



COMMUNICATION AND PUBLIC EDUCATION COMMITTEE

Ricardo Sanchez, Public Member, Chair
Debbie Veale, Licensee Member, Vice Chair
Ryan Brooks, Public Member
Amjad Khan, Public Member
Victor Law, Licensee Member

- 1. Call to Order and Establishment of Quorum**
- 2. Public Comment for Items Not on the Agenda; Matters for Future Meetings**

The committee may not discuss or take action on any matter raised during the public comment section that is not included on this agenda, except to decide to place the matter on the agenda of a future meeting. Government Code Sections 11125 & 11125.7(a).

- 3. Presentation by Ramón Castellblanch, Ph.D., Regarding Prescription Drug Overdose Prevention and Corresponding Responsibility**

Dr. Ramon Castellblanch, a former board member, is expected to address the board on educational needs regarding prescription overdose prevention and corresponding responsibility.

- 4. Discussion and Consideration of a Proposal for a Public Service Billboard Message and Related Communications Materials on Drug Abuse**

Background

At the September 2016 committee meeting, the committee recommended a concept for a billboard message about drug abuse prevention developed by Mr. Brooks' firm, Outfront Media. The full board approved the billboard message at the October 2016 board meeting.

At the September 2017 committee meeting, members discussed and considered choosing a more factual and positive message than the initial concept. The committee voted to recommend that the board move forward with a new billboard message with a theme based on "Be Aware. Don't Share. Lock Your Meds." The committee also authorized the chairperson and the executive officer to work with Outfront on the project.

At the November 2017 board meeting, the board reviewed and considered several samples of possible wording for a billboard message. After a lengthy discussion and a straw poll, the board voted to move forward with a billboard based on one of the following themes:

- "Use, Don't Abuse. Safely Dispose of Unused Medications. Stop Prescription Drug Abuse."
- "Your Meds, No One Else's."

- “Take Your Prescription, Toss the Rest, Talk to Your Kids About Prescription Drug Abuse.”

The board also directed the committee chairperson and executive officer to select the final billboard message and work on the project with Outfront.

Update

The committee chairperson and executive officer met in December 2017 and chose “Use, Don’t Abuse” for the billboard message. The board’s graphic artist, Victor Perez, and a DCA graphic artist were asked to create design concepts. The committee chairperson and executive officer reviewed nine submitted design concepts and chose one for the billboard. Staff is preparing to submit the design to Outfront, which has agreed to donate five billboards: two in Northern California, two in Southern California and one in the Central Valley.

In addition, staff has begun revamping the Prescription Drug Abuse Prevention page on the board’s website with updated resources and a fresh design. Staff plans to have the webpage up and running before the billboards are erected. Staff will keep the committee updated on the project and timeline.

A copy of the billboard design and a rough draft of the new Prescription Drug Abuse Prevention webpage design are in **Attachment 1**.

5. Discussion and Consideration of Possible Options for Consumer and Pharmacist Education Regarding Safe Medication Transitions for Patients upon Discharge from Health Care Facilities and Any Necessary Statutory or Regulatory Changes

Background

At the July 2017 board meeting, the board directed the committee to discuss developing materials to educate consumers and pharmacists about the importance of having a patient medication history on hand when admitted to a hospital. At the September 2017 committee meeting, members discussed possibly developing a phone app for storing medication history. However, it was noted that such apps already exist.

At the November 2017 board meeting, members asked staff to develop public outreach materials for the website. Staff is also planning an article about safe medication transitions in an upcoming issue of The Script.

At This Meeting

The committee will have an opportunity to continue discussing this topic. **Attachment 2** includes information about medication list errors provided by Rita Shane, Pharm.D.; and a January 2018 [article](#) from U.S. News and World Report, “9 Strategies for Reducing Emergency Room Medication Errors.”

6. Discussion and Consideration of Educational Materials Regarding Drug Take-Back Collection Receptacles and Providing Public Access to Such Information

Background

At the July 2017 board meeting, the board directed the committee to develop consumer information on accessing drug take-back programs. At the September 2017 committee meeting, staff reported that online forms were being developed to allow pharmacies to register collection receptacles with the board.

Update

Staff has posted forms to report [installing or discontinuing a collection receptacle](#) and to report [tampering, damage or theft of a receptacle](#) on the board's website. An announcement about the forms was posted on the website and sent out to pharmacies in a subscriber alert. Copies of the forms are in **Attachment 3**.

Staff will use the forms to develop an online locator that consumers can use to find drug take-back programs. Staff also plans to organize easy-to-find consumer information about take-back programs on the board's website.

7. Discussion and Consideration of Creating Webinar Course to Satisfy Education Requirement for Pharmacists to Furnish Naloxone

Background

SB 493 authorized the board to address the problem of restricted public access to naloxone, which reverses opioid overdose. The board responded in 2015 with an emergency regulation establishing a protocol for pharmacists to furnish naloxone without a prescription. The regulation was made permanent in 2016.

However, there are reports that many California pharmacies still do not carry or furnish naloxone. At the March 2017 committee meeting, Dr. Rebecca Trotzky of LA County-USC Medical Center reported a survey that found only 2 percent of independent pharmacies and 30 percent of chain pharmacies in the area carried naloxone. In December 2017, a California Healthline news article reported that pharmacists gave several reasons for not furnishing naloxone, including lack of public awareness, heavy workloads, concerns about reimbursement, and reluctance to treat drug abusers.

The board has taken steps to assist pharmacists in taking advantage of the naloxone protocol in California Code of Regulations (CCR) section 1746.3. Last year, the board and the U.S. Drug Enforcement Administration (DEA) cohosted training sessions for pharmacists throughout the state that included one hour of CE credit to meet the naloxone education requirement in CCR section 1746.3. The board and DEA are planning additional training sessions in 2018.

At This Meeting

Staff requests the committee to discuss and consider approval of a proposed webinar course to satisfy the one-hour CE requirement for furnishing naloxone. The course was

developed by Talia Puzantian, Pharm.D., of Keck Graduate Institute School of Pharmacy and James J. Gasper, Pharm.D., California Department of Health Care Services.

Copies of the webinar course guide, [CCR section 1746.3](#) and the California Healthline [news article](#) are in **Attachment 4**.

8. Discussion and Consideration of UC Berkeley Study of the Availability of Contraception Prescribed by Pharmacists in California

A UC Berkeley study published in December 2017 in the *Journal of the American Medical Association* reported that only 11 percent of pharmacies in California are dispensing hormonal contraception to women without a prescription, as authorized by SB 493.

The study was based on a survey of California pharmacies between February 2017 and April 2017 – one year after the board adopted a protocol for pharmacists to furnish self-administered hormonal contraception in CCR section 1746.1. The study identified several barriers to implementation of the contraception portion of SB 493, including pharmacists' concerns about training, liability, staffing and lack of reimbursement.

Copies of the UC Berkeley study and [CCR section 1746.1](#) are in **Attachment 5**.

9. Discussion and Consideration of FDA Proposal to Increase Consumer Protection from High-Risk Homeopathic Drugs

In December 2017, the Food and Drug Administration (FDA) announced plans to change the way it regulates homeopathic drugs to a new approach based on potential risk to patients.

The new FDA policy would focus on enforcement and regulation of homeopathic drugs that pose the greatest risk to patients. These include:

- Products with reported safety concerns.
- Products that contain or claim to contain ingredients associated with potentially significant safety concerns.
- Products intended for serious or life-threatening conditions, such as cancer or heart disease.
- Products for vulnerable groups, such as children.
- Products for routes of administration other than oral and topical.
- Products that do not meet standards of quality, strength or purity as required under the law.

The FDA has not updated its regulatory policy for homeopathic drug products since 1988. Since then, homeopathic drugs have grown from a small market to a \$3 billion industry. Consumers may choose to use such products for various health issues.

Copies of the FDA [news release](#) and an FDA [draft guidance](#) are in **Attachment 6**.

At this meeting, the committee will have an opportunity to discuss what consumer education, if any, it may wish to pursue in this area.

10. Discussion and Consideration of FDA Guidance, “Evaluating Drug Effects on the Ability to Operate a Motor Vehicle”

In November 2017, the FDA issued a guidance, “Evaluating Drug Effects on the Ability to Operate a Motor Vehicle.” The guidance notes the importance of preventing motor vehicle accidents that result from drug-impaired driving and the need for drug manufacturers to evaluate the effect of a drug on driving ability.

The guidance was issued seven months after the board began requiring California pharmacists to include a written label on prescription drug containers warning the drug may impair a person’s ability to operate a vehicle or vessel. The board amended CCR section 1744, which also identifies specific classes of drugs that may impair a person’s ability to drive a vehicle or vessel. In addition, the regulation requires pharmacists to add a written warning to the container of any drug that, based on a pharmacist’s professional judgment, may impair a person’s ability to operate a vehicle or vessel.

The amendments to CCR section 1744 took effect April 1, 2017. A copy of the [FDA guidance](#) and [section 1744](#) is in **Attachment 7**.

At this meeting, the committee will have an opportunity to discuss the FDA guidance and determine whether California’s labeling requirements need amendment.

11. Discussion and Consideration of *Journal of the American Pharmacists Association* Article, “Enhancing the Educational Value of Direct-to-Consumer Advertising of Prescription Drugs”

A study in the September/October 2017 issue of the *Journal of American Pharmacists Association* looked at how well consumers understand and retain information about the benefits and risks of a prescription drug that is conveyed in direct-to-consumer advertising (DTCA) by pharmaceutical companies.

The study compared an original print DTCA with an ad modified by health literacy principles. The modified ad avoided medical terms and used simple plain language; used sentences with 10 or fewer words; used paragraphs with 10 or fewer lines; used active voice; used headers, bullets and table boxes to organize information; used at least 12-point font; and contained information written at or below an eighth-grade reading level.

Researchers found that participants who viewed the modified ad understood and retained information about the drug’s benefits and risks better than participants who viewed the original DTCA ad. Comprehension and retention were especially better for risk information – suggesting that risk information presented in the original DTCA ad was overwhelming.

The study may be viewed online [here](#). A hard copy is in **Attachment 8**.

12. Discussion and Consideration of Annual Report of the Research Advisory Panel of California

California Health and Safety (HSC) Code sections 11480 and 11481 require proposed research projects using certain opioid, stimulant and hallucinogenic drugs classified as Schedule I and Schedule II controlled substances as their main study drugs to be reviewed and authorized by the Research Advisory Panel of California in the Attorney General's Office.

The panel primarily seeks to ensure the safety and protection of participating human research subjects and adequate security of the controlled substances used in the study. The panel evaluates the scientific validity of each proposed project and may reject proposals where the research is poorly conceived, would produce conclusions of little scientific value, or would not justify the exposure of California subjects to the risk of research.

The panel has submitted its annual report to the Legislature and Governor and released it [online](#). A copy is in **Attachment 9**.

13. Discussion and Consideration of Granting Continuing Education Credit for Reading *The Script*

Background

At the November 2017 board meeting, board members discussed the importance of *The Script* as a means of communicating important information and training for licensees. Several members asked the committee to discuss and consider possible efforts to encourage newsletter readership, including possibly awarding CE credit to licensees for reading *The Script*.

Currently, *The Script* is distributed posted and available on the board's website immediately upon publication. Staff uses subscriber alerts to notify licensees of publication, including a brief description of key articles. Because the board now has email addresses of pharmacists, interns, pharmacy technicians and designated representatives, it is simple to email them a link to the newsletter.

A notice of publication also is posted on the website homepage under "What's New."

At This Meeting

The committee will have an opportunity to discuss and consider this item.

14. Update and Discussion of Communication and Public Education Activities by Board Staff

a. Communication Plan for Consumers and Licensees

The committee has approved a communication plan in accordance with the board's Strategic Plan goal to "(educate) consumers, licensees and stakeholders about the practice and regulation of the profession." Since the September 2017 committee meeting, staff has carried out specific activities in accordance with the plan, including:

- Posted online announcements about drug take-back registration forms and adoption of a new emergency compounding regulation.
- Co-hosted major CE training events with the DEA in San Diego and San Francisco.
- Attended the California Opioid Policy Summit in San Diego.
- Updated the online Pharmacy Lawbook for 2018.
- Issued subscriber alert reminding pharmacists about the board's naloxone protocol.
- Issued alerts about emergency pharmacy regulations to assist consumers evacuated during Northern and Southern California wildfires.

A copy of the communication plan is in **Attachment 10**.

b. The Script

Staff is finalizing the newsletter for publication.

c. News Media

The board's executive officer and public information officer participated in interviews or provided background information in response to the following media inquiries:

- **Columbus Dispatch**, Oct. 18: Marla Rose, Cardinal Health accusation
- **Drug Topics Magazine**, Oct. 24: Fred Gebhart, Northern California wildfire impact on pharmacists and patients.
- **Rewire**, Oct. 27: Nicole Knight, compensation for pharmacists who furnish contraception.
- **23ABC**, Oct. 30: Jessica Harrington, Adventist Health Bakersfield pharmacy inspection.
- **Santa Barbara Independent**, Oct. 31: Nick Welsh, San Ysidro Pharmacy
- **Kaiser Health News**, Nov. 30: Anna Gorman, pharmacists furnishing naloxone
- **KGO ABC 7**, Dec. 7: Ken Miguel, pharmacists furnishing naloxone
- **Los Angeles Times**, Dec. 12: Soumya Karlamangla, UC Berkeley study on pharmacies furnishing hormonal contraception
- **Sacramento Bee**, Dec. 26: Molly Sullivan, services provided by pharmacists without a doctor's prescription

d. Public Outreach

- Nov. 2: Supervising Inspector Michael Ignacio spoke about compliance with corresponding responsibility and the board's Drug Diversion and Fraud Team at the Monterey County Prescription Drug Abuse & Diversion Summit.
- Nov. 9: Inspector Anna Kalantar spoke about sterile compounding issues and regulations at a Vizient pharmacists meeting in Southern California

- Jan. 20, 2018: Supervising Inspector Christine Acosta presenting an overview of new sterile and nonsterile compounding regulations at California Northstate University.
- Jan. 27: Executive Officer Virginia Herold, Enforcement Chief Tom Lenox, Supervising Inspector Janice Dang, Supervising Inspector Antony Ngondara and Inspector Steven Kyle presenting at CE training on CURES, prescription drug abuse and preventing drug diversion at UC San Francisco School of Pharmacy.

15. Review and Discussion of News or Journal Articles

Below are summaries of articles of possible interest to committee members. Click on the headlines to read the stories online.

[Enabling patient-facing care: Pharmacists at the top of their licenses](#)

Drug Store News

Jan. 8, 2018

Pharmacists still are waiting for the handcuffs to come off. That's the consensus of industry leaders who are frustrated with the challenges of getting reimbursements for a wider range of services these professionals can perform. It's a topic at the center of enabling patient care in community-based pharmacy.

[California bills aim to tackle opioid addiction by curbing excessive prescriptions](#)

Los Angeles Times

Jan. 4, 2018

Assemblyman Evan Low (D-Campbell) has authored three bills meant to provide a better understanding of patients' access to highly addictive prescription drugs. One proposal would enable California's database for tracking prescriptions to link up with other states in order to trace "doctor shopping" for multiple opioid prescriptions in multiple states.

[Cedars-Sinai pharmacy staff uses data to cut patient drug errors by 80%](#)

Health Data Management

Dec. 6, 2017

Errors in medication histories inadvertently put into electronic health records can have potentially disastrous consequences for patients admitted to the hospital. However, Cedars-Sinai Medical Center in Los Angeles is turning to pharmacists and pharmacy technicians—instead of clinicians—to accurately capture the information.

[Pharmacies now can offer birth control to women without a prescription, but few do](#)

Los Angeles Times

Dec. 12, 2017

A new law in California allows women to pick up birth control pills from pharmacies without a doctor's prescription. But more than a year after the law took effect, women say they're still struggling to get the medicines, in part because they can't find pharmacies offering them.

16. Future Meeting Dates in 2018

- April 25, 2018
- July 11, 2018
- Oct. 11, 2018

Attachment 1

Use, Don't Abuse

Safely Dispose of Unused Medications

Stop Prescription Drug Abuse



For more information visit: www.pharmacy.ca.gov



California State
Board of Pharmacy



USE, DON'T ABUSE

Prescription drugs can improve health and save lives if they are used as medically intended. But if misused or abused by you or by someone who takes your medications, they can endanger health and lives.

The California State Board of Pharmacy is committed to protecting and promoting the health and safety of Californians by pursuing the highest quality of pharmacist care and the appropriate use of pharmaceuticals. The board encourages consumers to secure and monitor their prescription medications, use them as directed, and prevent them from being abused.

