-sterile-to-sterile batch drug preparations do not require end product testing for sterility and pyrogens:

(A) Preparations for self-administered ophthalmic drops in a quantity sufficient for administration to a single patient for 30 days or less pursuant to a prescription.

(B) Preparations for self-administered inhalation in a quantity sufficient for administration to a single patient for 5 days or less pursuant to a prescription.

(C) Preparations noted as "Currently in Shortage" on the FDA website for a single patient on a one time basis for 21 days or less pursuant to a prescription. The pharmacy shall retain a copy of the documentation of the shortage and the specific medical need as part of the pharmacy record.

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

STRENGTH AND STABILITY TESTING FOR COMPOUNDED PREPARATIONS[i]

USP Compounding Expert Committee:[a] Loyd V Allen Jr, PhD,[b] Gus S Bassani, PharmD,[c] Edmund J Elder Jr, PhD,[d] Alan F Parr, PharmD[e]

[a] Correspondence should be addressed to: Rick Schnatz, PharmD, Manager Compounding and Healthcare Standards, US Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. 301.816.8526; e-mail rxs@usp.org.
[b] International Journal of Pharmaceutical Compounding, Edmond, OK.
[c] PCCA, Houston, TX.
[d] University of Wisconsin, Madison, WI.
[e] GlaxoSmithKline, Research Triangle Park, NC.

ABSTRACT

Tests for strength are designed to determine how much of an active ingredient is in a sample. Stability tests are used to determine an expiration date of a product or a beyond-use date of a preparation. Being able to understand the difference between strength testing versus stability testing is the key to using the proper method to determine strength or stability. To determine strength, a method may or may not be stability indicating. When determining stability, the method must be stability-indicating. When using a stability-indicating method, both strength and stability can be determined. It is important that compounding practitioners understand the difference between strength and stability tests and how they are determined. Quality assurance programs are essential to establishing standards for compounded preparations.

INTRODUCTION

The terms “strength” and “potency” are often used interchangeably, with “potency” being used more by the general public and “strength” being used more by practitioners and within the official compendia. “What is the difference between strength (potency) and stability?” This seems like a rather simple question, and in some respects, it is. However, the cost of a full stability test for a formulation is considerably higher than that of a strength-overtime-test. To answer this question, one must understand the methods used to analyze the strength and stability of a compound.

The most common flaw in determining stability is failure to use an analytical method that has been demonstrated to be a stability-indicating method. The most important aspects of determining strength and stability are the methods used in the process. A stability-indicating method must be used to determine stability. Although stability-indicating methods have the capability of also determining strength, the reverse is not so—not all strength tests are capable of determining stability. The purpose of this communication is to explain the difference between strength and stability, why they are of importance, and how they are determined. The method used to determine the concentration of the active pharmaceutical ingredient (API) is the most critical step in the process and takes into account other variables, such as solubility, polymorphic forms, and others.

STRENGTH

Strength can be described as the concentration of the drug in a product or preparation. Strength tests are known as quantitative tests and are designed to determine how much of an API is in a sample. High-performance liquid chromatography (HPLC) is the typical methodology used in determining strength. HPLC is a preferred method because it is specific and efficient. Although HPLC can be used in stability-indicating methods, not all HPLC procedures are stability indicating—and they must not be assumed to be so.

Other methods used to test strength include titration, which uses the principles of chemistry, and microbial assays, which are sometimes used to test antibiotics. Titration is based upon a known chemical reaction with the desired drug. A microbial assay is performed by using bacteria and the antibiotic of choice and by examining the "zones of inhibition". Ultraviolet (UV)-visible spectrophotometry also can be used to determine strength, but when used alone (without chromatography), UV-visible spectrophotometry can determine strength only for single analytes in solutions. Multiple compounds could interfere with UV absorption, resulting in erroneous results when UV-visible spectrophotometry is used alone. When performing a strength test, the methods used determine whether one will be able to determine stability as well.

The purpose of strength, or potency, testing is to establish or verify the concentration (strength, potency) of the API in the compounded preparation. USP has established that the acceptable range of most compounded preparations is typically ±10%, or within the range of 90.0%–110.0%. The issue is that many "strength" tests do not separate the intact drug from the degradation products, and the degradation products show up under one peak in the chromatogram, thus giving the false information that the drug concentration has not changed, when it actually has. A stability-indicating assay, properly performed, will separate the degradation products/peaks and show the intact drug peak as it decreases in area or height, reflecting a change in the concentration of the intact drug.

STABILITY, INSTABILITY, AND INCOMPATIBILITY

Stability is the extent to which a product retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture. The *United States Pharmacopeia 36/National Formulary 31 (USP 36/NF 31)*, in the table within general information chapter <1191> *Stability Considerations in Dispensing Practice*, provides definitions for five general types of stability:

- **Chemical:** Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
- **Physical:** The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
- **Microbiological:** Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
- **Therapeutic:** The therapeutic effect remains unchanged.
- **Toxicological:** No significant increase in toxicity occurs.

Instability describes chemical reactions that are "...incessant, irreversible, and result in distinctly different chemical entities (degradation products) that can be both therapeutically inactive and possibly exhibit greater toxicity".

Incompatibility is different from instability but must be considered in the overall stability evaluation of a preparation. Incompatibility generally refers to visually evident and "...physicochemical phenomena such as concentration-dependent precipitation and acid–base reactions, with the products of reaction manifested as a change in physical state, including protonation–deprotonation equilibria".

Example

Some compounding practitioners have misconceptions about extending beyond-use dates, based for example on the notion of contracting with analytical laboratories to conduct a strength (potency) test that does not use stability-indicating methods, running assays at time 0, at 30 days, and at 60 days. Take for example a target concentration of the compound intended to be 10 mg/mL. The test result was one that indicated only strength, not stability, because the test did not use a stability-indicating method. In other words, at those predefined time points of day 0, 30 days, and 60 days, the lab analyzed only how much of the compound was present. The lab could not, however, differentiate the compound of interest from degradants or excipients in the preparation that may have been "co-eluting" in the chromatogram. The results might be reported that the compounded preparation was at a concentration of 10 mg/mL at each time point.

The results cannot be interpreted to determine a stability of 60 days, because in the analysis there could have been degradants or excipients that were present but not detected (again assuming that a stability-indicating method was not used in the analysis). To put it into numbers, the actual concentration of the active ingredient could have been 6 mg/mL, with 3 mg/mL of degradants and 1 mg/mL of excipients. The most important point to realize in this scenario is that strength but not stability can be determined, because stability-indicating methods were not used. Had stability-indicating methods been used to determine strength, then the results could have been used to determine a beyond-use date, otherwise referred to as stability. Using the previous example, if the concentration at time 60 days was 10 mg/mL and stability-indicating methods were used, one could be sure of looking at only the active ingredient.

Figure 1 represents a chromatogram of a nonstability-indicating HPLC method that can be used to quantitate the analyte of interest. *Figures 2* and *3* represent a chromatogram of a nonstability-indicating HPLC method containing analyte and degradant sample peaks that are not resolved. All that can be concluded is that there are degradants present in the sample at the time of the analysis. In *Figures 2* and *3*, no conclusions can be made about strength or stability. As for strength, the peaks are not resolved, which does not allow one to properly quantitate the analyte of interest. Stability <u>cannot</u> be determined, because stability-indicating methods were not used.

STABILITY TESTING

Stability testing includes method development, method validation, and a stability study. Method development will separate the active ingredient from its degradants and impurities, as well as any

other excipients in the preparation. This is done by force-degrading the active ingredient and inactive ingredients to ensure that no degradants are interfering with the analysis. In the process of forced degradation, high heat and humidity, UV radiation, acid exposure, base exposure, and peroxide exposure are performed on the compound. It is this step that is different from a simple strength test. *Figure 4* shows an example of a chromatogram of a stability-indicating HPLC method containing analyte and degradant peaks that are fully resolved from one another. When looking at this chromatogram, it is important to notice that the active ingredient, or analyte, is completely separated from its degradants and excipients. Stability can be determined from this type of study, because stability-indicating methods were used in the analysis.

The method validation confirms that the method meets certain criteria. The typical analytical characteristics used in method validation include accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and ruggedness, as outlined in general information chapter <1225> *Validation of Compendial Procedures*.

The stability study includes storing the preparation in stability chambers, testing the preparation at predetermined time points, and then determining its stability. These time points can be specified by the compounder or may be limited based on the particular compound. Once again, it is crucial to understand that the methods used to determine stability must be stability-indicating. Equally important to understand is that a strength test that uses stability-indicating methods can determine strength as well as stability.

HPLC DIODE–ARRAY DETECTORS

The PDA (photodiode array) detector is a device that scans from about 200 nm up to 400 nm in the UV range (and can reach 700 nm in the visible range in some instruments). The full array scans the eluent coming from the HPLC every second or so. The software starts at the beginning of a peak and makes scans (basically by “slicing” it into pieces) and then completes the scan instantly. The scans are compared (overlaid), and any change is identified. By using an algorithm, the software calculates the “peak purity” by comparing the middle peak scans with those of the leading and trailing tails. If the scans overlay perfectly, then the peak purity will be 100%. If the scans do not overlay perfectly, then the result is a calculated percentage. The issue with this approach is that a UV scan is not necessarily specific, and small changes in a drug molecule can occur that may not be detected by the scan but may alter the drug strength, although based on the assay, the strength may not have changed. The molecule contains “chromophores” that absorb the UV light at different wavelengths and efficiencies. If a molecule degrades but the change is not in a strong chromophore, then the change will not appear in the scan, and the strength will not be determined accurately.

Peak purity evaluation should be performed during validation as part of the specificity test of the forced-degradation samples. The peak purity test helps to ensure that the method can separate degradation products during a stability study, and “strength” of the API can be assessed versus the reference standard. One can apply peak purity analysis to compounded preparations for routine strength testing and maybe time point testing, as part of the beyond-use date of the compounded preparations. But the method itself still needs to be validated to become a standard monograph method. The PDA method for peak purity determination can be used to “supplement or support” a stability-indicating analytical method but should not be used in place of it.

SUMMARY

In summary, the practitioner who extemporaneously compounds must ensure the strength, quality, identity, and purity of compounded preparations. An outsourced analytical laboratory can assist by providing quality control and quality assurance. Determination of strength or concentration is invaluable in maintaining good preparations that are accurate and precise. A stability-indicating method must be used to determine the beyond-use date of a compounded preparation.

FIGURES[1]

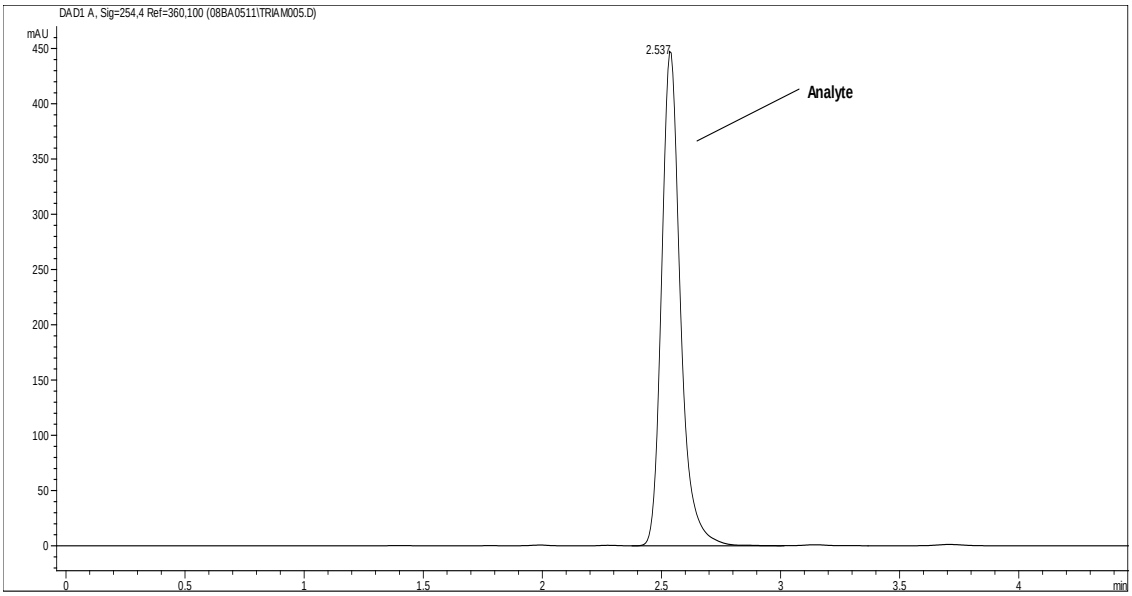


Figure 1. An example chromatogram of a nonstability-indicating HPLC method that evaluates the potency of a single analyte.

[1] Figures reproduced with permission from Kupiec TC, Skinner R, Lanier L. Stability Versus Potency Testing: The Madness is in the Method. Int J Pharm Compd. 2008 Jan/Feb; 12(1): 50-53.

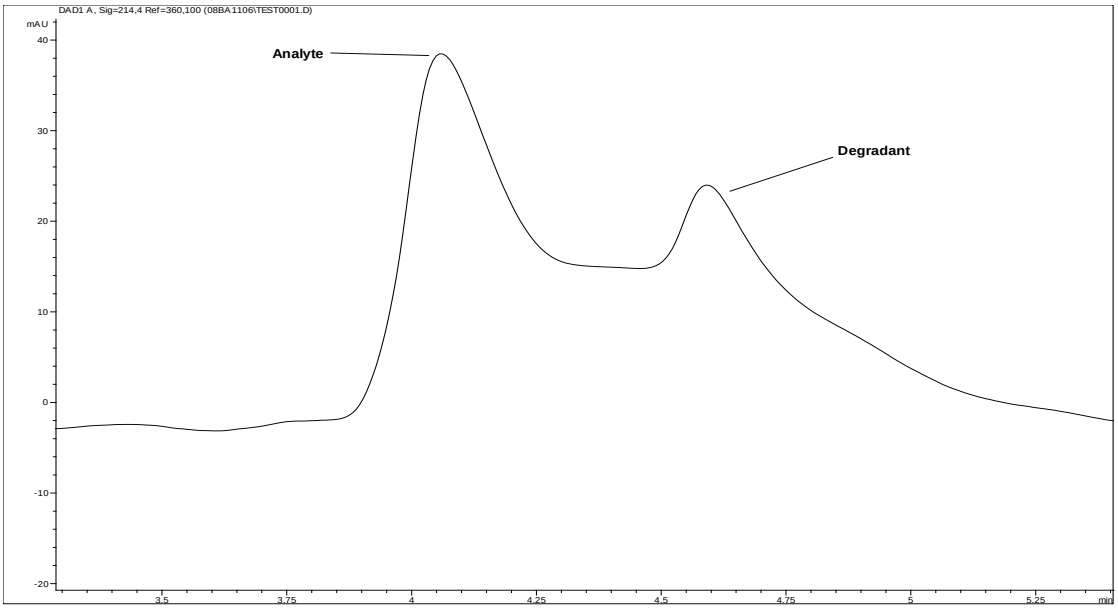


Figure 2. An example chromatogram of a nonstability-indicating HPLC method that evaluates the analyte and degradant sample peaks.