Where Can I Get Information about Prescription Drug Abuse?



The [California State Board of Pharmacy](http://www.pharmacy.ca.gov) has created 30-second and 60-second public service announcements to raise public awareness about prescription drug abuse.



The [Partnership for Drug-Free Kids](http://www.drugfreekids.org) provides information and resources for families to talk to their kids about prescription drug abuse and get help for substance abuse problems. In addition to [live, one-on-one help](#) available by phone and live chat, the website offers [guides, fact sheets and other materials](#) that can be downloaded and printed for use.



The U.S. Drug Enforcement Administration (DEA) sponsors [Get Smart About Drugs](http://www.getsmartaboutdrugs.com), a website with drug abuse information and resources for parents, educators and caregivers. The DEA also sponsors a similar website for teens, [Just Think Twice](http://www.justthinktwice.com).



The [Substance Abuse and Mental Health Services Administration](#) (SAMHSA) is a comprehensive federal resource agency for information, research and services related to substance abuse and mental disorders.



The National Institute on Drug Abuse (NIDA) sponsors [NIDA for Teens](#), which offers information for teens, teachers and parents about the effects of drug use on the bodies, brains and lives of teenagers.

How and Where Can I Get Treatment for Prescription Drug Abuse?



The [National Institute on Drug Abuse](#) (NIDA) offers a guide on [questions to ask when searching for a treatment program](#). The institute also provides scientific information on the causes and consequences of drug use and addiction.



The [California Department of Health Care Services](#) (DHCS) provides information on [narcotic treatment programs](#), including a [directory of treatment program locations](#).



The [Substance Abuse and Mental Health Services Administration](#) (SAMHSA) operates a [treatment referral and information helpline](#) at 1-800-662-HELP (4357) and a [treatment services locator](#) that is searchable by city or zip code.

How and Where Can I Dispose of Unused Prescription Drugs?



The U.S. [Food and Drug Administration](#) (FDA) offers information about options for disposing of unused medications, including collections bins sponsored by law enforcement and step-by-step instructions on disposing of unused drugs at home.



The U.S. [Environmental Protection Agency](#) (EPA) offers information on [how to dispose of unwanted medications](#) and [safe options for home needle disposal](#).



The U.S. [Drug Enforcement Administration](#) (DEA) offers online [information about drug disposal](#) and sponsors [National Prescription Drug Take Back Day](#) events twice a year in communities nationwide. In addition, the website includes a [searchable database](#) of authorized collectors of controlled substance medications.



[Dispose My Meds](#) operates an [online locator](#) of community pharmacies that offer medication disposal programs. The website is sponsored by the National Community Pharmacists Association Foundation and the National Community Pharmacists Association.



[CalRecycle](#) sponsors an [online database](#) of collection sites that accept home-generated sharps and unused medications.

Attachment 2

Up to 70% of Patients Have Errors on Their Medication Lists

Leveraging pharmacy staff prevents harm and increases clinician time for patient care functions



Problem

- 20% of admissions are medication-related¹
- High risk patients have 8 errors on admission medication lists.²
- Only 5.3% of patients 65 year or older on ≥ 5 medications have accurate lists³
- One third of inpatient orders have errors and 85% originate from the medication history⁴
- Up to 59% of errors can cause harm⁵
- Up to 80% of patients have at least 1 medication error at discharge⁶



Solution

- On admission, studies demonstrate increased accuracy of medication lists obtained by pharmacy staff vs usual care
 - Accuracy rates: Nurses, 20%; Hospitalists, 50%; Technicians, 100%⁷
 - Nurses 14% vs pharmacy technicians 94% ($p < 0.0001$)⁸
- At discharge, pharmacists identified errors in medication lists in 49% of patients and problems in an additional 16% vs usual care⁹



Cost of Harm

- Cost of adverse drug event (ADE): \$2,262- \$5,790^{7,10-13}
- Increased length of stay due to ADE: 3.1 days¹³
- Cost/readmission ~ \$12,300-13,800¹⁴

Business Case

Benefits

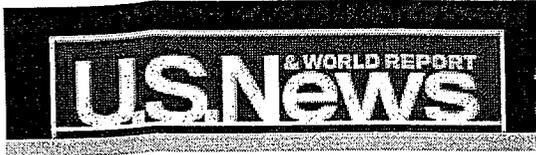
- 75% reduction in ADEs⁷
- 41 minutes of nursing time saved/patient¹⁶
- Cost-effective to utilize technicians for medication histories; \$830,000⁷
- Patients have an accurate medication list upon discharge
- Reduced readmissions
- Enables clinicians to practice at the highest level of their license and training



Recommendation: For high risk patients, pharmacy will ensure the accuracy of the medication list at admission and discharge

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9 Strategies for Reducing Emergency Room Medication Errors

To prevent mistakes, keep a drug inventory, and ask lots of questions.



By Ruben Castaneda, Staff Writer | Jan. 4, 2018, at 2:06 p.m.



Inaccurate records can cause emergency room medication errors.

Medication errors at emergency departments lead to hundreds of thousands of injuries annually, says Rita Shane, chief pharmacy officer and professor of medicine at Cedars-Sinai Medical Center in Los Angeles. Emergency rooms at U.S. hospitals handle more than 141



(Getty Images)

million visits annually, treating heart attacks, fractures and other ailments, according to the Centers for Disease Control and Prevention, and medication errors can happen when hospital staff rely on incomplete or outdated prescription records or when patients transition from one setting to another and current medication information isn't passed along.

Relying on pharmacy professionals greatly reduces errors.

Mistakes in drug orders can be reduced by more than 80 percent when pharmacy professionals – in collaboration with doctors and nurses – take the medical histories of high-risk patients admitted through the emergency department, according to a recent Cedars-Sinai

study. Investigators focused on 306 patients who took at least 10 medications or had a history of heart failure or other serious medical issues. In response to the findings, Cedars-Sinai now assigns pharmacy staff members to record medication histories for high-risk patients admitted to the hospital through the emergency room. You, the patient, can also take steps to prevent medication errors. Here are nine strategies to guard against emergency room-related medication errors:



(Getty Images)

Compile and carry a current drug inventory.

Carry a list of your prescription medications and dosages in your purse or wallet at all times, and update it when you add or stop taking a medicine, says Dr. Joshua Pevnick, associate director of the division of informatics at Cedars-Sinai. Note any drug allergies. If you arrive in the emergency room



(Getty Images)

unconscious or with compromised ability to communicate, this list can be vital. "Obtaining accurate medication histories is a huge challenge, particularly in emergency situations," Pevnick says.

Include over-the-counter medications on your list.

If you're taking herbal remedies, laxatives, over-the-counter pain relievers, cough or cold medications or vitamins, include them on your drug list. Some of these products may interact with drugs that you're prescribed at the hospital, or they could have harmful side effects,

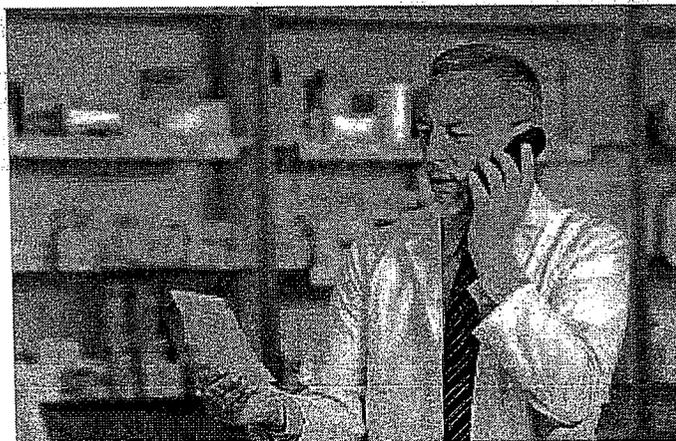
Shane says. For instance, some herbal medications may interact with blood thinners, increasing the risk of bleeding. Don't forget to note your caffeine intake through coffee, soft drinks or other beverages. "Caffeine can 'boost' the effect of certain asthma medications, for instance, causing symptoms such as a racing heartbeat," Shane says.



(Getty Images)

Carry your physician and pharmacy contacts.

Your doctor can provide background on why you're taking certain drugs, so carry his or her contact information, including phone number, email and fax number. If you have multiple physicians who prescribe you medication, carry their contact information, as well.



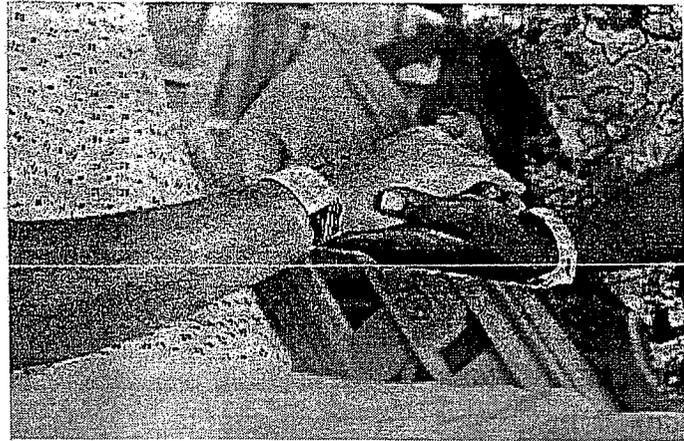
(Getty Images)

These doctors can provide your prescription drug history and discuss the reasons you've been prescribed the medication, which is valuable information for hospital pharmacists and physicians. Also carry contact information for your pharmacy.

NEXT: Be sure the hospital staff verifies your identification.

Be sure the hospital staff verifies your identification.

Before any hospital staff member administers a drug, be sure he or she checks your patient identification bracelet to confirm it matches the name on your medication record. This record shows the medications prescribed for you during your hospital admission. Many hospitals scan the identification bracelet and review prescription drugs before they're administered to ensure the drugs are correct. But later, confusion over patient IDs can cause a drug to be administered to the wrong person, in the wrong dose or at the wrong time.



(Getty Images)

Consider bringing a patient advocate to the hospital

Going to the emergency room is an extremely stressful experience, notes Teri Dreher, a registered nurse and owner of NShore Patient Advocates in Chicago. Patients under that kind of stress sometimes forget parts of their medical history, including the prescription and over-the-counter medications they take, allergies and past adverse reactions to drugs. A patient advocate can be a trusted family member, a close friend or a hired private patient advocate, Dreher says. If you become incapacitated, your advocate can relay wishes about your treatment – including medication choices – to doctors. You can arrange for your advocate to speak for the rest of your family, according to the National Patient Safety Foundation.



(Getty Images)

Don't hesitate to ask questions.

When you receive a drug for the first time, ask a hospital staff member to explain the medication's purpose, its benefits, its risks, whether it interacts with other medications and its possible side effects. Be sure to ask whether taking the medication requires monitoring; some drugs, for example, can affect kidney function and require you to undergo specific blood tests. If you're worried about a particular medication's risks or side effects, ask about possible alternatives. If you don't feel fully informed by the staff member's answers, ask for the doctor or pharmacist on duty.



(Getty Images)

Review your medication regimen.

As you're being discharged from the hospital, review with the hospital pharmacist the full list of drugs you'll be taking, along with doses and instructions. Verify which of the drugs you were taking before you entered the hospital should be continued, and whether any new drugs you received during your stay should be discontinued. Ask about the purpose of each medication, and write everything down. Call your pharmacy to find out how much any new medications will cost you after insurance contributions. If the prices seem prohibitive, talk to your pharmacist and your physician about potential strategies to reduce your costs.



(Getty Images)

Be sure your caregiver understands your new drug regimen.

Everyone who helps you take medications – whether it's a professional caregiver, spouse or partner or a close family member – should be brought into the loop on your post-discharge drug regimen, Shane says. Bring your caregiver or close family member or partner to your post-discharge drug consultation to provide a second set of eyes and ears. In particular, older adults or those with disabilities should make sure to update any family members or caregivers who may help them by buying medications, picking up refills, arranging medications in a pillbox and confirming that medications have been taken as prescribed.



(Getty Images)

Update your home pharmacy.

After confirming your new drug regimen with your primary care physician and any relevant specialists, contact your pharmacy and ask them to remove your prescriptions for discontinued medications from their records.

"When patients go back to their pharmacy after being discharged,

the staff there sometimes inadvertently provides refills of medications that were discontinued during the hospitalization," Pevnick says. "For instance, a patient may be hospitalized for a bleeding problem, and so the previously prescribed anticoagulant is discontinued. Then the home pharmacy gives the patient a refill from the old anticoagulant prescription when they visit the pharmacy to get their post-discharge medications."



(Getty Images)

Attachment 3



**NOTIFICATION OF INSTALLATION OR DISCONTINUANCE OF A
 PRESCRIPTION DRUG TAKE-BACK COLLECTION RECEPTACLE
 (California Code of Regulations, Title 16, Article 9.1 of Division 17)**

Pharmacies and hospitals/clinics with onsite pharmacies licensed by the board may, under the requirements in California pharmacy regulations (CCR, Title 16, Article 9.1 of Division 17), offer specified prescription drug take-back services through collection receptacles and/or mail back envelopes/packages to provide options for the public to discard unwanted, unused or outdated prescription drugs. Each entity that offers specified prescription drug take-back services through collection receptacles must comply with regulations of the federal Drug Enforcement Administration (DEA) and the Board of Pharmacy's requirements.

One requirement is to notify the Board of Pharmacy of the location of the collection receptacle in writing within 30 days. This includes collection receptacles operated by pharmacies in licensed skilled nursing facilities. This form is intended to assist pharmacies in notifying the Board of Pharmacy. In addition, entities must notify the board within 30 days of discontinuance.

Pharmacy Operating the Collection Receptacle:

Name of Pharmacy:		Pharmacy License Number:	DEA Registration Number for Take-Back:
Address of Pharmacy: Number and Street		City	State Zip
Name of person authorized to clarify information provided on this form:			
Telephone Number:		Email Address:	

Location of the Collection Receptacle (if different than the above location):

Facility Name:	Type of Facility:	Check Box if Facility is a Licensed Skilled Nursing Facility <input type="checkbox"/>	Skilled Nursing Facility License Number (if applicable):
Facility Address: Number and Street (including room number when appropriate)		City	State Zip Code
Contact Person at Facility:	Telephone Number:	Email Address:	

Installation/Discontinuance of the Collection Receptacle:

Date Installed at Facility:	Date Removed from Facility:
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Signature of Pharmacist-in-Charge	Pharmacist Name	RPH License Number	Date
For Office Use Only			
Geo ____ PHY ____	Registration Number: _____	Date Processed: _____ By: _____	
Sup RPH ____ PIC ____		Date Approved: _____ By: _____	
Enf ____			

Article 9.1 (commencing with Section 1776) of the California Code of Regulations**Prescription Drug Take-Back Services**

§ 1776. Prescription Drug Take-Back Services: Authorization.

Pharmacies, hospitals/clinics with onsite pharmacies, distributors and reverse distributors licensed by the board may offer, under the requirements in this article, specified prescription drug take-back services through collection receptacles and/or mail back envelopes or packages to provide options for the public to discard unwanted, unused or outdated prescription drugs. Each entity must comply with regulations of the federal Drug Enforcement Administration (DEA) and this article.

Only California-licensed pharmacies, hospitals/clinics with onsite pharmacies, and drug distributors (licensed wholesalers and third-party logistics providers) who are registered with the DEA as collectors and licensed in good standing with the board may host a pharmaceutical take-back receptacle as authorized under this article.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4005, 4026.5 and 4301, Business and Professions Code; and Section 1317.40, Title 21, Code of Federal Regulations.

§ 1776.1. Pharmacies.

(a) Pharmacies may provide take-back services to the public. Retail pharmacies and hospital/clinics with onsite pharmacies may maintain collection receptacles in their facilities. Pharmacies may offer drug take-back services as specified in section 1776.4 in skilled nursing facilities licensed under Health and Safety Code section 1250(c).

(b) There are multiple federal, state and local requirements governing the collection and destruction of dangerous drugs. Pharmacies are expected to know and adhere to these requirements when operating a prescription drug take-back program.

(c) For purposes of this article, prescription drugs means dangerous drugs as defined by Business and Professions Code section 4022, which includes controlled substances. Controlled substances may be commingled in collection receptacles or mail back envelopes or packages with other dangerous drugs.

(d) Once drugs are deposited into a collection receptacle or mail back envelopes or packages by a consumer, they are not to be removed, counted, sorted or otherwise individually handled.