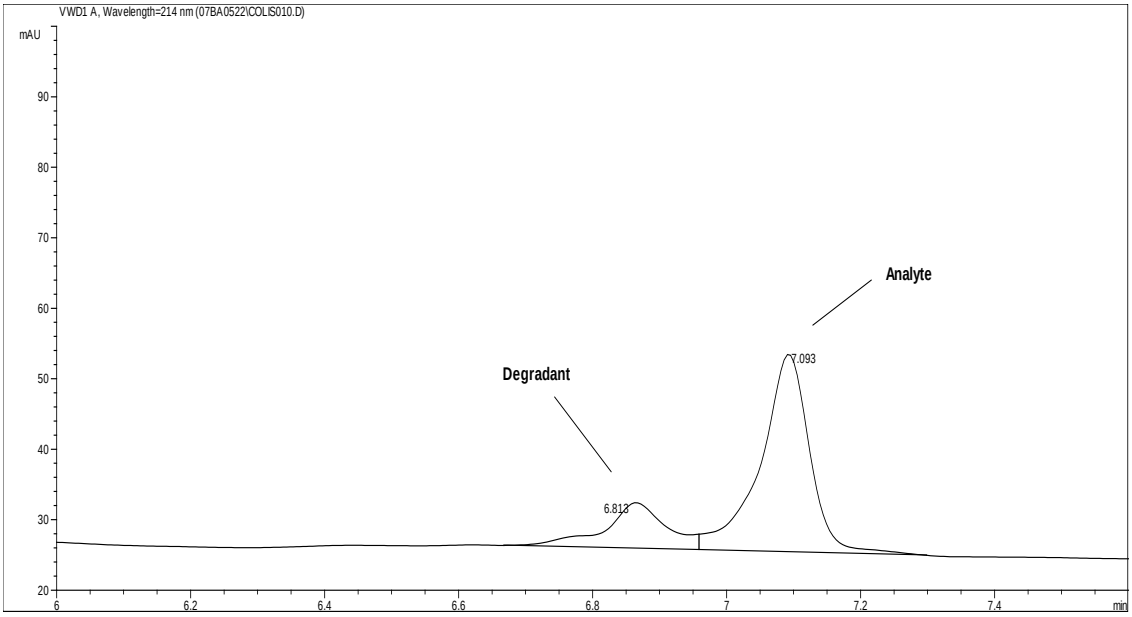


Figure 3. An example chromatogram of a nonstability-indicating HPLC method that evaluates the analyte and degradant peaks that are not fully resolved from one another.

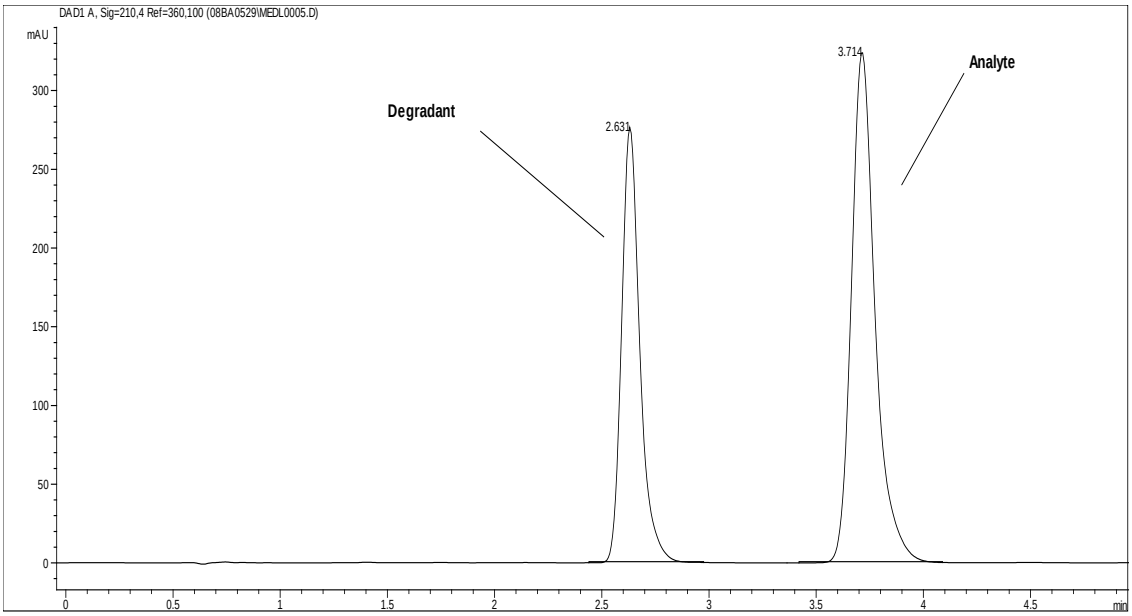


Figure 4. An example chromatogram of a stability-indicating HPLC method that evaluates the analyte and degradant peaks that are fully resolved from one another.

[i] Published January 13, 2014. Revised May 11, 2015 [added footnote to Figures].

Stability Studies

DYNALABS™
Quality Assured

Focusing on patient safety, affordable healthcare and business success.

Potency Over Time?

Studies that lack validation work are not stability indicating and do not provide an adequate data set for determination of Beyond Use Date.

Be leery of references to these ‘other’ studies; such as, potency over time, non-GMP studies, information only, and non-FDA

What is a Stability Study?

“Stability is the extent to which a product retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture.”

--STRENGTH AND STABILITY TESTING FOR COMPOUNDED PREPARATIONS by USP Compounding Expert Committee

What is Required?

USP <1191> Stability Considerations in Dispensing Practice adds more definition to the desired attributes sought for confirmation

TESTING

- **Chemical-** Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
- **Physical-** The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
- **Microbiological-** Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.

Pharmaceutical Expertise

- **Therapeutic-** The therapeutic effect remains unchanged.
- **Toxicological-** No significant increase in toxicity occurs.

Translation to Testing

USP <797> States Requirements for every compounded sterile product

Microbial contamination (non-sterility)

USP <71> Sterility

Excessive bacterial endotoxins

USP <85> Endotoxin

Variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles

Potency Testing

Unintended chemical and physical contaminants

Visual Inspection

pH

Particulate Matter USP <788>, <789>

How does this become a stability study?

USP <71> Sterility Tests requires Method Suitability

"This method suitability is performed (a) when the test for sterility has to be carried out on a new product; and (b) whenever there is a change in the experimental conditions of the test."

--From USP <71> Sterility Tests

USP <85> Bacterial Endotoxin requires Endotoxin Validation (Test for Interfering Factors)

The test is considered valid when all replicates of Solutions A and D show no reaction and the result of Solution C confirms the labeled sensitivity, 'as defined in the Test for Interfering Factors'.

--From USP <85> Bacterial Endotoxin Testing

Potency Testing requires a Stability Indicating Method

"A stability-indicating method will be able to quantitate the active ingredient and its degradation products or related impurities in the preparation by separating the inactive ingredient from its degradation products and impurities, and to show a change in the concentration of the active ingredient with increasing storage time. A stability-indicating method is used to determine stability of a drug and used to establish the BUD."

-From USP FAQs for compounding: Is there a difference between testing stability with a strength (potency) or a stability-indicating method?

Stability Indicating Method Creation per USP

Development Work ALWAYS starts with the active outside of the formulation

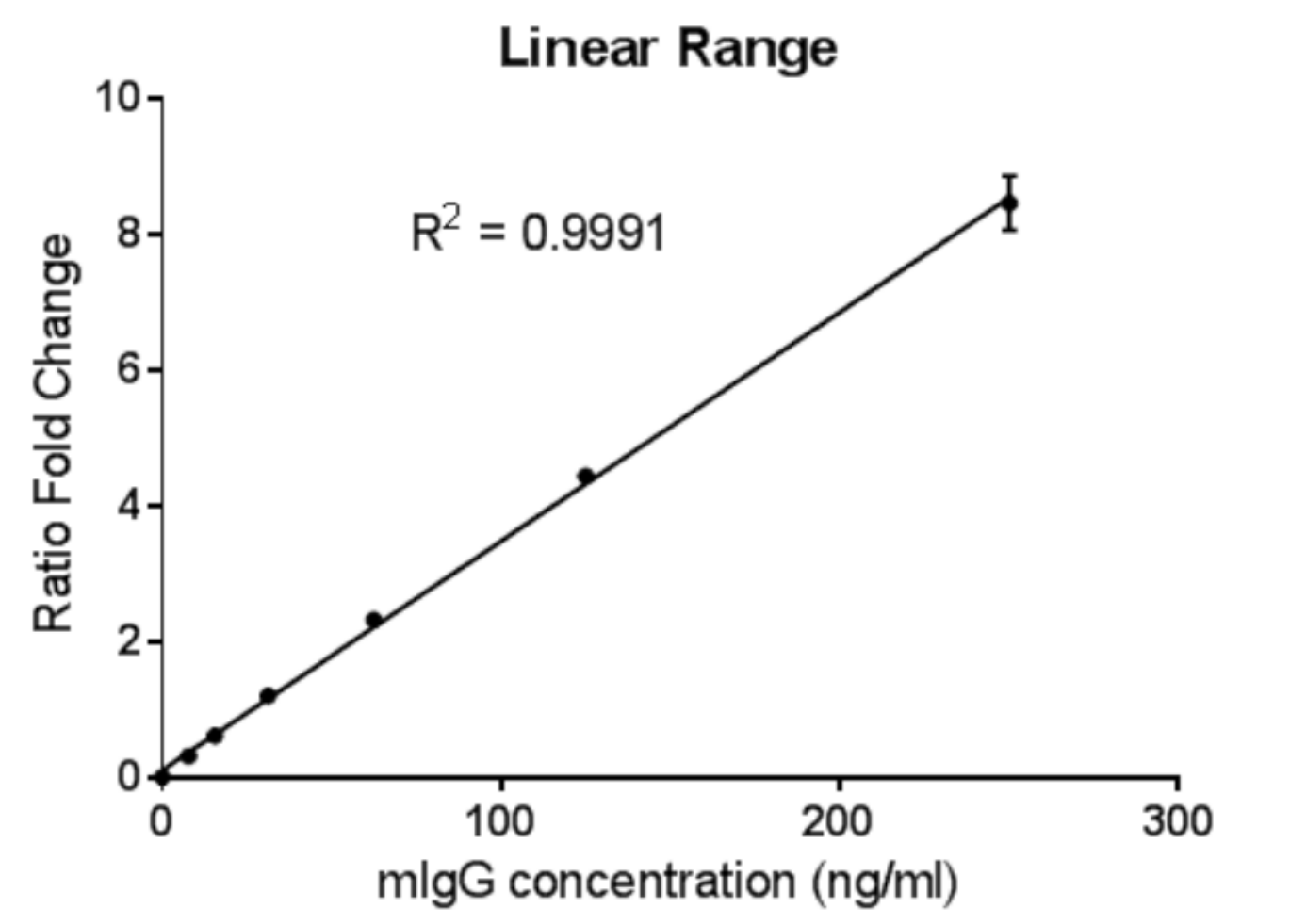
Linearity	Robustness
Accuracy	Range
Precision	Active Forced Degradation

Only one aspect of a validation requires the use of sample…

SPECIFICITY- IS YOUR PRODUCT COMPATIBLE WITH THE POTENCY METHOD?

The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as **impurities**, **degradation products**, and **matrix components**.