(e) The collection receptacle shall contain signage that includes:

(1) The name and phone number of the responsible pharmacy;

(2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and

(3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

(f) Prescription drugs that are eligible for collection as part of drug take-back services maintained by pharmacies are only those prescription drugs that have been dispensed by any pharmacy or practitioner to a consumer. Dangerous drugs that have not been dispensed to consumers for use (such as outdated drug stock in a pharmacy, drug samples provided to a medical practitioner or medical waste) may not be collected as part of a pharmacy's drug take-back service.

(g) As part of its drug take-back services, a pharmacy shall not:

(1) Review, accept, count, sort, or otherwise individually handle any prescription drugs from consumers.

(2) Accept or possess prescription drugs from skilled nursing facilities, residential care homes, health care practitioners or any other entity.

(3) Dispose of quarantined, recalled or outdated prescription drugs from pharmacy stock.

(h) A pharmacy must be registered with the federal DEA as a collector for purposes of maintaining a prescription drug take-back collection receptacle. Such pharmacies cannot employ anyone convicted of a felony related to controlled substances, or anyone who has had a DEA permit denied, surrendered or revoked.

(i) Any pharmacy that maintains a drug take-back collection receptacle as authorized in this article shall notify the board in writing within 30 days of establishing the collection program. Additionally:

(1) Any pharmacy that ceases to maintain a drug take-back collection receptacle shall notify the board in writing within 30 days.

(2) Any pharmacy maintaining a collection receptacle shall disclose to the board that it provides such services annually at the time of renewal of the pharmacy license, and shall identify all locations where its collection receptacles are located.

(3) Any tampering with a collection receptacle or theft of deposited drugs shall be reported to the board in writing within 14 days.

(4) Any tampering, damage or theft of a removed liner shall be reported to the board in writing within 14 days.

(j) If the pharmacy ceases to maintain a registered collection receptacle, the pharmacy must notify the DEA within 30 days.

(k) A pharmacy shall not provide take-back services to consumers if, in the professional judgment of the pharmacist-in-charge, the pharmacy cannot comply with the provisions of this article or the DEA rules.

(l) A pharmacy shall not provide take-back services to consumers if the pharmacy or the pharmacist-in-charge is on probation with the board, and, if the pharmacy had previously provided take-back services, the pharmacist-in-charge shall notify the board and the DEA as required in subsections (i) and (j), above.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4005 and 4022, Business and Professions Code; and Sections 1301.71, 1317.30 and 1317.40, Title 21, Code of Federal Regulations.

§ 1776.2. Pharmacies Offering Mail Back Envelope or Package Services.

(a) Pharmacies that provide prescription drug take-back services may do so by providing preaddressed mailing envelopes or packages to allow a consumer to return prescription drugs to an authorized DEA destruction location.

(b) All envelopes and packages must be preaddressed to a location registered with the DEA as a collector. The pharmacy is responsible for ensuring that all preaddressed envelopes and packages it makes available to the public are preaddressed for delivery to facilities that comply with this section.

(c) The preaddressed envelopes and packages must be water and spill proof, tamper evident, tear resistant and sealable. The exterior shall be nondescript and not include markings that indicate the envelope or package contains prescription drugs. Postage shall be prepaid on each envelope or package.

(d) The preaddressed envelope and package shall contain a unique identification number for each envelope and package, and instructions for users that indicate the process to mail back drugs.

(e) A pharmacy shall not accept any mail back packages or envelopes that contain drugs unless they are registered as a collector and have an onsite method of destruction that complies with the DEA requirements. Instead, consumers shall be directed to mail the envelopes or packages.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Section 1317.70, Title 21, Code of Federal Regulations.

§ 1776.3. Collection Receptacles in Pharmacies.

(a) A pharmacy may maintain a collection receptacle for the public to deposit their unwanted prescription drugs for destruction. The pharmacy is responsible for the management and maintenance of the receptacle. The receptacle shall be substantially constructed, with a permanent outer container and a removable inner liner. The collection receptacle shall be locked at all times to prevent access to the inner liner.

(b) A pharmacy maintaining a collection receptacle must securely fasten the receptacle to a permanent structure so it cannot be removed. The receptacle shall be installed in an inside location. Except as provided in subsection (c), the receptacle is visible to pharmacy or DEA registrant employees, but not located in or near emergency areas, nor behind the pharmacy's counter.

(c) In hospitals/clinics with a pharmacy on the premises, the collection receptacle must be located in an area that is regularly monitored by pharmacy or DEA registrant employees and not in the proximity of any emergency or urgent care areas. When no pharmacy or DEA registrant employees are present, the collection receptacle shall be locked so that drugs may not be deposited into the collection receptacle.

(d) The receptacle shall include a small opening that allows deposit of drugs into the inside of the receptacle directly into the inner liner, but does not allow for an individual to reach into the receptacle's contents. During hours when the pharmacy is closed, the collection receptacle shall not be accessible to the public for deposit of drugs. The pharmacy shall lock the deposit opening on the collection receptacle.

(e) A pharmacy shall direct consumers to directly deposit drugs into the collection receptacle. A pharmacy shall not accept, count, sort or otherwise handle prescription drugs from consumers.

(f) A liner as used in this article shall be made of material that is certified by the manufacturer to meet the American Society for Testing Materials (ASTM) D1709 standard test for impact resistance of 165 grams (drop dart test), and the ASTM D1922 standards for tear resistance of 480 grams in both parallel and perpendicular planes.

(1) The liner shall be waterproof, tamper evident and tear resistant.

(2) The liner shall be opaque to prevent viewing or removal of any contents once the liner has been removed from a collection receptacle. The liner shall be clearly marked to display the maximum contents (for example, in gallons). The liner shall bear a permanent, unique identification number established by the pharmacy or pre-entered onto the liner by the liner's manufacturer or distributor.

(g) The liner shall be removable as specified in this section. The receptacle shall allow the public to deposit prescription drugs into the receptacle for containment into the inner liner, without permitting access to or removal of prescription drugs already deposited into the collection receptacle and liner. Once a prescription drug or any other item is placed in the collection receptacle, the prescription drug or item cannot be removed, counted, sorted or otherwise individually handled.

(h) If the liner is not already itself rigid or already inside of a rigid container when it is removed from the collection receptacle, the liner must be immediately, without interruption, placed in a rigid container for storage, handling and transport. A rigid container may be disposable, reusable, or recyclable. Rigid containers shall be leak resistant, have sealable tight-fitting covers, and be kept clean and in good repair.

(i) The liner may be removed from a locked collection receptacle only by or under the supervision of two employees of the pharmacy. Upon removal, the liner shall be immediately, without interruption, sealed and the pharmacy employees shall record, in a log, their participation in the removal of each liner from a collection receptacle. Liners and their rigid containers shall not be opened, x-rayed, analyzed or penetrated at any time by the pharmacy or pharmacy personnel.

(j) Liners and their rigid containers that have been filled and removed from a collection receptacle must be stored in a secured, locked location in the pharmacy no longer than 14 days.

(k) The pharmacy shall make and keep the records specified in 1776.6.

(l) The pharmacy shall ensure the sealed inner liners and their contents are shipped to a reverse distributor's registered location by common or contract carrier (such as UPS, FEDEX or USPS) or by licensed reverse distributor pick-up at the licensed pharmacy's premises.

(m) The collection receptacle shall contain signage that includes:

- (1) The name and phone number of the responsible pharmacy;
- (2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and
- (3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Sections 1304.22, 1317.05, 1317.60 and 1317.75, Title 21, Code of Federal Regulations.

§ 1776.4. Drug Take-Back Services in Skilled Nursing Facilities.

A pharmacy may offer drug take-back services in skilled nursing facilities licensed under Health and Safety Code section 1250(c) as authorized by this article.

(a) Skilled nursing facility employees or person lawfully entitled to dispose of the resident decedent's property may dispose of unwanted or unused prescription drugs by using mail back envelopes or packages. The pharmacy shall require skilled nursing facility employees to keep records noting the specific quantity of each prescription drug mailed back, the unique identification number of the mail back package and the preaddressed location to which the mail back envelope is sent.

(b) Only pharmacies and hospitals/clinics with onsite pharmacies may establish collection receptacles in skilled nursing facilities for the collection and ultimate disposal of unwanted prescription drugs. A pharmacy and hospital/clinic with an onsite pharmacy maintaining a collection receptacle in a skilled nursing facility shall:

- (1) Be registered and maintain registration with the DEA as a collector.
- (2) Notify the board in writing within 30 days of establishing a collection receptacle.
- (3) Notify the board in writing within 30 days when they cease to maintain the collection receptacle.
- (4) Notify the board in writing within 14 days of any tampering of the collection receptacle or theft of deposited drugs.
- (5) Notify the board in writing within 14 days of any tampering, damage or theft of a removed liner.
- (6) List all collection receptacles it maintains annually at the time of renewal of the pharmacy license.

(d) Within three business days after the permanent discontinuation of use of a medication by a prescriber, as a result of the resident's transfer to another facility or as a result of death, the skilled nursing facility may place the patient's unneeded prescription drugs into a collection receptacle. Records of such deposit shall be made in the patient's records, with the name and signature of the employee discarding the drugs.

(e) A collection receptacle must be located in a secured area regularly monitored by skilled nursing facility employees.

(f) The collection receptacle shall be securely fastened to a permanent structure so that it cannot be removed. The collection receptacle shall have a small opening that allows deposit of drugs into the inside of the collection receptacle and directly into the inner liner, but does not allow for an individual to reach into the receptacle's contents.

(g) The receptacle shall be securely locked and substantially constructed, with a permanent outer container and a removable inner liner.

(1) The liner shall comply with provisions in this article. The receptacle shall allow deposit of prescription drugs into the receptacle for containment into the inner liner, without permitting access to or removal of prescription drugs already deposited into the collection receptacle and liner. Once a prescription drug or any other item is placed in the collection receptacle, the prescription drug or item cannot be removed, sorted, counted, or otherwise individually handled.

(2) If the liner is not already itself rigid or already inside of a rigid container when it is removed from the collection receptacle, the liner must be immediately placed in a rigid container for storage, handling and transport. A rigid container may be disposable, reusable, or recyclable. Rigid containers shall be leak resistant, have sealable tight-fitting covers, and be kept clean and in good repair.

(h) A liner as used in this article shall be made of material that is certified by the manufacturer to meet American Society for Testing Materials (ASTM) D1709 standard test for impact resistance of 165 grams (drop dart test), and the ASTM D1922 standards for tear resistance of 480 grams in both parallel and perpendicular planes.

(1) The liner shall be waterproof, tamper evident and tear resistant.

(2) The liner shall be opaque to prevent viewing and discourage removal of any contents once the liner has been removed from a collection receptacle. The liner shall be clearly marked to display the maximum contents (for example, in gallons). The liner shall bear a permanent, unique identification number.

(i) The collection receptacle shall contain signage that includes:

(1) The name and phone number of the responsible pharmacy;

(2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and

(3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

(j) Once deposited, the prescription drugs shall not be counted, sorted or otherwise individually handled.

(k) The installation, removal, transfer and storage of inner liners shall be performed only by:

(1) One employee of the authorized collector pharmacy and one supervisory level employee of the long-term care facility (e.g., a charge nurse or supervisor) designated by the authorized collector, or

(2) By or under the supervision of two employees of the authorized collector pharmacy.

(l) Sealed inner liners that are placed in a container may be stored at the skilled nursing facility for up to three business days in a securely locked, substantially constructed cabinet or a securely locked room with controlled access until transfer to a reverse distributor for destruction.

(m) Liners still housed in a rigid container may be delivered to a reverse distributor for destruction by common or contract carrier or by reverse distributor pickup at the skilled nursing facility.

(n) A pharmacy maintaining a collection receptacle in a skilled nursing facility shall make and keep the records as specified in 1776.6.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Sections 1304.22, 1317.05, 1317.40, 1317.60, 1317.75, 1317.80 and 1317.95, Title 21, Code of Federal Regulations

§ 1776.5. Reverse Distributors.

(a) A licensed reverse distributor (either a reverse wholesaler or a reverse third-party logistics provider) registered with the DEA may accept the sealed inner liners of collection receptacles at the reverse distributor's registered location by common or contract carrier pick-up, or by reverse distributor pick-up at the collector's authorized collection location. Once received, the reverse distributor shall establish records required by this section.

(b) A licensed reverse distributor may not open, survey, or otherwise analyze the contents of inner liners. All liners shall be destroyed by an appropriately licensed and registered DEA reverse distributor in a manner that makes the drugs irretrievable.

(c) If a reverse distributor picks up the sealed inner liners from the collector's authorized location, at least two employees of the reverse distributor shall be present. If the sealed inner liners are delivered to the reverse distributor via common or

contract carrier, at least one employee of the reverse distributor shall accept the receipt of the inner liners at the reverse distributor's registered location.

(d) A reverse distributor shall not employ as an agent or employee anyone who has access to or influence over controlled substances, any person who has been convicted of any felony offense related to controlled substances or who at any time had a DEA registration revoked or suspended, or has surrendered a DEA registration for cause.

(e) For each sealed liner or mail back envelopes or packages received pursuant to federal Title 21 CFR section 1317.55, the reverse distributor shall maintain records of the number of sealed inner liners or mail back envelopes or packages, including the:

- (1) Date of acquisition;
 - (2) Number and the size (e.g., five 10-gallon liners, etc.);
 - (3) Unique Identification number of each liner or envelope/package;
 - (4) The method of delivery to the reverse distributor, the signature of the individuals delivering the liners to the reverse distributor, and the reverse distributor's employees who received the sealed liner;
 - (5) The date, place and method of destruction;
 - (6) Number of packages and inner liners received;
 - (7) Number of packages and inner liners destroyed;
 - (8) The name and signature of the two employees of the registrant that witnessed the destruction.
- (e) For liners only, the information specified in subsection (e)(1)-(8) above shall be created at the time of receipt and at the time of destruction.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Section 1301.71, 1304.21, 1304.22, 1317.15, 1317.55 and 1317.95, Title 21, Code of Federal Regulations.

§ 1776.6. Record Keeping Requirements for Board Licensees Providing Drug Take-Back Services.

Each entity authorized by this article to collect unwanted prescription drugs from consumers shall maintain the records required by this article for three years.

(a) For pharmacies maintaining collection receptacles, the pharmacy shall make and keep the following records for each liner:

- (1) Date each unused liner is acquired, its unique identification number and size (e.g., 5 gallon, 10 gallon). The pharmacy shall assign the unique identification number if the liner does not already contain one.
- (2) Date each liner is installed in a collection receptacle, the address of the location where each liner is installed, the unique identification number and size (e.g., 5 gallon, 10 gallon), the registration number of the collector pharmacy, and the names and signatures of the two employees that witnessed each installation.
- (3) Date each inner liner is removed and sealed, the address of the location from which each inner liner is removed, the unique identification number and size (e.g., 5 gallon, 10 gallon) of each inner liner removed, the registration number of the collector pharmacy, and the names and signatures of the two employees that witnessed the removal and sealing.
- (4) Date each sealed inner liner is transferred to storage, the unique identification number and size (e.g., 5 gallon, 10 gallon) of each inner liner stored, and the names and signatures of the two employees that transferred each sealed inner liner to storage.
- (5) Date each sealed inner liner is transferred for destruction, the address and registration number of the reverse distributor or distributor to whom each sealed inner liner was transferred, the unique Identification number and the size (e.g., 5 gallon, 10 gallon) of each liner transferred, and the names and signatures of the two employees who transferred each sealed inner liner to the reverse distributor or distributor, or the common carrier who delivered it, the company used, and any related paperwork (invoice, bill of lading).

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Section 1304.22, Title 21, Code of Federal Regulations.

Article 9.1 (commencing with Section 1776) of the California Code of Regulations**Prescription Drug Take-Back Services**

§ 1776. Prescription Drug Take-Back Services: Authorization.

Pharmacies, hospitals/clinics with onsite pharmacies, distributors and reverse distributors licensed by the board may offer, under the requirements in this article, specified prescription drug take-back services through collection receptacles and/or mail back envelopes or packages to provide options for the public to discard unwanted, unused or outdated prescription drugs. Each entity must comply with regulations of the federal Drug Enforcement Administration (DEA) and this article.

Only California-licensed pharmacies, hospitals/clinics with onsite pharmacies, and drug distributors (licensed wholesalers and third-party logistics providers) who are registered with the DEA as collectors and licensed in good standing with the board may host a pharmaceutical take-back receptacle as authorized under this article.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4005, 4026.5 and 4301, Business and Professions Code; and Section 1317.40, Title 21, Code of Federal Regulations.

§ 1776.1. Pharmacies.

(a) Pharmacies may provide take-back services to the public. Retail pharmacies and hospital/clinics with onsite pharmacies may maintain collection receptacles in their facilities. Pharmacies may offer drug take-back services as specified in section 1776.4 in skilled nursing facilities licensed under Health and Safety Code section 1250(c).

(b) There are multiple federal, state and local requirements governing the collection and destruction of dangerous drugs. Pharmacies are expected to know and adhere to these requirements when operating a prescription drug take-back program.

(c) For purposes of this article, prescription drugs means dangerous drugs as defined by Business and Professions Code section 4022, which includes controlled substances. Controlled substances may be commingled in collection receptacles or mail back envelopes or packages with other dangerous drugs.

(d) Once drugs are deposited into a collection receptacle or mail back envelopes or packages by a consumer, they are not to be removed, counted, sorted or otherwise individually handled.

(e) The collection receptacle shall contain signage that includes:

(1) The name and phone number of the responsible pharmacy;

(2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and

(3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

(f) Prescription drugs that are eligible for collection as part of drug take-back services maintained by pharmacies are only those prescription drugs that have been dispensed by any pharmacy or practitioner to a consumer. Dangerous drugs that have not been dispensed to consumers for use (such as outdated drug stock in a pharmacy, drug samples provided to a medical practitioner or medical waste) may not be collected as part of a pharmacy's drug take-back service.

(g) As part of its drug take-back services, a pharmacy shall not:

(1) Review, accept, count, sort, or otherwise individually handle any prescription drugs from consumers.

(2) Accept or possess prescription drugs from skilled nursing facilities, residential care homes, health care practitioners or any other entity.

(3) Dispose of quarantined, recalled or outdated prescription drugs from pharmacy stock.

(h) A pharmacy must be registered with the federal DEA as a collector for purposes of maintaining a prescription drug take-back collection receptacle. Such pharmacies cannot employ anyone convicted of a felony related to controlled substances, or anyone who has had a DEA permit denied, surrendered or revoked.

(i) Any pharmacy that maintains a drug take-back collection receptacle as authorized in this article shall notify the board in writing within 30 days of establishing the collection program. Additionally:

(1) Any pharmacy that ceases to maintain a drug take-back collection receptacle shall notify the board in writing within 30 days.

(2) Any pharmacy maintaining a collection receptacle shall disclose to the board that it provides such services annually at the time of renewal of the pharmacy license, and shall identify all locations where its collection receptacles are located.

(3) Any tampering with a collection receptacle or theft of deposited drugs shall be reported to the board in writing within 14 days.

(4) Any tampering, damage or theft of a removed liner shall be reported to the board in writing within 14 days.

(j) If the pharmacy ceases to maintain a registered collection receptacle, the pharmacy must notify the DEA within 30 days.

(k) A pharmacy shall not provide take-back services to consumers if, in the professional judgment of the pharmacist-in-charge, the pharmacy cannot comply with the provisions of this article or the DEA rules.

(l) A pharmacy shall not provide take-back services to consumers if the pharmacy or the pharmacist-in-charge is on probation with the board, and, if the pharmacy had previously provided take-back services, the pharmacist-in-charge shall notify the board and the DEA as required in subsections (i) and (j), above.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4005 and 4022, Business and Professions Code; and Sections 1301.71, 1317.30 and 1317.40, Title 21, Code of Federal Regulations.

§ 1776.2. Pharmacies Offering Mail Back Envelope or Package Services.

(a) Pharmacies that provide prescription drug take-back services may do so by providing preaddressed mailing envelopes or packages to allow a consumer to return prescription drugs to an authorized DEA destruction location.

(b) All envelopes and packages must be preaddressed to a location registered with the DEA as a collector. The pharmacy is responsible for ensuring that all preaddressed envelopes and packages it makes available to the public are preaddressed for delivery to facilities that comply with this section.

(c) The preaddressed envelopes and packages must be water and spill proof, tamper evident, tear resistant and sealable. The exterior shall be nondescript and not include markings that indicate the envelope or package contains prescription drugs. Postage shall be prepaid on each envelope or package.

(d) The preaddressed envelope and package shall contain a unique identification number for each envelope and package, and instructions for users that indicate the process to mail back drugs.

(e) A pharmacy shall not accept any mail back packages or envelopes that contain drugs unless they are registered as a collector and have an onsite method of destruction that complies with the DEA requirements. Instead, consumers shall be directed to mail the envelopes or packages.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Section 1317.70, Title 21, Code of Federal Regulations.

§ 1776.3. Collection Receptacles in Pharmacies.

(a) A pharmacy may maintain a collection receptacle for the public to deposit their unwanted prescription drugs for destruction. The pharmacy is responsible for the management and maintenance of the receptacle. The receptacle shall be substantially constructed, with a permanent outer container and a removable inner liner. The collection receptacle shall be locked at all times to prevent access to the inner liner.

(b) A pharmacy maintaining a collection receptacle must securely fasten the receptacle to a permanent structure so it cannot be removed. The receptacle shall be installed in an inside location. Except as provided in subsection (c), the receptacle is visible to pharmacy or DEA registrant employees, but not located in or near emergency areas, nor behind the pharmacy's counter.

(c) In hospitals/clinics with a pharmacy on the premises, the collection receptacle must be located in an area that is regularly monitored by pharmacy or DEA registrant employees and not in the proximity of any emergency or urgent care areas. When no pharmacy or DEA registrant employees are present, the collection receptacle shall be locked so that drugs may not be deposited into the collection receptacle.

(d) The receptacle shall include a small opening that allows deposit of drugs into the inside of the receptacle directly into the inner liner, but does not allow for an individual to reach into the receptacle's contents. During hours when the pharmacy is closed, the collection receptacle shall not be accessible to the public for deposit of drugs. The pharmacy shall lock the deposit opening on the collection receptacle.

(e) A pharmacy shall direct consumers to directly deposit drugs into the collection receptacle. A pharmacy shall not accept, count, sort or otherwise handle prescription drugs from consumers.

(f) A liner as used in this article shall be made of material that is certified by the manufacturer to meet the American Society for Testing Materials (ASTM) D1709 standard test for impact resistance of 165 grams (drop dart test), and the ASTM D1922 standards for tear resistance of 480 grams in both parallel and perpendicular planes.

(1) The liner shall be waterproof, tamper evident and tear resistant.

(2) The liner shall be opaque to prevent viewing or removal of any contents once the liner has been removed from a collection receptacle. The liner shall be clearly marked to display the maximum contents (for example, in gallons). The liner shall bear a permanent, unique identification number established by the pharmacy or pre-entered onto the liner by the liner's manufacturer or distributor.

(g) The liner shall be removable as specified in this section. The receptacle shall allow the public to deposit prescription drugs into the receptacle for containment into the inner liner, without permitting access to or removal of prescription drugs already deposited into the collection receptacle and liner. Once a prescription drug or any other item is placed in the collection receptacle, the prescription drug or item cannot be removed, counted, sorted or otherwise individually handled.

(h) If the liner is not already itself rigid or already inside of a rigid container when it is removed from the collection receptacle, the liner must be immediately, without interruption, placed in a rigid container for storage, handling and transport. A rigid container may be disposable, reusable, or recyclable. Rigid containers shall be leak resistant, have sealable tight-fitting covers, and be kept clean and in good repair.

(i) The liner may be removed from a locked collection receptacle only by or under the supervision of two employees of the pharmacy. Upon removal, the liner shall be immediately, without interruption, sealed and the pharmacy employees shall record, in a log, their participation in the removal of each liner from a collection receptacle. Liners and their rigid containers shall not be opened, x-rayed, analyzed or penetrated at any time by the pharmacy or pharmacy personnel.

(j) Liners and their rigid containers that have been filled and removed from a collection receptacle must be stored in a secured, locked location in the pharmacy no longer than 14 days.

(k) The pharmacy shall make and keep the records specified in 1776.6.

(l) The pharmacy shall ensure the sealed inner liners and their contents are shipped to a reverse distributor's registered location by common or contract carrier (such as UPS, FEDEX or USPS) or by licensed reverse distributor pick-up at the licensed pharmacy's premises.

(m) The collection receptacle shall contain signage that includes:

- (1) The name and phone number of the responsible pharmacy;
- (2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and
- (3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Sections 1304.22, 1317.05, 1317.60 and 1317.75, Title 21, Code of Federal Regulations.

§ 1776.4. Drug Take-Back Services in Skilled Nursing Facilities.

A pharmacy may offer drug take-back services in skilled nursing facilities licensed under Health and Safety Code section 1250(c) as authorized by this article.

(a) Skilled nursing facility employees or person lawfully entitled to dispose of the resident decedent's property may dispose of unwanted or unused prescription drugs by using mail back envelopes or packages. The pharmacy shall require skilled nursing facility employees to keep records noting the specific quantity of each prescription drug mailed back, the unique identification number of the mail back package and the preaddressed location to which the mail back envelope is sent.

(b) Only pharmacies and hospitals/clinics with onsite pharmacies may establish collection receptacles in skilled nursing facilities for the collection and ultimate disposal of unwanted prescription drugs. A pharmacy and hospital/clinic with an onsite pharmacy maintaining a collection receptacle in a skilled nursing facility shall:

- (1) Be registered and maintain registration with the DEA as a collector.
- (2) Notify the board in writing within 30 days of establishing a collection receptacle.
- (3) Notify the board in writing within 30 days when they cease to maintain the collection receptacle.
- (4) Notify the board in writing within 14 days of any tampering of the collection receptacle or theft of deposited drugs.
- (5) Notify the board in writing within 14 days of any tampering, damage or theft of a removed liner.
- (6) List all collection receptacles it maintains annually at the time of renewal of the pharmacy license.

(d) Within three business days after the permanent discontinuation of use of a medication by a prescriber, as a result of the resident's transfer to another facility or as a result of death, the skilled nursing facility may place the patient's unneeded prescription drugs into a collection receptacle. Records of such deposit shall be made in the patient's records, with the name and signature of the employee discarding the drugs.

(e) A collection receptacle must be located in a secured area regularly monitored by skilled nursing facility employees.

(f) The collection receptacle shall be securely fastened to a permanent structure so that it cannot be removed. The collection receptacle shall have a small opening that allows deposit of drugs into the inside of the collection receptacle and directly into the inner liner, but does not allow for an individual to reach into the receptacle's contents.

(g) The receptacle shall be securely locked and substantially constructed, with a permanent outer container and a removable inner liner.

(1) The liner shall comply with provisions in this article. The receptacle shall allow deposit of prescription drugs into the receptacle for containment into the inner liner, without permitting access to or removal of prescription drugs already deposited into the collection receptacle and liner. Once a prescription drug or any other item is placed in the collection receptacle, the prescription drug or item cannot be removed, sorted, counted, or otherwise individually handled.

(2) If the liner is not already itself rigid or already inside of a rigid container when it is removed from the collection receptacle, the liner must be immediately placed in a rigid container for storage, handling and transport. A rigid container may be disposable, reusable, or recyclable. Rigid containers shall be leak resistant, have sealable tight-fitting covers, and be kept clean and in good repair.

(h) A liner as used in this article shall be made of material that is certified by the manufacturer to meet American Society for Testing Materials (ASTM) D1709 standard test for impact resistance of 165 grams (drop dart test), and the ASTM D1922 standards for tear resistance of 480 grams in both parallel and perpendicular planes.

(1) The liner shall be waterproof, tamper evident and tear resistant.

(2) The liner shall be opaque to prevent viewing and discourage removal of any contents once the liner has been removed from a collection receptacle. The liner shall be clearly marked to display the maximum contents (for example, in gallons). The liner shall bear a permanent, unique identification number.

(i) The collection receptacle shall contain signage that includes:

(1) The name and phone number of the responsible pharmacy;

(2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and

(3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

(j) Once deposited, the prescription drugs shall not be counted, sorted or otherwise individually handled.

(k) The installation, removal, transfer and storage of inner liners shall be performed only by:

(1) One employee of the authorized collector pharmacy and one supervisory level employee of the long-term care facility (e.g., a charge nurse or supervisor) designated by the authorized collector, or

(2) By or under the supervision of two employees of the authorized collector pharmacy.

(l) Sealed inner liners that are placed in a container may be stored at the skilled nursing facility for up to three business days in a securely locked, substantially constructed cabinet or a securely locked room with controlled access until transfer to a reverse distributor for destruction.

(m) Liners still housed in a rigid container may be delivered to a reverse distributor for destruction by common or contract carrier or by reverse distributor pickup at the skilled nursing facility.

(n) A pharmacy maintaining a collection receptacle in a skilled nursing facility shall make and keep the records as specified in 1776.6.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Sections 1304.22, 1317.05, 1317.40, 1317.60, 1317.75, 1317.80 and 1317.95, Title 21, Code of Federal Regulations

§ 1776.5. Reverse Distributors.

(a) A licensed reverse distributor (either a reverse wholesaler or a reverse third-party logistics provider) registered with the DEA may accept the sealed inner liners of collection receptacles at the reverse distributor's registered location by common or contract carrier pick-up, or by reverse distributor pick-up at the collector's authorized collection location. Once received, the reverse distributor shall establish records required by this section.

(b) A licensed reverse distributor may not open, survey, or otherwise analyze the contents of inner liners. All liners shall be destroyed by an appropriately licensed and registered DEA reverse distributor in a manner that makes the drugs irretrievable.

(c) If a reverse distributor picks up the sealed inner liners from the collector's authorized location, at least two employees of the reverse distributor shall be present. If the sealed inner liners are delivered to the reverse distributor via common or

contract carrier, at least one employee of the reverse distributor shall accept the receipt of the inner liners at the reverse distributor's registered location.

(d) A reverse distributor shall not employ as an agent or employee anyone who has access to or influence over controlled substances, any person who has been convicted of any felony offense related to controlled substances or who at any time had a DEA registration revoked or suspended, or has surrendered a DEA registration for cause.

(e) For each sealed liner or mail back envelopes or packages received pursuant to federal Title 21 CFR section 1317.55, the reverse distributor shall maintain records of the number of sealed inner liners or mail back envelopes or packages, including the:

- (1) Date of acquisition;
 - (2) Number and the size (e.g., five 10-gallon liners, etc.);
 - (3) Unique Identification number of each liner or envelope/package;
 - (4) The method of delivery to the reverse distributor, the signature of the individuals delivering the liners to the reverse distributor, and the reverse distributor's employees who received the sealed liner;
 - (5) The date, place and method of destruction;
 - (6) Number of packages and inner liners received;
 - (7) Number of packages and inner liners destroyed;
 - (8) The name and signature of the two employees of the registrant that witnessed the destruction.
- (e) For liners only, the information specified in subsection (e)(1)-(8) above shall be created at the time of receipt and at the time of destruction.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Section 1301.71, 1304.21, 1304.22, 1317.15, 1317.55 and 1317.95, Title 21, Code of Federal Regulations.

§ 1776.6. Record Keeping Requirements for Board Licensees Providing Drug Take-Back Services.

Each entity authorized by this article to collect unwanted prescription drugs from consumers shall maintain the records required by this article for three years.

(a) For pharmacies maintaining collection receptacles, the pharmacy shall make and keep the following records for each liner:

- (1) Date each unused liner is acquired, its unique identification number and size (e.g., 5 gallon, 10 gallon). The pharmacy shall assign the unique identification number if the liner does not already contain one.
- (2) Date each liner is installed in a collection receptacle, the address of the location where each liner is installed, the unique identification number and size (e.g., 5 gallon, 10 gallon), the registration number of the collector pharmacy, and the names and signatures of the two employees that witnessed each installation.
- (3) Date each inner liner is removed and sealed, the address of the location from which each inner liner is removed, the unique identification number and size (e.g., 5 gallon, 10 gallon) of each inner liner removed, the registration number of the collector pharmacy, and the names and signatures of the two employees that witnessed the removal and sealing.
- (4) Date each sealed inner liner is transferred to storage, the unique identification number and size (e.g., 5 gallon, 10 gallon) of each inner liner stored, and the names and signatures of the two employees that transferred each sealed inner liner to storage.
- (5) Date each sealed inner liner is transferred for destruction, the address and registration number of the reverse distributor or distributor to whom each sealed inner liner was transferred, the unique Identification number and the size (e.g., 5 gallon, 10 gallon) of each liner transferred, and the names and signatures of the two employees who transferred each sealed inner liner to the reverse distributor or distributor, or the common carrier who delivered it, the company used, and any related paperwork (invoice, bill of lading).

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code; and Section 1304.22, Title 21, Code of Federal Regulations.