Linearity and Range

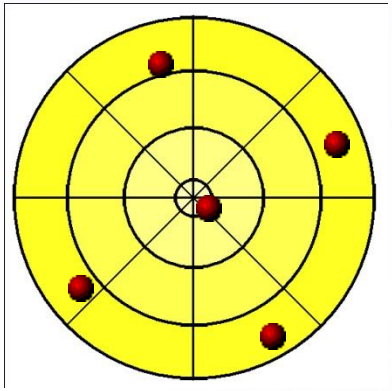


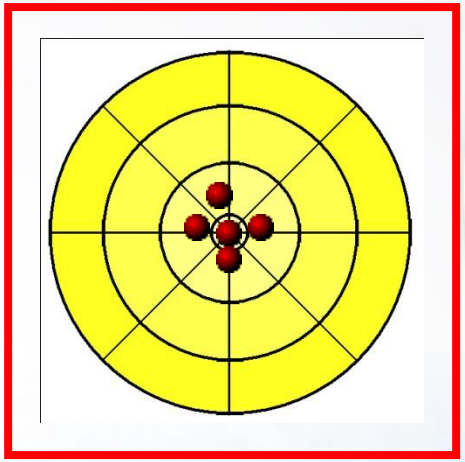
Accuracy and Precision

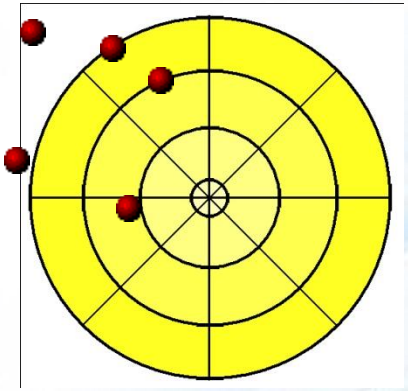
High Accuracy

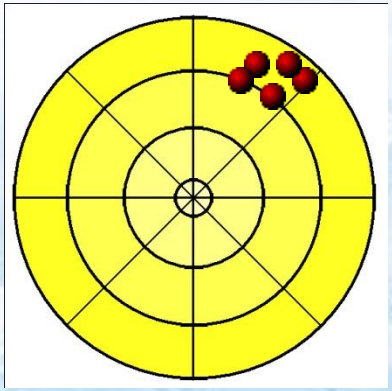
Accuracy Represents Closeness to Target

Low Accuracy







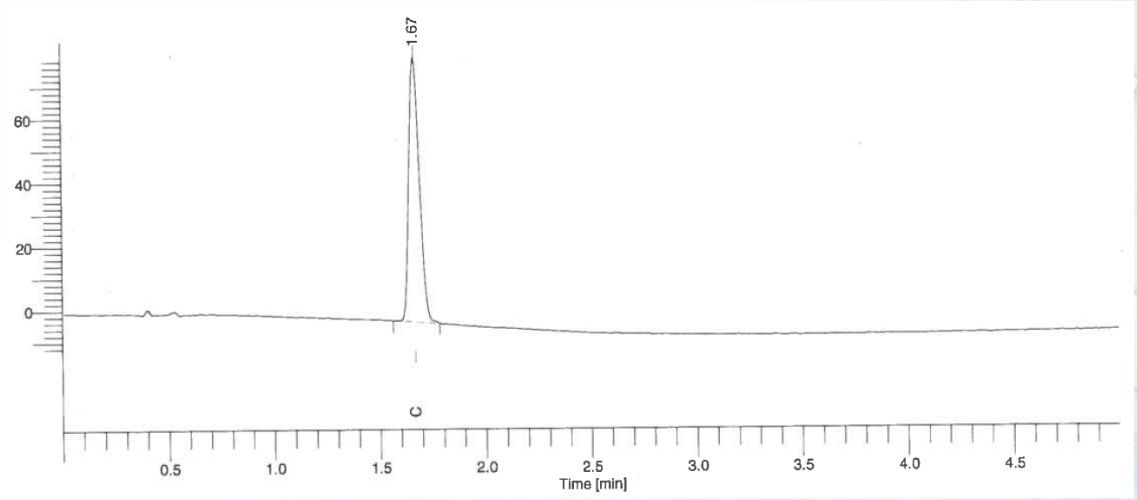


Low Precision High Precision

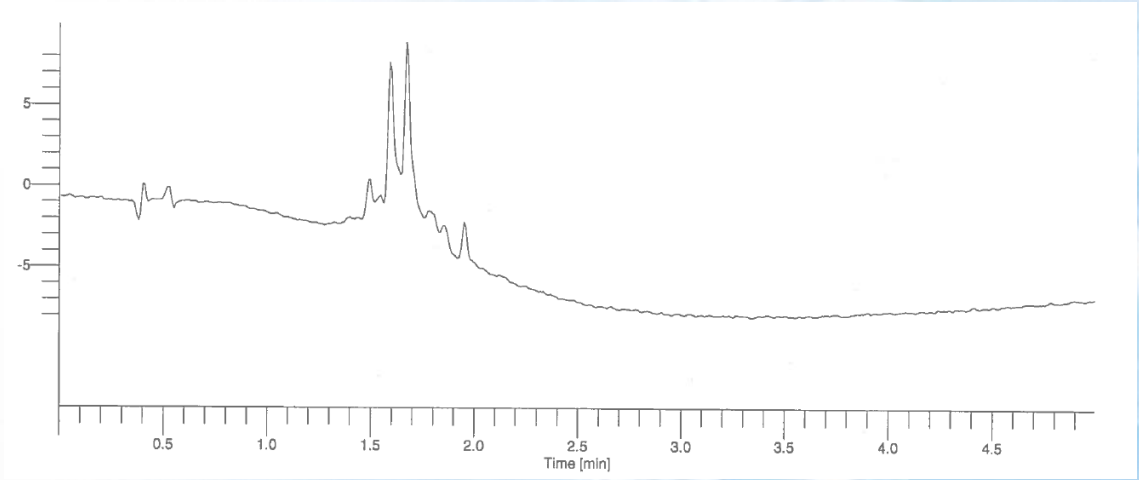
Precision Represents Repeatability

Forced Degradation Studies (Cyanocobalamin)

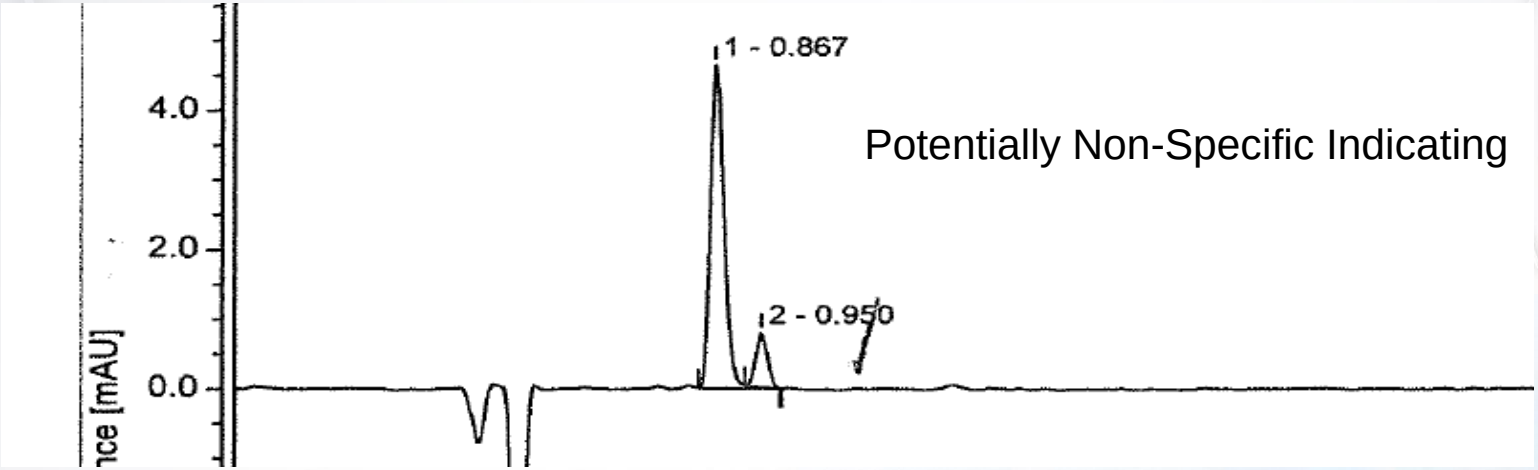
- Standard
- Heat
- Light
- Acid
- Oxidation