Attachment 4

Opioid Safety: Focus on Furnishing Naloxone

A GUIDE FOR CALIFORNIA COMMUNITY PHARMACISTS



Purpose of this guide

Community pharmacists are uniquely poised to engage in efforts to reduce opioid misuse and opioid related overdose. Pharmacists are often in the difficult position of distinguishing between patients in dire need of pain relief and patients struggling with addiction to opioids.

Pharmacists can effectively address and significantly impact our current epidemic of opioid misuse and overdose because they are trusted, knowledgeable, and accessible members of our communities.

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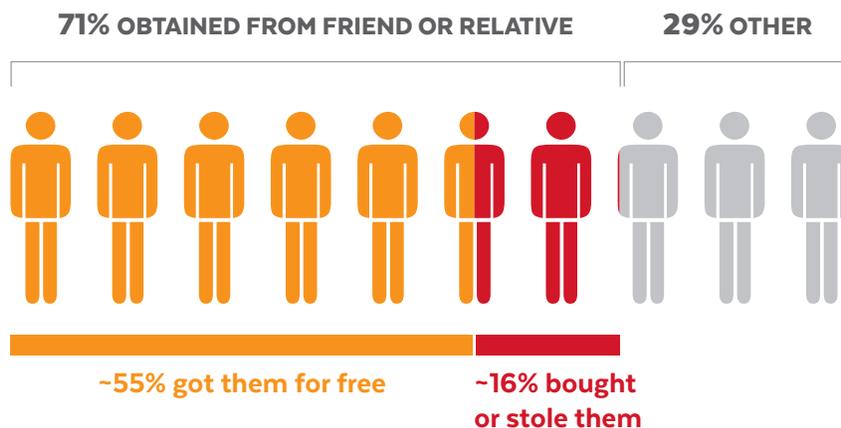
Epidemiologic trends in opioid use and overdose

➤➤ Since 1999, sales of prescription opioids in the U.S. have **quadrupled**.¹



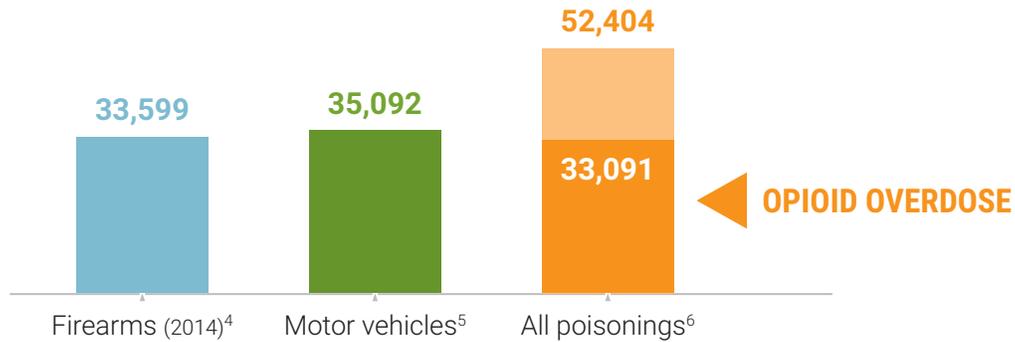
➤➤ In 2014, **10.3 million persons** reported using prescription opioids non-medically.²

➤➤ **71% of people who abuse prescription opioids get them from a friend or relative.**³

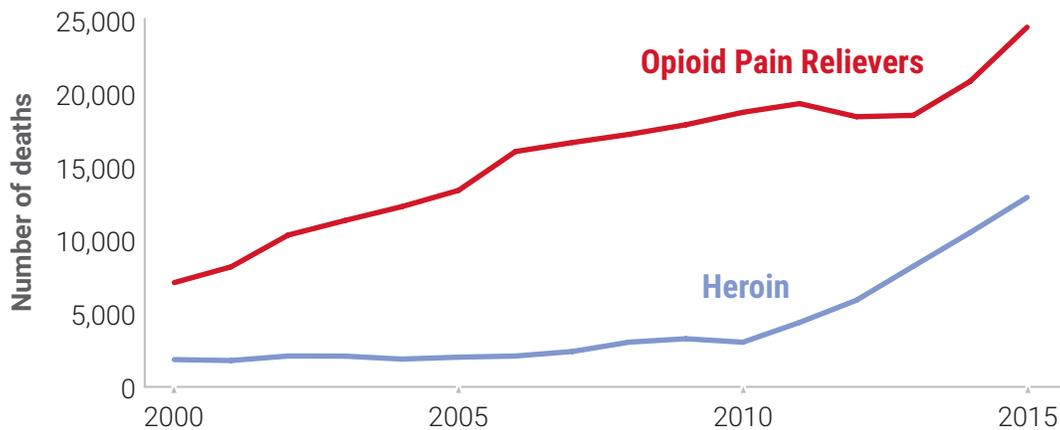


Overdose deaths

DRUG OVERDOSE IS THE LEADING CAUSE OF INJURY-RELATED DEATH IN THE U.S.⁴



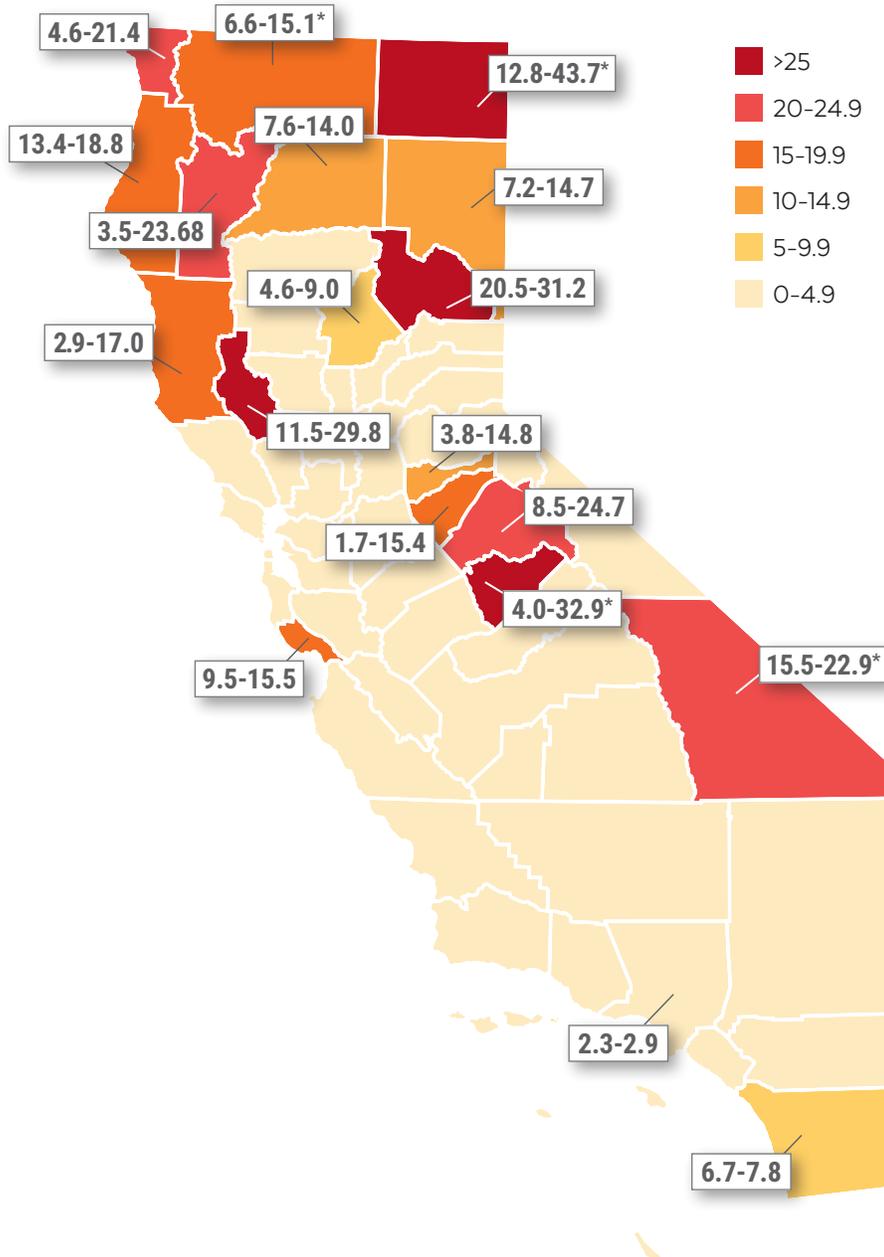
DRUG OVERDOSE DEATH RATES, INCLUDING THOSE INVOLVING PRESCRIPTION OPIOIDS AND HEROIN, CONTINUE TO INCREASE IN THE U.S.⁷



91
AMERICANS die every day from an opioid overdose
(that includes prescription opioids and heroin)⁸

Opioid overdose deaths in California

AGE-ADJUSTED RATE PER 100,000 RESIDENTS BY COUNTY, 2012-2016⁹



*The following counties had zero deaths in noted years. **Inyo:** 2012, 2014, 2015. **Mariposa:** 2016. **Modoc:** 2015, 2016. **Plumas:** 2016. **Siskiyou:** 2013.

The community pharmacist's role in opioid safety



It is clear we are amid an epidemic.

To halt the epidemic, new cases of opioid addiction must be prevented and access to treatment for those who have already developed a substance use disorder must be expanded.



Make a positive impact

- **Ensure the appropriate use of opioids.** Be well-versed in pain management and work with prescribers and patients to appropriately manage pain.
- **Read the CDC Guideline for Prescribing Opioids for Chronic Pain**, which addresses how to optimally manage pain while preventing opioid use disorder (dependence, addiction, abuse) and overdose. The guideline was developed to:
 - Improve communication between providers and patients about risks and benefits of opioids
 - Improve safety and effectiveness of pain treatment
 - Reduce risks associated with long-term opioid therapy, including opioid use disorder and overdose
- **Recognize legitimate uses for opioids**, including short-term treatment of acute pain, cancer pain, or end-of-life care.
- **Limit access to opioids for illegitimate use.** For red flags, refer to *California's Prescription Drug Monitoring Program (PDMP): Controlled Substances Utilization Review and Evaluation System (CURES)*.
- **Become aware of treatment resources** in your community and refer patients for medication-assisted treatment (MAT) with methadone or buprenorphine.
- **Provide opportunities for drug destruction and take-back** for individuals in the community to dispose of controlled substances safely: [tinyurl.com/3ogb85c](https://www.tinyurl.com/3ogb85c).
- **Educate individuals at risk for overdose about, and expand access to, life-saving naloxone.**



Access the CDC Guideline for Prescribing Opioids for Chronic Pain: [tinyurl.com/kdy59jc](https://www.tinyurl.com/kdy59jc)





Evaluate opioid prescriptions

Validity:

- Has prescription been forged or altered?
- Has prescriber's DEA number been verified?
- Is prescription within the prescriber's scope of practice?
- Has patient's identity been verified?
- Has CURES been checked?



Appropriateness:

- Is opioid indicated for patient's pain?
- Have other agents been tried?
- Is current regimen meeting treatment goals?
- Can opioids be reduced to a lower dosage or discontinued?

Safety:

- Are there any medications that may interact (e.g., benzodiazepines)?
- Is patient using alcohol or illicit substances?



Look for red flags

Look for signs of opioid use disorder or diversion of prescription opioids. CURES will help identify some of these red flags.

- Forged prescriptions presented with unusual wording or abbreviations, absence of typical abbreviations, overly meticulous writing, or an unusual signature
- Altered prescriptions presented with multiple colors, ink types, or handwriting styles on one prescription
- Patients or prescriptions originating from outside the local geographic area
- Prescribers practicing outside their scope of practice
- Prescriptions for high dosages or high quantities
- Patients appearing intoxicated
- Patients who pay with cash only
- Patients who ask for early refills
- Patients with multiple prescribers or multiple pharmacies



If prescription opioid misuse is suspected:

- Consider pharmacists' corresponding responsibility in ensuring prescriptions are legal and not for purposes of abuse: tinyurl.com/mqmxlpb.
- When misuse is suspected, a pharmacist should contact the prescriber to obtain more information. If a pharmacist cannot determine validity of a prescription, the prescription should be refused until validity can be determined.



Assess for risk of overdose

Patients at highest risk of overdose include:

- Those who have had a prior overdose
- Those taking higher doses of opioids (≥ 50 morphine milligram equivalents or MME/day; resource for calculating MME: tinyurl.com/lvfdksv)
- Those who use opioids while they are alone (not at greater risk for overdose, but at greater risk for fatal overdose)
- Those with reduced tolerance, e.g., period of abstinence (including incarceration or rehab) or a change in dose
- Those using other substances concomitantly, particularly alcohol, benzodiazepines, or cocaine
- Those with chronic medical illnesses that impact lung, liver, and kidney functions





How to talk about opioids

Communicating with patients

General tips:

- Be empathic. Don't be judgmental.
- Ask open-ended questions.
- Use active listening techniques.
- Use clear words. Avoid technical verbiage.
- The approach should be "risky medicines" not "risky patients."
- The term "overdose" carries stigma especially to prescription opioid users. Use terms such as "toxicity," "bad reaction," and "antidote."
- Direct patients to additional resources.



Questions you might ask to engage patients:

- What medications are you currently taking?
- What pain medications have you taken and how have they worked for you?
- How well is your medication working to relieve your pain?
- What other ways do you have to help manage your pain?
- Are you experiencing any side effects from your medications?
- Do you know which medications you should avoid taking with your opioid medication?
- Do you have any questions for me about any of your medications?

Provide education about:

- Pain management
- Proper use of opioids, including dosing and refill expectations
- Avoiding alcohol, benzodiazepines, and other CNS depressants when taking opioids
- Safe and secure storage which restricts access to others, and safe disposal of unused medication
- Opioid use disorder (provide resources and referral to treatment)
- Risks and signs of opioid overdose (provide resource such as "Opioid safety and how to use naloxone" trifold)
- Use of naloxone to reverse overdose



How to talk about opioids *(continued)*

Communicating with prescribers

When to call prescribers:

- Fraudulent prescription presented
- Patient appears intoxicated
- CURES elicits concern (e.g., multiple prescribers)
- Patient taking other CNS depressants (e.g., benzodiazepines)
- Patient presenting early for refill

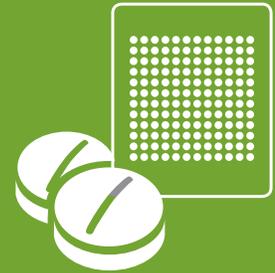


Benefits of communicating with prescribers:

- Collaborate with prescribers to optimize pain management for patients.
- Reduce potential for misuse or diversion by communicating about any red flags.
- Reduce potential for overdose by discussing concerns about concurrent medication or substance use.
- Provide recommendations to prescribers when medication assisted treatment (MAT) for opioid use disorder is indicated.
- Identify prescribers in your community who are pain management specialists.
- Identify prescribers in your community who provide MAT.



Treating opioid use disorder: medication-assisted treatment



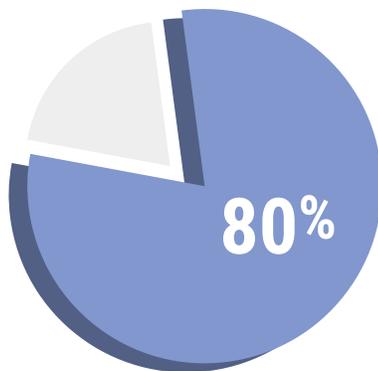
Use of medication-assisted treatment (MAT) has been shown to increase recovery rates, decrease overdose deaths, decrease criminal activity, and lower the risk of infections such as HIV and hepatitis C.



Overview

Medication-assisted treatment (MAT) is the use of medications such as buprenorphine, methadone, and extended release naltrexone, often in combination with counseling and behavioral therapies, to treat opioid use disorder.

- Barriers to MAT include stigma of addiction (substance use disorder), not recognizing opioid use disorder, a lack of awareness of treatments available, lack of physician training, and limited access to treatments and treatment providers.
- For more information and a detailed resource on MAT, go to tinyurl.com/lca54te for documents such as:
 - “Recovery Within Reach: Medication-Assisted Treatment of Opioid Addiction Comes to Primary Care”
 - “Primary Care Buprenorphine Programs: Ten Elements of Success”
 - “Buprenorphine: Everything You Need to Know”



Nearly 80% of those with an opioid use disorder don't receive treatment.¹⁰



Buprenorphine

Formulations

STANDARD FOR OPIOID USE DISORDER:

- Coformulated buprenorphine/naloxone SL tab
- Coformulated buprenorphine/naloxone film or implant



IF PATIENT DOES NOT TOLERATE/CANNOT ACCESS COFORMULATED PRODUCTS:

- Monoformulated buprenorphine SL tablets



Clinical pearls

- Partial opioid agonist with very high affinity, blocking effects of other opioids; 36 hour half life
- “Ceiling effect” due to partial agonism; lower potential for misuse, diversion, respiratory depression, and overdose than other opioids
- Reduced potential for diversion or injection due to coformulation with naloxone; combination product favored except in pregnant women
- Separate registration with DEA to obtain waiver, or “X” number, required to prescribe buprenorphine for opioid use disorder
- Patients treated in the office or at home
- Exhibition of mild to moderate opioid withdrawal symptoms before initiation; severe withdrawal symptoms if buprenorphine started too early
- Generally prescribed in very limited quantities to ensure close follow up, particularly early in treatment; opportunities for pharmacist to actively assist patients in treatment for opioid use disorder



Buprenorphine *(continued)*

Patient counseling tips

- **Sublingual tablets or film should be kept under tongue and buccal film should be placed on the inside of cheek until completely dissolved.** Due to low oral bioavailability, swallowing will result in reduced effect and may induce withdrawal symptoms.
- **Tablets, sublingual film, and buccal film are not equivalent;** some patients may require a change in dose when transitioning from one product to another.
- **Avoid combining with other CNS depressants,** such as alcohol or benzodiazepine, as this can increase the risk for respiratory depression and overdose toxicity. However, while the combination may increase risk, medication assisted treatment should not be withheld from patients taking other CNS depressants and buprenorphine may be a safer option than methadone.
- **Store in a safe and secure location** to prevent accidental ingestion by others.



Methadone

Clinical pearls

- Full opioid agonist
- Methadone for pain prescribed then dispensed by pharmacies, but methadone for opioid use disorder only dispensed through opioid treatment programs
- Long half life (up to 60 hours), may accumulate
- QT prolongation and increased risk for serious arrhythmias
- Potential for drug interactions
- Respiratory depression and overdose risk
- Methadone dispensed from opioid treatment programs not reported to CURES (prescriptions dispensed at pharmacies reported)

Patient counseling tips

- **Many medications may interact with methadone;** check with physician or pharmacist anytime you start or stop a new medicine.
- **Report excessive sedation, shallow breathing, or dizziness** to physician.
- **Avoid combining with other CNS depressants,** such as alcohol or benzodiazepine, as this can increase the risk for respiratory depression and overdose toxicity. However, while the combination may increase risk, medication assisted treatment should not be withheld from patients taking other CNS depressants.



Extended release naltrexone

Clinical pearls

- Opioid antagonist; blocks euphoric effects of opioid agonists
- No addiction potential; not a controlled substance; may be prescribed by any prescriber
- More effective than oral naltrexone for opioid use disorder but less favored by patients compared to buprenorphine or methadone
- Withdrawal may be precipitated if agonists (full or partial) are on board; must be 7-10 days without other opioids before starting naltrexone (up to 14 days after discontinuing long-acting opioids such as buprenorphine or methadone)
- Increased risk for overdose during washout period prior to starting treatment, or during treatment if large amounts of opioids used to overcome naltrexone's opioid blockade
- Increased risk of overdose with relapse after ER naltrexone discontinuation due to loss of tolerance
- Improved adherence with monthly dosing

Patient counseling tips

- Because a patient's tolerance to opioids may be reduced, the patient's risk for overdose is increased during the waiting period to initiate naltrexone and after stopping naltrexone.

Providing access to naloxone



Naloxone saves lives

Naloxone is a highly specific, high-affinity opioid antagonist used to reverse the effects of opioids.

In California, a licensed pharmacist may furnish naloxone by following the California State Board of Pharmacy protocol (16 CCR §1746.3):

[tinyurl.com/l25elze](https://www.tinyurl.com/l25elze)



Requirements of naloxone protocol in California

Naloxone prescriptions are treated like any other prescription. However, to furnish naloxone (dispense with the pharmacist as prescriber), pharmacist must:

- **Meet a training/CE requirement** of either one hour of approved CE specific to naloxone administration or an equivalent curriculum-based training in a board recognized school of pharmacy.
- **Screen the recipient of naloxone (or family member/friend)** to determine if the patient uses or has a history of using illicit or prescription opioids, or has a known hypersensitivity to naloxone. Screening questions are available in different languages from the Board of Pharmacy: [tinyurl.com/I45d5c3](https://www.tinyurl.com/I45d5c3).
- **Educate the person receiving the naloxone product regarding:**
 - Overdose prevention, recognition, and response
 - Safe administration of naloxone (dosing, effectiveness, storage conditions, shelf-life)
 - Potential side effects
 - Importance of seeking emergency medical care
 - Availability of drug treatment programs
 - Educational counseling may not be waived by the person receiving naloxone
- **Provide the naloxone fact sheet when furnishing naloxone.** This can be found in various languages on the Board of Pharmacy website: [tinyurl.com/I45d5c3](https://www.tinyurl.com/I45d5c3).
- **Notify patient's primary care provider if the naloxone is provided** to the intended patient and consent (either verbal or written) is given by the patient.
- **Maintain records of furnishing naloxone for at least three years** (e.g., prescription in the pharmacy database with the pharmacist as the prescriber on record).
- If naloxone is furnished to a third party (not the ultimate recipient of the rescue medication), the patient on record is the third party recipient.





Identifying patients for naloxone

- Patients who have previously experienced opioid intoxication or overdose
- Patients with recent period of opioid abstinence and reinitiation of opioid
- Patients on long-term opioid therapy, on high dose opioids (≥ 50 morphine milligram equivalents/day), or those with recent increase in dosage
- Patients with a history of nonmedical use of opioids or other substance use disorder (including, but not limited to, alcohol, marijuana, cocaine, methamphetamines)
- Patients on long-acting opioids (e.g., methadone, fentanyl patch) or on regimens of multiple opioids
- Patients on concurrent benzodiazepine or other CNS depressant
- Patients requesting access to naloxone
- Family members or friends of any patient meeting above criteria or anyone at risk of witnessing an overdose





How to furnish, order, and bill for naloxone

- **Obtain a National Provider Identifier (NPI)** to allow you to be the prescriber on record: <https://nppes.cms.hhs.gov>.
- **Pharmacists who prescribe/furnish medications must enroll with Medi-Cal** for the purpose of ordering, referring, or prescribing (ORP): tinyurl.com/k88vqgz.
- **Collect resources to have on hand:**
 - Naloxone products (see formulations on pages 24-25)
 - > Commercially available nasal spray
 - > Auto-injector
 - > Single dose vials and syringes
 - > Prefilled syringes and atomizers
 - > Devices for lay use (branded nasal spray and auto-injector) offer ease of use and are marketed with patient education materials. If pricing and access are issues, provide generic products with educational materials referenced below.
 - Patient education materials: tinyurl.com/k35fnch
 - Training devices for demonstration purposes (break open from stock or request placebo trainers from manufacturers)
- **Develop onsite procedures for naloxone requests** and proactive criteria for patient selection. Train pharmacy employees to ensure procedure is executed consistently.
- **Naloxone is covered by Medi-Cal as a “carve-out” medication so submit directly to Fee For Service Medi-Cal**, NOT to the Managed Care Medi-Cal plan. It is also covered by many other plans. Prices for cash payments vary widely by formulation.
- **The atomizer used with the assembly-required intranasal prefilled syringe kit (page 25) does not have an NDC** and cannot be billed through usual pharmacy billing routes. Some pharmacies are willing to cover the cost of the atomizer or patients may be requested to pay the cash price (around \$5 per atomizer).



Educate patients and caregivers about preventing overdose



How to counsel patients and caregivers

- Only take medicine prescribed to you.
- Don't take more than prescribed; call your doctor if pain not controlled.
- Don't mix with alcohol or sleeping pills.
- Don't use alone; don't use opioids from an unknown source.
- Abstinence lowers tolerance; take less upon restart.
- Store in a secure place.
- Dispose of unused medications.
- Teach your family and friends how to respond to an overdose and how to use naloxone.
- If you are having difficulty taking opioids safely, I can refer you to help.





How to respond to an overdose

1 Recognize the signs of an overdose

- Slow or shallow breathing; gasping for air while sleeping; pale, clammy, or bluish skin or fingernails; slowed heartbeat; low blood pressure; won't wake up or respond (rub knuckles on sternum)

2 Call 911 and give naloxone

- Administer dose per instructions in patient education guides provided with naloxone products, or view educational videos online: [prescribetoprevent.org/patient-education/videos](https://www.prescribetoprevent.org/patient-education/videos).
- Assess response; give repeat dose if no or minimal response in 2-3 minutes.
- Lay the person on his or her side to prevent choking.
- Quick response improves survival.
- Say “Someone is unresponsive and not breathing.” Give clear address and location.

3 Follow 911 dispatcher instructions

- Clear airway, give rescue breaths if not breathing and/or chest compressions.
- With victim laying flat on back, put one hand on chin, tilt head back, pinch nose closed, make seal over mouth, and breathe 1 breath every 5 seconds. Chest should rise, not stomach.

4 Stay until help arrives—naloxone effects last 30-90 minutes

- Patient can go back into overdose if long-acting opioids were taken (e.g., fentanyl patch, methadone, extended release formulations of morphine or oxycodone).
- Following up naloxone administration with medical care is important.



Naloxone formulations

These devices are designed for lay use. Manufacturers provide written patient education.

INTRANASAL (NARCAN)

- Naloxone 4mg (two pack, NDC: 69547-353-02)
- Dispense #1
- SIG: Use as needed for suspected opioid overdose. Spray into one nostril upon signs of opioid overdose. Repeat into other nostril after 2-3 minutes if no or minimal response. Call 911.



AUTO-INJECTOR (EVZIO)

- Naloxone auto-injector 2mg (two pack, NDC: 60842-051-01)
- Dispense #1
- SIG: Use as needed for suspected opioid overdose. Inject IM into outer thigh, depress and hold for 5 seconds, as directed by voice prompt system upon signs of opioid overdose. Repeat with second device in 2-3 minutes if no or minimal response. Call 911.



Note: Evzio 0.4 mg auto-injector no longer manufactured.

- Inform patients to alert others about naloxone, how to use it and where it's kept, as it is generally not self-administered.
- Shelf life is 12-24 months; store at room temperature.
- Side effects include risk for withdrawal, anxiety, sweating, nausea/vomiting, or shaking.



Naloxone formulations (continued)

If the devices on the previous page are not available, dispense the following formulations and provide thorough education on assembly and use.

INTRANASAL—ASSEMBLY REQUIRED

- Naloxone 2mg/2ml prefilled needleless syringe (NDC: 76329-3369-01)
 - Dispense #2
 - SIG: Use as needed for suspected opioid overdose. Spray ½ of syringe into each nostril upon signs of opioid overdose. Repeat after 2-3 minutes if no or minimal response. Call 911.
- Mucosal atomizer device (MAD-300) nasal adapter produced by Teleflex
 - Dispense #2
 - Use as directed for naloxone administration.



Note: Atomizer considered durable medical equipment.

INJECTABLE

- Naloxone 0.4mg/ml 1ml single dose vial (NDC: Hospira 00409-1215-01; Mylan 67457-292-00)
 - Dispense #2
 - SIG: Use as needed for suspected opioid overdose. Inject 1 ml IM in shoulder or thigh upon signs of opioid overdose. Repeat after 2-3 minutes if no or minimal response. Call 911.
- 3ml syringe with 25g 1” needle
 - Dispense #2
 - Use as directed for naloxone administration.



Clinical pearls

- Can use 3ml syringe with 23-35 gauge 1-1.5 inch needles
- All components available at community pharmacies
- Third party reimbursement possible
- Some patients may not be comfortable with needles



Frequently asked questions

Who is the prescriber on record when naloxone is furnished by pharmacists?

The pharmacist who furnished the naloxone should be identified as the prescriber on record in the pharmacy prescription database using his or her individual National Provider Identifier.

What laws in California address health care providers prescribing or furnishing naloxone?

CALIFORNIA CIVIL CODE §1714.22

- Allows for licensed health care providers to prescribe naloxone to both persons at risk of an opioid overdose and their friends and family members (also known as third party prescribing).
- Provides protection to licensed health care providers acting with reasonable care from civil and criminal liability when they prescribe, dispense, or oversee naloxone distribution and for the lay persons who may administer naloxone to someone suspected of an opioid overdose.

What laws in California address lay persons possessing and administering naloxone?

CALIFORNIA CIVIL CODE §1714.22

- Provides protection for anyone who has received a prescription for naloxone from a prescriber, pharmacy, or overdose prevention program who possesses and administers naloxone during a suspected overdose.

CALIFORNIA HEALTH AND SAFETY CODE §11376.5

- Protects lay persons from arrest for use or possession of small amounts of drugs when seeking medical assistance for a suspected drug overdose.

Can a patient's insurance be billed for naloxone?

Yes, naloxone furnished under the statewide protocol can be billed to insurance companies. Although third party prescribing is permitted for naloxone, it must be billed under and dispensed to the person requesting it at the pharmacy.

Additional resources

Centers for Disease Control and Prevention (CDC) Clinical Tools: tinyurl.com/ltduw3v

- *Guideline for Prescribing Opioids for Chronic Pain*
- *Pharmacists: On the Front Lines*
- *Tapering Opioids for Chronic Pain*
- *Nonopioid Treatments for Chronic Pain*
- *Assessing Benefits and Harms of Opioid Therapy*
- *Calculating Total Daily Dose of Opioids for Safer Dosage*
- *Prescription Drug Monitoring Programs*
- **Free Opioid Guide App** (calculate total daily opioid dose, clinical guidance, motivational interviewing communication skills): tinyurl.com/kw4jbav
- **Prescription Opioids: What You Need to Know**: One-page patient education fact sheet for patients taking prescription opioids: tinyurl.com/n3ylg6p

Substance Abuse and Mental Health Services Administration (SAMHSA): www.samhsa.gov/medication-assisted-treatment

- Regulations, training resources, and treatment guidelines for medication-assisted treatment (MAT) of opioid use disorder with buprenorphine, methadone, and naltrexone
- Opioid treatment program directory (services locator)

College of Psychiatric and Neurologic Pharmacists (CPNP)

- **Opioid Use Disorders: Interventions for Community Pharmacists**: Guideline to educate community pharmacists on interventions to provide safe access to opioids while protecting communities from consequences of misuse: cpnp.org/guideline/opioid
- **Naloxone Access: A Practical Guide for Pharmacists**: Guideline to educate community pharmacists on increasing access to naloxone: cpnp.org/guideline/naloxone

Additional resources *(continued)*

Prescribe to Prevent: prescribetoprevent.org

- Information on prescribing and dispensing naloxone
- Resources targeted to prescribers and pharmacists
- Excellent resources for patient education including posters and videos
- Resources related to legal and advocacy issues

California State Board of Pharmacy Naloxone Information: tinyurl.com/l45d5c3

- Naloxone protocol
- Sample naloxone Rx labels
- Naloxone fact sheets for patients in several languages
- Naloxone screening questions in several languages

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About this publication

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The recommendations contained in this brochure are general and informational only; specific clinical decisions should be made by providers on an individual case basis.



SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH



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Design and layout: Amy Braddock

BOARD OF PHARMACY
ORDER OF ADOPTION

Add and Adopt §1746.3, which is new regulation text, as follows:

§1746.3 Protocol for Pharmacists Furnishing Naloxone Hydrochloride

~~(a)~~ A pharmacist furnishing naloxone hydrochloride pursuant to ~~Section~~ 4052.01 of the Business and Professions Code shall ~~follow the protocol specified in subdivision (b)~~ satisfy the requirements of this section.

~~(a)~~ As used in this section:

~~(1)~~ “Opioid” means naturally derived opiates as well as synthetic and semi-synthetic opioids.

~~(2)~~ “Recipient” means the person to whom naloxone hydrochloride is furnished.

~~(b)~~ Training. Prior to furnishing naloxone hydrochloride, pharmacists who use this protocol must have successfully completed a minimum of one hour of an approved continuing education program specific to the use of naloxone hydrochloride in all routes of administration recognized in subsection (c)(4) of this protocol, or an equivalent curriculum-based training program completed in a board recognized school of pharmacy.