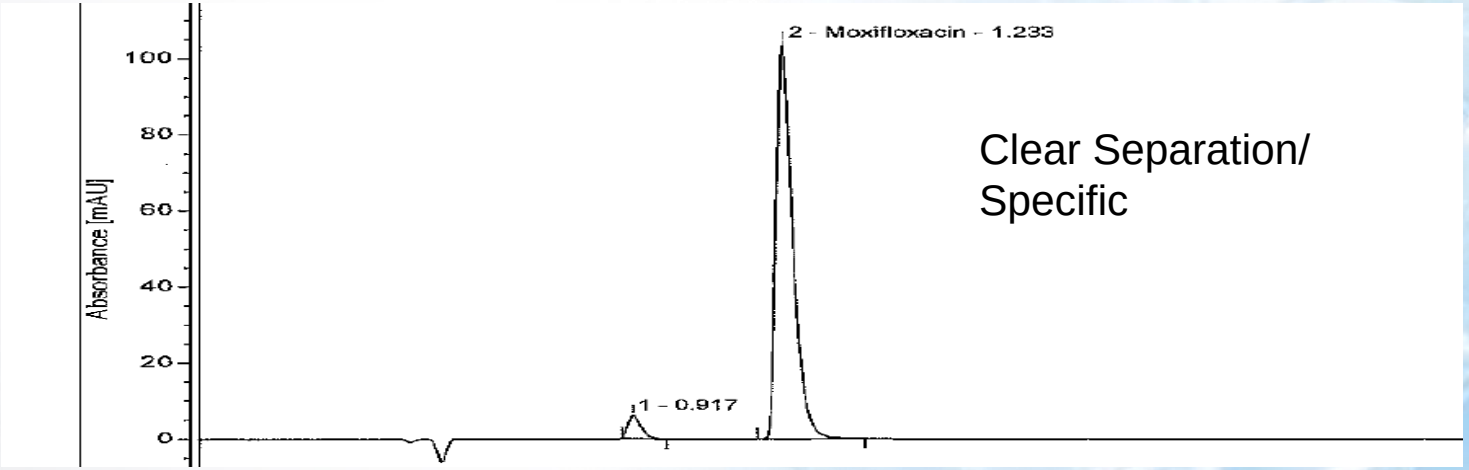
- Base



Validation Extension/ Specificity



Potentially Non-Specific Indicating



Clear Separation/
Specific

Summary of Differences between POT vs SIM Study

Method Attribute	Non-SIM (POT*)	SIM**
Linearity	✓	✓
Accuracy	✓	✓
Precision	✓	✓
Range	✓	✓
Robustness	✓	✓
Ruggedness	✓	✓
Intermediate Precision	✓	✓
Specificity ***		✓

* Potency Over Time
** Stability Indicating Method
*** Includes forced degradation studies

Specificity aka Validation Extension

DYNALABS has outlined a process to accomplish stability indicating methodology without reinventing the wheel and performing redundant work.

- DYNALABS performs the **Degradation** work on the active outside of the formulation to ensure the **Impurities** from **Forced Degradation** studies do not interfere with the active peak. This only needs to be done one time.

Validation Extension Process is performed on EACH product.

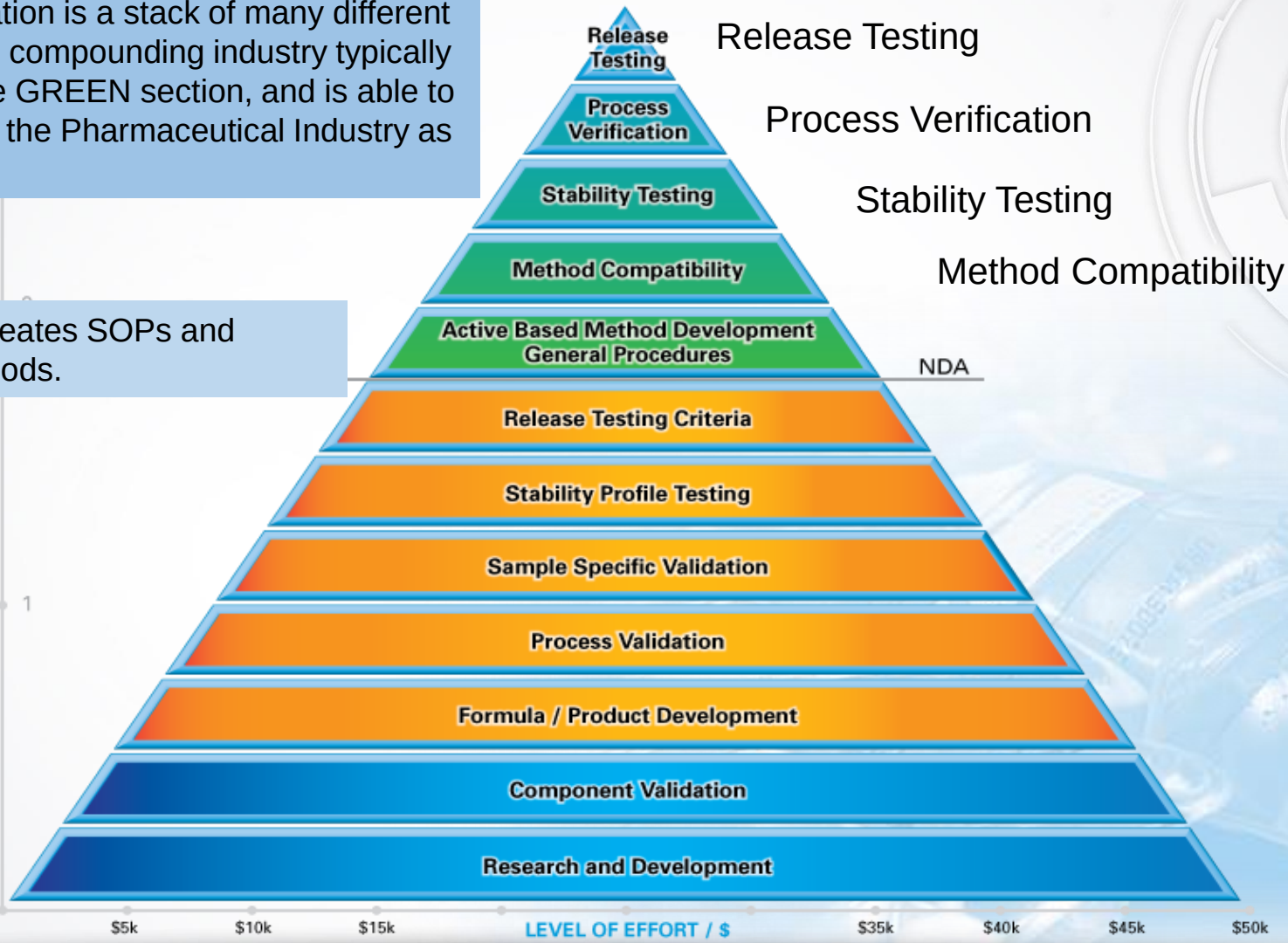
- Ensures that **Matrix Components** (e.g. excipients, leachates, and other actives) do NOT interfere with the active peak.
- Ensures that the heated placebo does NOT create **Degradants** or **Extractables** that interfere with the active peak. (UV exposure can be included, if applicable)

The specific formulation is tested for method precision (repeatability).

Stability Studies are Built on Process Validation

Process Validation is a stack of many different functions. The compounding industry typically functions in the GREEN section, and is able to do so by using the Pharmaceutical Industry as base.

DYNALABS creates SOPs and Validates Methods.



Does cGMP apply to me?

"It should be recognized that the truly valid evidence of stability for predicting beyond-use dating can be obtained only through product-specific experimental studies." – USP <797>

The information presented is based in sound scientific principal which aligns with cGMP ideology.

The requirements do not exist to create a need of excess testing, only to provide Patient Safety.

Q & A

2327 Chouteau Avenue | St. Louis, MO 63103
314.241.3962
www.dynalabs.us

For any questions, please contact:
Christine R. Versichele
916.987.2999
cversichele@dynalabs.us

Attachment 7

Board of Pharmacy Enforcement Statistics
Fiscal Year 2017/2018

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 17/18
Complaints/Investigations					
Received	676	630			1306
Closed	676	783			1459
4301 letters	6	5			11
Pending (at the end of quarter)	2283	2028			2028
Cases Assigned & Pending (by Team) at end of quarter*					
Compliance / Routine Team	992	952			952
Drug Diversion/Fraud	370	307			307
RX Abuse	185	132			132
Compounding	130	86			86
Outsourcing	43	29			29
Probation/PRP	63	49			49
Mediation/Enforcement **	190	143			143
Criminal Conviction	320	330			330
Application Investigations					
Received	228	96			324
Closed					
Approved	92	125			217
Denied	17	20			37
Total ***	126	177			303
Pending (at the end of quarter)	192	153			153
Letter of Admonishment (LOA) / Citation & Fine					
LOAs Issued	30	73			103
Citations Issued	425	610			1035
Total Fines Collected ****	$535,944	$501,038			$1,036,982

* This figure includes reports submitted to the supervisor and cases with SI awaiting assignment.

** This figure include reports submitted to the citation and fine unit, AG referral, as well as cases assigned to enf. Staff

*** This figure includes withdrawn applications.

****Fines collected (through 12/31/2017 and reports in previous fiscal year.)

Board of Pharmacy Enforcement Statistics
Fiscal Year 2017/2018

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 17/18
Administrative Cases (by effective date of decision)					
Referred to AG's Office*	83	102			185
Accusations Filed	78	43			121
Statement of Issues Filed	10	7			17
Petitions to Revoke Filed	2	0			2
Pending					
Pre-accusation	204	200			200
Post Accusation	245	237			237
Total*	471	516			497
Closed					
Revocation					
Pharmacist	7	2			9
Intern Pharmacist	1	0			1
Pharmacy Technician	22	17			39
Designated Representative	0	0			0
Wholesaler	0	1			1
Sterile Compounding	1	0			1
Pharmacy	2	1			3
Revocation,stayed; suspension/probation					
Pharmacist	2	3			5
Intern Pharmacist	0	0			0
Pharmacy Technician	0	0			0
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	1	0			1
Revocation,stayed; probation					
Pharmacist	9	13			22
Intern Pharmacist	1	0			1
Pharmacy Technician	0	1			1
Designated Representative	1	2			3
Wholesaler	0	1			1
Sterile Compounding	3	0			3
Pharmacy	9	12			21
Surrender/Voluntary Surrender					
Pharmacist	2	3			5
Intern Pharmacist	0	0			0
Pharmacy Technician	4	3			7
Designated Representative	0	2			2
Wholesaler	1	0			1
Sterile Compounding	2	2			4
Pharmacy	6	3			9

Board of Pharmacy Enforcement Statistics
Fiscal Year 2017/2018

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 17/18
Public Reproval/Reprimand					
Pharmacist	5	3			8
Intern Pharmacist	0	0			0
Pharmacy Technician	0	2			2
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	1	0			1
Pharmacy	3	2			5
Licenses Granted					
Pharmacist	1	1			2
Intern Pharmacist	1	3			4
Pharmacy Technician	1	2			3
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	0	0			0
Licenses Denied					
Pharmacist	0	0			0
Intern Pharmacist	0	0			0
Pharmacy Technician	0	4			4
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	1	0			1
Pharmacy	0	0			0
Cost Recovery Requested**	$357,388	$439,458			$796,845.59
Cost Recovery Collected**	$238,133	$19,505			$257,638.07

* This figure includes Citation Appeals

** This figure includes administrative penalties

Immediate Public Protection Sanctions					
Interim Suspension Order	0	3			3
Automatic Suspension / Based on Conviction	2	0			2
Penal Code 23 Restriction	3	3			6
Cease & Desist - Sterile Compounding	1	0	0		1

Board of Pharmacy Enforcement Statistics
Fiscal Year 2017/2018

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 17/18
Probation Statistics					
Licenses on Probation					
Pharmacist	194	211			211
Intern Pharmacist	5	8			8
Pharmacy Technician	32	29			29
Designated Representative	1	3			3
Pharmacy	68	75			75
Sterile Compounding	15	16			16
Wholesaler	3	4			4
Probation Office Conferences	27	36			63
Probation Site Inspections	145	165			310
Successful Completion	6	7			13
Probationers Referred to AG for non-compliance	1	5			6

As part of probation monitoring, the board requires licensees to appear before the supervising inspector at probation office conferences. These conferences are used as 1) an orientation to probation and the specific requirements of probation at the onset, 2) to address areas of non-compliance when other efforts such as letters have failed, and 3) when a licensee is scheduled to end probation.

As of December 31, 2017.

California State Board of Pharmacy
Citation and Fine Statistics
October 1, 2017 - December 31, 2017

610 Citations were Issued this Quarter

Citation Breakdown by license type

Total issued	RPH with fine	RPH no fine	PHY with Fine	PHY no Fine	PIC with Fine**	PIC no Fine**	TCH with Fine	TCH no Fine
610	214	25	175	90	102	46	42	0

Citation Breakdown by Miscellaneous license type

Wholesalers	Exemptee's	Clinics	Drug Room	Exempt Hosp.	Hosp. Pharmacy	Misc.*	Unlicensed Premises	Unlicensed person
8	7	0	0	3	9	2	9	1

*Intern Pharmacist, Licensed Correctional Facilities, Exempt Pharmacies, Non-Resident Pharmacies, and Vet Retailers

**These numbers are also represented in the RPH columns, but reflect how many RPHs were cited as PICs

Top Ten Violations by license type
10/01/2017- 12/31/2017

Pharmacists	%	Pharmacies	%	Pharmacists In Charge	%
1716 - Variation from prescription	34%	1709(a) - Names of Owners and Pharmacist in Charge; Each permit to operate a pharmacy shall show the name and address of the pharmacy, the form of ownership, the pharmacist in charge and the names of	36%	1716 - Variation from prescription	28%
11164(a)/1761(a) - Prescriptions for schedule II, III, IV, and controlled substance: form and content; record of practitioner dispensing schedule II controlled substance/No pharmacist shall compound o	13%	1716 - Variation from prescription	23%	1714(d) - Operational Standards and Security; Pharmacist responsible for pharmacy security	24%
1714(d) - Operational Standards and Security; Pharmacist responsible for pharmacy security	11%	1714(b) - Operational Standards and Security; pharmacy responsible for pharmacy security	10%	1714(c) - Operational Standards and Security; Pharmacy, fixtures and equipment shall be maintained in a sanitary and orderly condition	10%
4301(g) - Unprofessional Conduct - Knowingly making or signing any certificate or other document that falsely represents the existence or nonexistence of a state of facts	9%	4113(d) - Every pharmacy shall notify the board in writing within 30 days of the date of a change in pharmacist-in-charge	7%	1714(b) - Operational Standards and Security; pharmacy responsible for pharmacy security	7%
4231(d)/1732.5 - Failure to provide documentation substantiating completion of continuing education/Renewal Requirements for Pharmacist	8%	11164(a)/1761(a) - Prescriptions for schedule II, III, IV, and controlled substance: form and content; record of practitioner dispensing schedule II controlled substance/No pharmacist shall compound o	6%	1764/56.10(a) - Unauthorized disclosure of prescription and medical information	6%
1764/56.10(a) - Unauthorized disclosure of prescription and medical information	7%	1764/56.10(a) - Unauthorized disclosure of prescription and medical information	5%	11164(a)/1761(a) - Prescriptions for schedule II, III, IV, and controlled substance: form and content; record of practitioner dispensing schedule II controlled substance/No pharmacist shall compound o	6%
1707.2(b)(1)(A) - In addition to the obligation to consult…a pharmacist shall provide oral consultation to his or her patients…whenever the prescription drug has not previously been dispensed to a pat	6%	4305(b) - Disciplinary Grounds: Failure of Pharmacy or Pharmacist to Notify Board of Termination of Pharmacist-in-Charge; Continuing to Operate Without Pharmacist; Operation of a pharmacy for more tha	5%	4081(a) - Records of Dangerous Drugs and Devices Kept Open for Inspection; Maintenance of Records, Current Inventory	5%
1714(c) - Operational Standards and Security; Pharmacy, fixtures and equipment shall be maintained in a sanitary and orderly condition	5%	1714(c) - Operational Standards and Security; Pharmacy, fixtures and equipment shall be maintained in a sanitary and orderly condition	4%	4081(a)/1718 - Records of Dangerous Drugs and Devices Kept Open for Inspection; Maintenance of Records, Current Inventory/Current Inventory Defined	5%
1714(b) - Operational Standards and Security; pharmacy responsible for pharmacy security	4%	1707.2(b)(1)(A) - In addition to the obligation to consult…a pharmacist shall provide oral consultation to his or her patients…whenever the prescription drug has not previously been dispensed to a pat	2%	1761(a)&(b) - No pharmacist shall compound or dispense any prescription, which contains any significant error or omission…/A pharmacist shall not compound or dispense a prescription for a controlled s	4%
11164(a) - Prescriptions for schedule II, III, IV, and controlled substance: form and content; record of practitioner dispensing schedule II controlled substance	3%	1761(a)&(b) - No pharmacist shall compound or dispense any prescription, which contains any significant error or omission…/A pharmacist shall not compound or dispense a prescription for a controlled s	2%	11165(d) - For each prescription for a Schedule II or Schedule III controlled substance, the dispensing pharmacy shall report to the Department of Justice...	4%