~~(b)-(c)~~ Protocol for Pharmacists Furnishing Naloxone Hydrochloride. Before providing naloxone hydrochloride, the pharmacist shall:

~~(1)~~ Authority: Section 4052.01(a) of the California Business and Professions Code authorizes a pharmacist to furnish naloxone hydrochloride in accordance with a protocol approved by the California State Board of Pharmacy and the Medical Board of California. Use of the protocol in this section satisfies that requirement.

~~(2)~~ Purpose: To provide access to naloxone hydrochloride via standardized procedures so that pharmacists may educate about and furnish naloxone hydrochloride to decrease harm from opioid¹ overdose.

~~(3)~~ Procedure: When someone requests naloxone hydrochloride, or when a pharmacist in his or her professional judgment decides to advise of the availability and appropriateness of naloxone hydrochloride, the pharmacist shall complete the following steps:

¹For purposes of this protocol, “opioid” is used generally to cover both naturally derived opiates and synthetic and semi-synthetic opioids.

²These screening questions shall be made available in alternate languages for patients whose primary language is not English.

³For purposes of this protocol, “recipient” means the person to whom naloxone hydrochloride is furnished.

~~(A)-(1) Screen for the following conditions the potential recipient by asking the following questions:²~~

- ~~(i.)-(A) Whether the potential recipient³ currently uses or has a history of using illicit or prescription opioids. (If the recipient answers yes, the pharmacist may skip screening question B.ii and continue with Procedure);~~
- ~~(ii.)-(B) Whether the potential recipient is in contact with anyone who uses or has a history of using illicit or prescription opioids. (If the recipient answers yes, the pharmacist may continue with Procedure);~~
- ~~(iii.)-(C) Whether the person to whom the naloxone hydrochloride would be administered has a known hypersensitivity to naloxone.² (If the recipient answers yes, the pharmacist may not provide naloxone. do not furnish. If the recipient responds no, the pharmacist may continue.)~~

The screening questions shall be made available on the Board of Pharmacy's website in alternate languages for patients whose primary language is not English.

- ~~(B)-(2) Provide the recipient training in opioid overdose prevention, recognition, response, and administration of the antidote naloxone.~~
- ~~(C)-(3) When naloxone hydrochloride is furnished:~~
 - ~~(i.)-(A) The pharmacist shall provide the recipient with appropriate counseling and information on the product furnished, including dosing, effectiveness, adverse effects, storage conditions, shelf-life, and safety. The recipient is not permitted to waive the required consultation.~~
 - ~~(ii.)-(B) The pharmacist shall provide the recipient with any informational resources on hand and/or referrals to appropriate resources if the recipient indicates interest in addiction treatment, recovery services, or medication disposal resources at this time.~~
 - ~~(iii.)-(C) The pharmacist shall answer any questions the recipient may have regarding naloxone hydrochloride.~~

(4) Product Selection: Naloxone hydrochloride may be supplied as an intramuscular injection, intranasal spray, and auto-injector. Other FDA approved products may be used. Those administering naloxone should choose the route of administration based on the formulation available, how well they can administer it, the setting, and local context. A pharmacist shall advise the recipient on how to choose the route of administration based on the formulation available, how well it can likely be administered, the setting, and local context. A pharmacist may supply naloxone hydrochloride as an intramuscular injection, intranasal spray, auto-injector or in another FDA- approved product form. A pharmacist may also recommend optional items when appropriate, including alcohol pads, rescue breathing masks, and rubber gloves.

(5) Suggested Kit Labeling:

Intramuscular	Intranasal	Auto-Injector
<p>Naloxone 0.4mg/1ml single dose vial, # 2 vials SIG: Inject 1 ml intramuscularly upon signs of opioid overdose. Call 911. May repeat x 1.</p> <p>Syringe 3ml 25G X 1" # 2 SIG: Use as directed for naloxone administration.</p> <p>Kit should contain 2 vials and 2 syringes.</p>	<p>Naloxone needleless prefilled syringe (1mg/1ml concentration) 2ml, # 2 syringes SIG: Spray one half (1ml) of the naloxone into each nostril upon signs of opioid overdose. Call 911. May repeat x 1.</p> <p>Mucosal Atomization Device (MAD) # 2 SIG: Use as directed for naloxone administration.</p> <p>Kit should contain 2 prefilled needleless syringes and 2 atomizers.</p>	<p>Naloxone 0.4mg/0.4ml #1 twin pack SIG: Use one auto-injector upon signs of opioid overdose. Call 911. May repeat x 1.</p> <p>Kit is commercially available as a twin pack with directions for administration included.</p>

Optional items for the kits include alcohol pads, rescue breathing masks, and rubber gloves.

Kit labels shall include an expiration date for the naloxone hydrochloride furnished. An example of appropriate labeling is available on the Board of Pharmacy website.

(5) Labeling: A pharmacist shall label the naloxone hydrochloride consistent with law and regulations. Labels shall include an expiration date for the naloxone hydrochloride furnished. An example of appropriate labeling is available on the Board of Pharmacy's website.

(6) Fact Sheet: The pharmacist shall provide the recipient a copy of the current naloxone fact sheet approved by the Board of Pharmacy. This fact sheet shall be made available on the Board of Pharmacy's website in alternate languages for patients whose primary language is not English.

(7) Notifications: If the recipient of the naloxone hydrochloride is also the person to whom the naloxone hydrochloride would be administered, then the naloxone recipient is considered a patient for purposes of this protocol and notification may be required under this section.

If the patient gives verbal or written consent, then the pharmacist shall notify the patient's primary care provider of any drug(s) and/or device(s) furnished, or enter the appropriate information in a patient record system shared with the primary care provider, as permitted by the patient and that primary care provider.

If the patient does not have a primary care provider, or chooses not to give notification consent, then the pharmacist shall provide a written record of the drug(s) and/or device(s) furnished and advise the patient to consult an appropriate health care provider of the patient's choice.

(8) Documentation: Each naloxone hydrochloride product furnished by a pharmacist pursuant to this protocol shall be documented in a medication record for the naloxone recipient, and securely stored within the originating pharmacy or health care facility for a period of at least three years from the date of dispense. The medication record shall be maintained in an automated data processing or manual record mode such that the required information under title 16, sections ~~1717 and 1707.1 and 1717~~ of the California Code of Regulations is readily retrievable during the pharmacy or facility's normal operating hours.

~~(9) Training: Prior to furnishing naloxone hydrochloride, pharmacists who participate in this protocol must have successfully completed a minimum of one hour of an approved continuing education program specific to the use of naloxone hydrochloride, or an equivalent curriculum-based training program completed in a board recognized school of pharmacy.~~

~~(10)~~ (9) Privacy: All pharmacists furnishing naloxone hydrochloride in a pharmacy or health care facility shall operate under the pharmacy or facility's policies and procedures to ensure that recipient confidentiality and privacy are maintained.

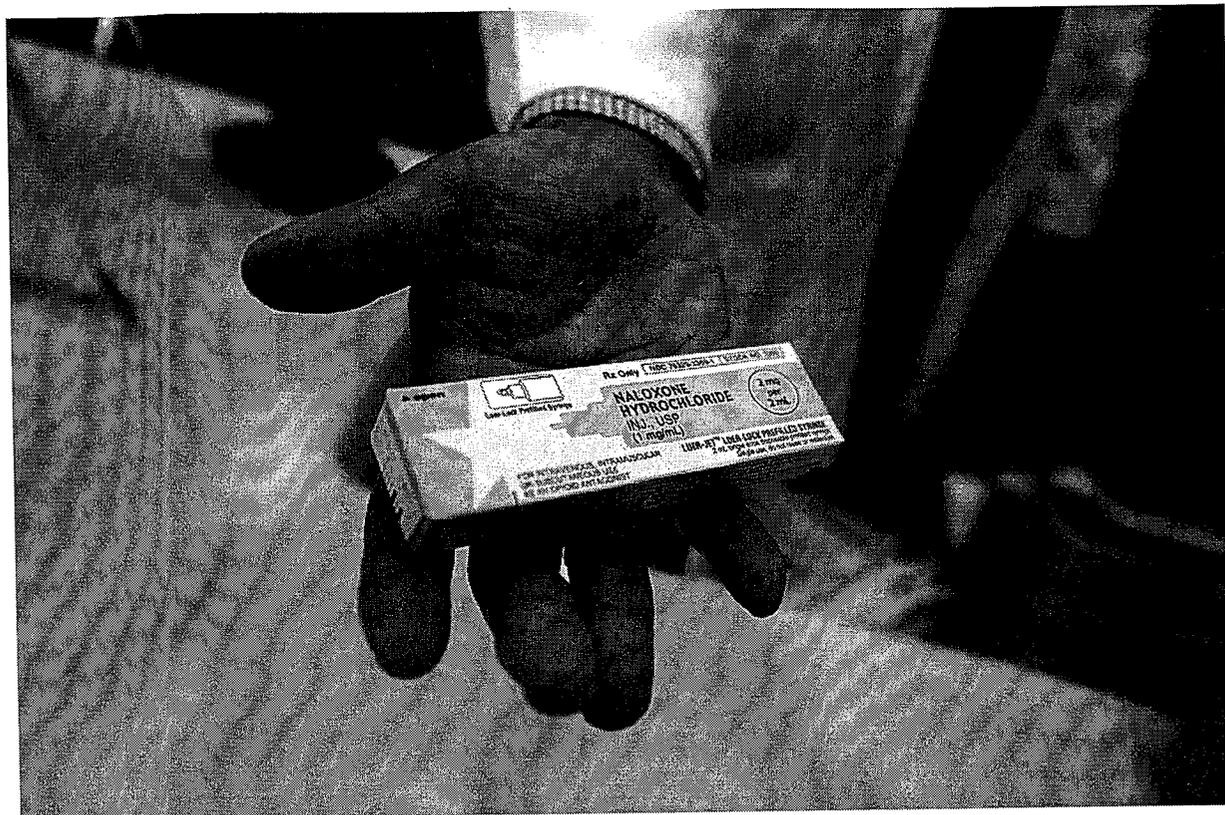
~~Authority and Reference:~~ Section 4052.01, Business and Professions Code.

Reference: Section 4052.01, Business and Professions Code.

Pharmacists Slow To Dispense Lifesaving Overdose Drug

By Anna Gorman (<https://californiahealthline.org/news/author/anna-gorman/>)

December 20, 2017



A pharmacist at a Walgreens store in New York City holds a box of the overdose antidote naloxone in 2016. Laws in most states, including California, allow pharmacists to provide naloxone without a doctor's prescription, but many don't do so. (Spencer Platt/Getty Images)

Gale Dunham, a pharmacist in Calistoga, Calif., knows the devastation the opioid epidemic has wrought, and she is glad the anti-overdose drug naloxone is becoming more accessible.

But so far, Dunham said, she has not taken advantage of a California law that allows pharmacists to dispense the medication to patients without a doctor's prescription. She said she plans to take the training required at some point but has not yet seen much demand for the drug.

"I don't think people who are heroin addicts or taking a lot of opioids think that they need it," Dunham said. "Here, nobody comes and asks for it."

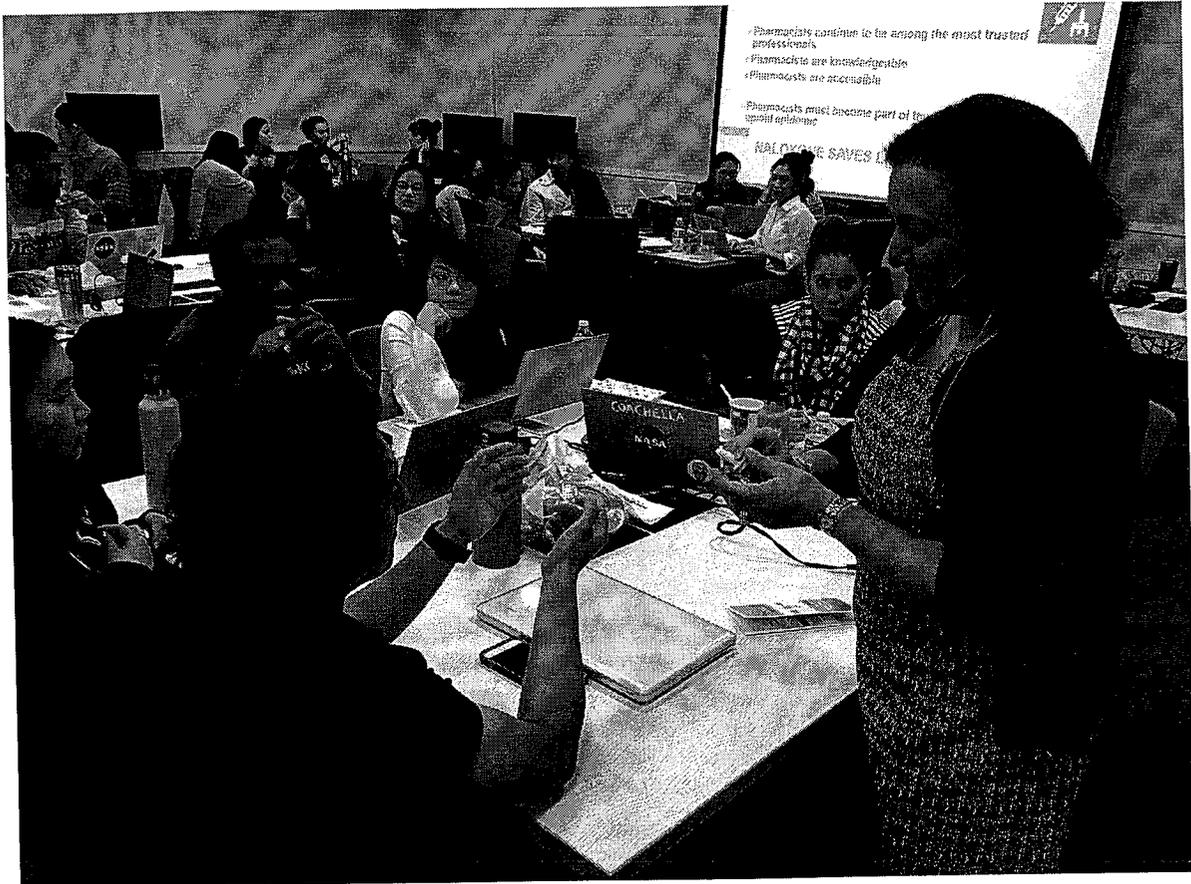
In the three years since the California law took effect, pharmacists have been slow to dispense naloxone, which reverses the effects of an overdose. They cite several reasons, including low public awareness, heavy workloads, fear that they won't be adequately paid and reluctance to treat drug-addicted people.

In 48 states and Washington, D.C., pharmacists have flexibility in supplying the drug without a prescription to patients, or to their friends or relatives, according to the National Alliance of State Pharmacy Associations. But as in California, pharmacists in many states, including Wisconsin and Kentucky, have divergent opinions about whether to dispense naloxone.

"The fact that we don't have wider uptake ... is a public health emergency in and of itself," said Virginia Herold, executive officer of the California State Board of Pharmacy. She said both pharmacists and the public need to be better educated about the drug.

Pharmacists are uniquely positioned to identify those at risk and help save the lives of patients who overdose on opioids, said Talia Puzantian, a pharmacist and associate professor of clinical sciences at Keck Graduate Institute School of Pharmacy in Claremont, Calif.

"There's a Starbucks on every corner. What else is on every corner? A pharmacy. So we are very accessible," Puzantian told a group of pharmacy students recently as she trained them on providing naloxone to customers. "We are interfacing with patients who may be at risk. We can help reduce overdose deaths by expanding access to naloxone."



Talia Puzantian, associate professor of clinical sciences at Keck Graduate Institute School of Pharmacy in Claremont, Calif., teaches students about naloxone, which reverses the effects of an opioid overdose. Puzantian got a federal grant to teach more pharmacists around California about naloxone. (Ivan Alber/Keck Graduate Institute)

Opioid overdoses killed 2,000 people in California and 15,000 nationwide in 2015.

Naloxone can be administered via nasal spray, injection or auto-injector. Prices for it vary widely, but insurers often cover it. The drug binds to opioid receptors, reversing the effect of opioids and helping someone who has overdosed to breathe again.

At least 26,500 overdoses were reversed from 1996 to 2014 because of naloxone administered by laypeople, according to the [National Institute on Drug Abuse \(https://www.drugabuse.gov/publications/naloxone-opioid-overdose-life-saving-science/naloxone-opioid-overdose-life-saving-science\)](https://www.drugabuse.gov/publications/naloxone-opioid-overdose-life-saving-science/naloxone-opioid-overdose-life-saving-science). Since then, the drug has become much more widely available among first responders, law enforcement officers and community groups. The drug is safe and doesn't have serious side effects, apart from putting someone into immediate withdrawal, according to the institute.