SB 1441 – Program Statistics

Licensees with substance abuse problems who are either on board probation and/or participating in the Pharmacist Recovery Program (PRP)

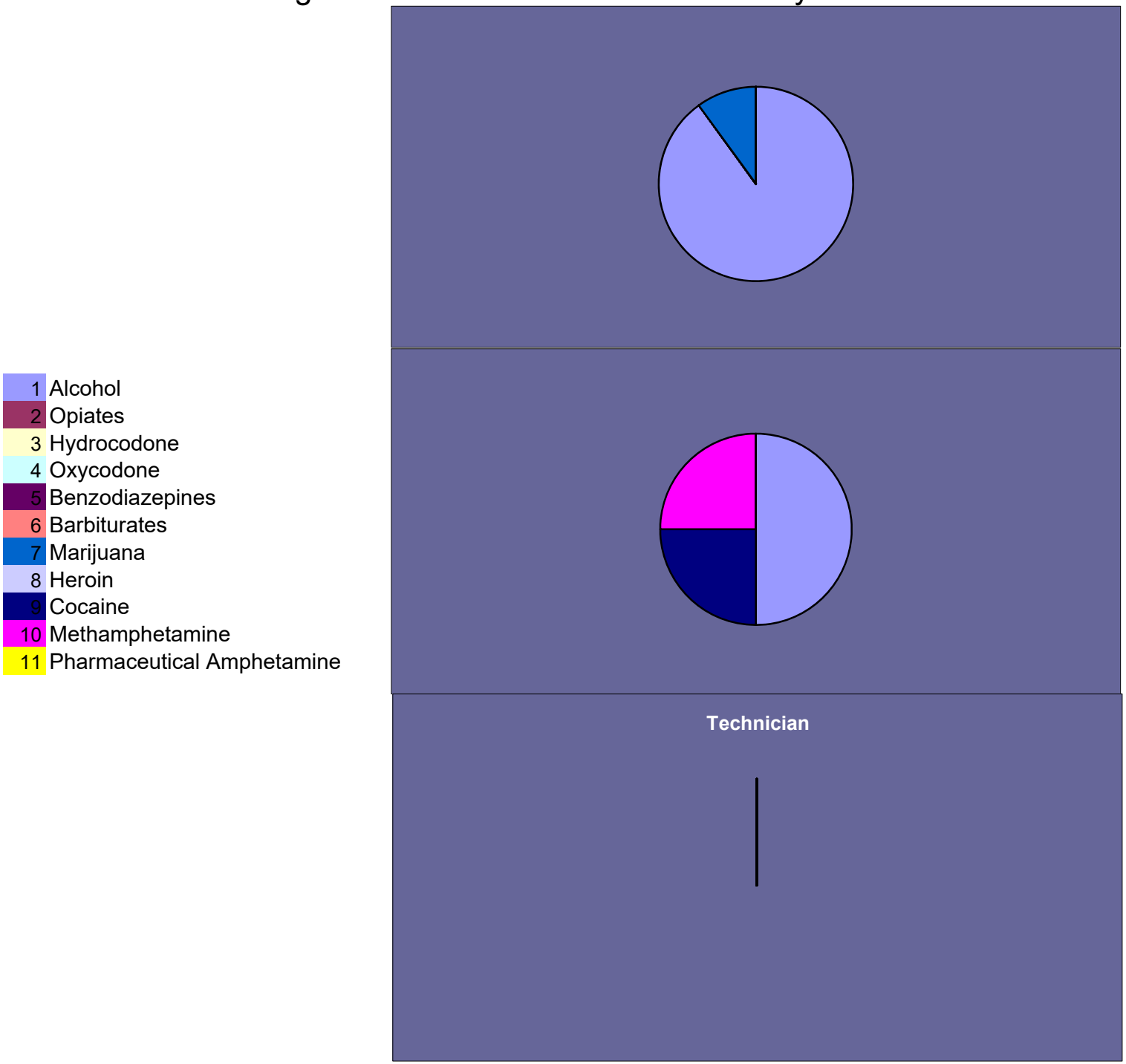
Board of Pharmacy	July -Sep	Oct – Dec	Jan-Mar	Apr-Jun	Total 17/18
PRP Intakes					
PRP Self-Referrals		1			1
PRP Board Referrals	5	5			10
PRP Under Investigation	2				2
PRP In Lieu Of	1				1
Total Number of PRP Intakes	8	6			14
New Probationers					
Pharmacists	5	9			14
Interns					
Technicians					
Total New Probationers	5	9			14
PRP Participants and Contracts					
Total PRP Participants	49	47			N/A
Contracts Reviewed	40	49			89
Probationers and Inspections					
Total Probationers	77	81			N/A
Inspections Completed	145	165			310
PRP Referrals to Treatment					
Referrals to Treatment	1	6			7
Drug Tests					
Drug Test Ordered	858	846			1704
Drug Tests Conducted	844	843			1687
Relapse					
Relapsed	1	9			10
Major Violation Actions					
Cease Practice/Suspension	9	9			18
Termination - PRP	2	4			6
Referral for Discipline	1	2			3
Exit from PRP or Probation					
Successful Completion	5	14			19
Termination - Probation	1	1			2
Voluntary Surrender	4	2			6
Surrender as a result of PTR					
Public Risk	2	2			4
Non-compliance	15	20			35
Other	3	2			5
Patients Harmed					
Number of Patients Harmed	None	None	None	None	None

SB 1441 – Program Statistics

Licensees with substance abuse problems who are either on board probation and/or participating in the Pharmacist Recovery Program (PRP)

Board of Pharmacy	July -Sep	Oct – Dec	Jan-Mar	Apr-Jun	Total 17/18
Alcohol	5	4			
Ambien					
Opiates					
Hydrocodone					
Oxycodone					
Morphine					
Benzodiazepines		1			
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					
Alcohol	1	1			
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine	1				
Methamphetamine	1				
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					
Alcohol					
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					

Drug Of Choice - Data entered from July 2017 to June 2018



Printed on 1/22/2018