Information on how many pharmacists are dispensing naloxone is limited, but one [study \(https://californiahealthline.files.wordpress.com/2017/12/increase-in-nlx-rx-dispensed-in-us-since-2013-ajph-2016.pdf\)](https://californiahealthline.files.wordpress.com/2017/12/increase-in-nlx-rx-dispensed-in-us-since-2013-ajph-2016.pdf) last year showed access to the drug at retail pharmacies increased significantly from 2013 to 2015 from previously small numbers.

Interviews and available evidence from around the U.S. indicate that pharmacists have varying perspectives. In Kentucky, for example, one [study \(https://www.ncbi.nlm.nih.gov/pubmed/28139459\)](https://www.ncbi.nlm.nih.gov/pubmed/28139459) found that 28 percent of pharmacists surveyed were not willing to dispense naloxone.

In Pennsylvania, pharmacists weren't exactly lining up to hand out naloxone when the state passed a law in 2015 allowing them to do it, said Pat Epple, CEO of the Pennsylvania Pharmacists Association. She said there were some initial obstacles, including the cost of the drug and pharmacists' limited awareness of the law. The association worked with state health officials to raise awareness of naloxone among patients and pharmacists and reduce the stigma of dispensing it, Epple said.

Wisconsin is also among the states that allow pharmacists to dispense naloxone. Sarah Sorum, a vice president at the Pharmacy Society of Wisconsin, said the state's pharmacists want to expand their public health role and help curb the opioid epidemic. But reimbursement has been a challenge, she said.

Not all health plans across the nation cover the full cost of the drug, and pharmacists also are concerned about getting paid for the time it takes to counsel patients or their relatives.

California and other states require pharmacists to undergo training before they can dispense naloxone to patients who don't have a doctor's prescription. Puzantian and others say that in California not enough pharmacists are getting the training, which can be taken online or in person and can cost a few hundred dollars.

So far, the California State Board of Pharmacy has trained between 450 and 500 pharmacists, and the membership-based California Pharmacists Association has added an additional 170. Other smaller organizations offer the naloxone training, according to the association. There are about 28,000 licensed pharmacists in the state.

Once trained, California pharmacists who provide naloxone must screen patients to find out if they have a history of opioid use. They also must counsel people requesting the drug on how to prevent, recognize and respond to an overdose.

Some say training requirements are an unnecessary barrier, especially given the high level of education already required to become a pharmacist.

Some of the bigger pharmacy chains, including CVS, Rite Aid and Walgreens, have made the drug available without a prescription in the states that allow it. Walgreens has announced that it would stock the nasal spray version of naloxone at all of its pharmacies. It said it offers the drug in 45 states without requiring the patient to have a prescription.

Peter Lurie, president of the Center for Science in the Public Interest, said not every pharmacy has to dispense naloxone for people to have access to it. "But the greater the number of dispensing pharmacies the better," he said, adding that it is "especially important in more sparsely populated areas."

Corey Davis, deputy director of the Network for Public Health Law, said making naloxone available over the counter would also increase access, since people could buy it off the shelf without talking to a pharmacist.

Bryan Koschak, a community pharmacist at Shopko in Redding, Calif., said people should go to a hospital or doctor's office for naloxone. "I am not champing at the bit to do it," he said. "It is one more thing on my plate that I would have to do."

Michael Creason, a pharmacist in San Diego expressed a different view. He did the training after his employer, CVS, required it. He said pharmacies are a great vehicle for expanding access to naloxone because patients often develop a rapport with their pharmacists and feel comfortable asking for it.

Pharmacy associations should educate their members about the laws that allow naloxone to be provided without a doctor's prescription and persuade more of them to provide the drug to customers who need it, Lurie said. Others say more pharmacists should put up signs to make customers aware that naloxone is available in their shops.

The California Pharmacists Association said it is trying to raise awareness through newsletters and emails to pharmacists in the state. "We want to see every pharmacy be able to furnish naloxone and every person at risk have access to it," said Jon Roth, the association's CEO.

The state's pharmacy schools also include the training in their curriculum. One day recently, Puzantian explained to a classroom full of pharmacy students that naloxone is effective, safe and can prevent death.

"You can't get a dead addict into recovery," she told the students. Drug users "might have multiple overdoses, but each overdose reversal is a chance for them to get into recovery."

This story was produced by Kaiser Health News (<http://khn.org/>), an editorially independent program of the Kaiser Family Foundation (<http://kff.org/>).

Anna Gorman: agorman@kff.org (<mailto:agorman@kff.org>), [@AnnaGorman](http://twitter.com/AnnaGorman) (<http://twitter.com/AnnaGorman>)

Attachment)

Letters

RESEARCH LETTER

Availability of Pharmacist-Prescribed Contraception in California, 2017

California is 1 of 4 states currently permitting—but not requiring—pharmacists to prescribe contraception.¹ Since April 2016, patients can obtain hormonal contraceptive pills, injections, rings, and patches in California pharmacies offering this service.² After patients complete a health questionnaire (and, for combined hormonal contraception, a blood pressure reading), trained pharmacists determine medical eligibility for methods, conduct counseling, and prescribe contraception.² Although insurers are not required to reimburse pharmacies for this clinical service, pharmacies may charge patients fees.³

To date, the extent to which pharmacies are making pharmacist-prescribed contraception available under these nascent policies has not been estimated; this study does so at 1 year after implementation began in California.

Methods | The Office for Protection of Human Subjects at the University of California, Berkeley, deemed this study to be non-human subjects research. A telephone audit study of a representative sample of California pharmacies was conducted between February 2017 and April 2017. A list of all licensed pharmacies (n = 7048) was obtained from the California State Board of Pharmacy in October 2016. Hospital, clinic, university, and specialty and other non-full-service pharmacies (eg, long-term care, mail order) were identified and excluded. A random sample of 20% of included pharmacies was used—stratified by urbanity (census tract designation) and pharmacy type (retail chain or independent, defined as <5 locations). With a power level of 0.85 and an α of .05, the minimum sample size required to detect an effect size of 0.1 in χ^2 tests of independence comparing availability of pharmacist-prescribed contraception by urbanity or pharmacy type was 898.

To assess availability of pharmacist-prescribed contraception, trained interviewers used a structured data collection instrument. Posing as patients, interviewers called pharmacies and said: “I heard that you can get birth control from a pharmacy without a prescription from your doctor. Can I do that at your pharmacy?” If pharmacy staff responded affirmatively, interviewers inquired about service fees and method availability, documenting contraceptive methods spontaneously mentioned.

Proportions with 95% CIs, medians with interquartile ranges (IQRs), and χ^2 tests comparing differences in availability by urbanity and pharmacy type were estimated using Stata (StataCorp), version 13.1. Statistical significance was set at 2-tailed *P* value of less than .05.

Results | The sampling frame included 5291 community-based, retail pharmacies. A random sample of 1058 pharmacies was drawn, with data collected from 1008 (95.2%). Most pharmacies were urban (85.7%) and affiliated with chains (70.3%) (Table 1). Pharmacist-prescribed contraception was available in 11.1% (95% CI, 9.3%-13.2%) of pharmacies, with no significant availability differences by urbanity or pharmacy type. Among pharmacies offering this service (n = 112), 67.9% (95% CI, 58.5%-75.9%) indicated a specific fee requirement (median, \$45 [IQR, \$40-\$45]) (Table 2). Most chain pharmacies (86.3% [95% CI, 76.2%-92.6%]) had set fees compared with independent pharmacies (33.3% [95% CI, 20.2%-49.7%]) (*P* < .001). When queried about method availability, contraceptive pills were referenced most frequently (77.7%), followed by rings (40.2%), patches (38.4%), and injections (8.9%).

Discussion | One year after California pharmacists were permitted to prescribe contraception, a minority of pharmacies offered this service. Previous research highlights barriers to implementation, including concerns about training, liability,

Table 1. Availability of Hormonal Contraception Prescribed by a Pharmacist in California Pharmacies^a

	Total Pharmacies, No. (%)	Pharmacist-Prescribed Contraception Available, No. (%) [95% CI]	Pharmacist-Prescribed Contraception Not Available, No. (%) [95% CI]	<i>P</i> Value
Overall	1008 (100.0)	112 (11.1) [9.3-13.2]	896 (88.9) [86.8-90.7]	
Pharmacy type				
Chain	709 (70.3)	73 (10.3) [8.3-12.8]	636 (89.7) [87.2-91.7]	.21
Independent	299 (29.7)	39 (13.0) [9.7-17.4]	260 (87.0) [82.6-90.3]	
Setting				
Urban	864 (85.7)	96 (11.1) [9.2-13.4]	768 (88.9) [86.6-90.8]	>.99
Nonurban	144 (14.3)	16 (11.1) [6.9-17.4]	128 (88.9) [82.6-93.1]	

^a There were 1058 pharmacies sampled for inclusion. Data were not collected from 50 sampled pharmacies for the following reasons: no contact after 3 attempts (n = 22); pharmacy was permanently closed for business (n = 12);

pharmacy did not offer contraception (n = 9); no working phone number (n = 5); and availability of pharmacist-prescribed contraception was indeterminate after the phone call (n = 2).

Table 2. Characteristics of Pharmacist-Prescribed Hormonal Contraception in California Pharmacies

Characteristics	Pharmacies Offering Pharmacist-Prescribed Contraception, No. (%) [95% CI] (n = 112)	P Value
Pharmacy Service Fees for Prescribing Contraception		
Pharmacies with established fee requirements ^a	76 (67.9) [58.5-75.9]	
Fee requirements by pharmacy type		
Chain	63 (86.3) [76.2-92.6]	<.001
Independent	13 (33.3) [20.2-49.7]	
Fee requirements by urbanity		
Urban	65 (67.7) [57.6-76.4]	.93
Nonurban	11 (68.8) [42.2-86.9]	
Fee, median (IQR), \$	45.0 (40.0-45.0)	
Fee amounts		
<\$45	27 (35.5) [25.4-47.1]	
\$45	43 (56.6) [45.0-67.4]	
>\$45	6 (7.9) [3.5-16.7]	
Available Contraceptive Methods Spontaneously Mentioned by the Pharmacy Staff^b		
Oral contraception	87 (77.7) [68.9-84.5]	
Vaginal ring	45 (40.2) [31.4-49.6]	
Patch	43 (38.4) [29.7-47.8]	
Injectable contraception	10 (8.9) [4.8-15.9]	
Other ^c	16 (14.2) [8.9-22.2]	
Do not know	5 (4.4) [1.8-10.4]	

Abbreviation: IQR, interquartile range.

^a To assess fees for obtaining pharmacist-prescribed contraception, interviewers said, "I know my insurance covers birth control, but do I have to pay anything upfront?" When a fee range was provided, the midpoint was used to estimate the median. Data were missing for 6 pharmacies. In an additional 3 pharmacies, the staff member did not know whether a fee was required or not. Other responses were given by 5 pharmacies (4 indicated that the fees were dependent on insurance coverage; 1 pharmacy had not yet determined the fee amount).

^b To assess available contraceptive methods, interviewers said, "What type of birth control can I get?" and documented methods spontaneously mentioned. Availability of each method was not ascertained. Data were missing for 4 pharmacies.

^c Other responses included all methods; a method the caller had used in the past; and availability of methods will be determined based on health questionnaire responses.

and staffing.^{4,5} Most pharmacies offering pharmacist-prescribed contraception required a fee for this service, particularly retail chains. Even when contraception is available in pharmacies, it may not be economically accessible because of fees. In California, lack of insurance reimbursement may undergird low availability of pharmacist-prescribed contraception. Additional legislation (effective in July 2017) requires California's Medicaid program to reimburse for pharmacist services by July 2021⁶; the implementation timeline and lack of private insurance coverage may still present barriers to increasing availability of this service.

The strengths of this study include use of a large, representative sample of pharmacies and the high response rate. Limitations are assessment of service availability via phone and inclusion of only 1 state. Additionally, availability of each method was not systematically ascertained.

Pharmacist-prescribed contraception could facilitate contraceptive use for many women. With at least 9 states implementing or considering allowing pharmacist-prescribed contraception,¹ continued research is needed to identify barriers to accessibility of this clinical service.

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Author Contributions: Dr Gomez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Gomez.

Acquisition, analysis, or interpretation of data: Gomez.

Drafting of the manuscript: Gomez.

Critical revision of the manuscript for important intellectual content: Gomez.

Statistical analysis: Gomez.

Supervision: Gomez.

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BOARD OF PHARMACY
Department of Consumer Affairs

ORDER OF ADOPTION

Adopt §1746.1 of Article 5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

§ 1746.1 Protocol for Pharmacists Furnishing Self-Administered Hormonal Contraception.

(a) A pharmacist furnishing self-administered hormonal contraception pursuant to Section 4052.3 of the Business and Professions Code shall follow the protocol specified in subdivision (b) of this section.

(b) Protocol for Pharmacists Furnishing Self-Administered Hormonal Contraception

(1) Authority: Section 4052.3(a)(1) of the California Business and Professions Code authorizes a pharmacist to furnish self-administered hormonal contraceptives in accordance with a protocol approved by the California State Board of Pharmacy and the Medical Board of California. Use of the protocol in this section satisfies that requirement.

(2) Purpose: To provide timely access to self-administered hormonal contraception medication and to ensure that the patient receives adequate information to successfully comply with therapy.

(3) Definition of Self-Administered Hormonal Contraception: Hormonal contraception products with the following routes of administration are considered self-administered:

- (A) Oral;
- (B) Transdermal;
- (C) Vaginal;
- (D) Depot Injection.

(4) Procedure: When a patient requests self-administered hormonal contraception, the pharmacist shall complete the following steps:

- (A) Ask the patient to use and complete the self-screening tool;
- (B) Review the self-screening answers and clarify responses if needed;
- (C) Measure and record the patient's seated blood pressure if combined hormonal contraceptives are requested or recommended;
- (D) Before furnishing self-administered hormonal contraception, the pharmacist shall ensure that the patient is appropriately trained in

administration of the requested or recommended contraceptive medication.

- (E) When a self-administered hormonal contraceptive is furnished, the patient shall be provided with appropriate counseling and information on the product furnished, including:
1. Dosage;
 2. Effectiveness;
 3. Potential side effects;
 4. Safety;
 5. The importance of receiving recommended preventative health screenings;
 6. That self-administered hormonal contraception does not protect against sexually transmitted infections (STIs).

(5) Self-Screening Tool: The pharmacist shall provide the patient with a self-screening tool containing the list of questions specified in this protocol. The patient shall complete the self-screening tool, and the pharmacist shall use the answers to screen for all Category 3 and 4 conditions and characteristics for self-administered hormonal contraception from the current United States Medical Eligibility Criteria for Contraceptive Use (USMEC) developed by the federal Centers for Disease Control and Prevention (CDC). The patient shall complete the self-screening tool annually, or whenever the patient indicates a major health change.

A copy of the most recently completed self-screening tool shall be securely stored within the originating pharmacy or health care facility for a period of at least three years from the date of dispense.

This self-screening tool should be made available in alternate languages for patients whose primary language is not English.

(6) Fact Sheets:

(A) The pharmacist should provide the patient with a copy of a current, consumer-friendly, comprehensive birth control guide such as that created by the Food and Drug Administration (FDA). Examples of appropriate guides are available on the Board of Pharmacy's website.

(B) The pharmacist shall provide the patient with the FDA-required patient product information leaflet included in all self-administered hormonal contraception products, as required by Business and Professions Code Section 4052.3(c). The pharmacist shall answer any questions the patient may have regarding self-administered hormonal contraception.

(C) The pharmacist should provide the patient with a copy of an administration-specific factsheet. Examples of appropriate factsheets are available on the Board of Pharmacy's website.

(7) Follow-Up Care: Upon furnishing a self-administered hormonal contraceptive, or if it is determined that use of a self-administered hormonal contraceptive is not recommended, the pharmacist shall refer the patient for appropriate follow-up care to the patient's primary care provider or, if the patient does not have a primary care provider, to nearby clinics. A patient who is determined not to be an appropriate candidate for self-administered hormonal contraception shall be advised of the potential risk and referred to an appropriate health care provider for further evaluation.

(8) Notifications: The pharmacist shall notify the patient's primary care provider of any drug(s) or device(s) furnished to the patient, or enter the appropriate information in a patient record system shared with the primary care provider, as permitted by that primary care provider. If the patient does not have a primary care provider, or is unable to provide contact information for his or her primary care provider, the pharmacist shall provide the patient with a written record of the drug(s) or device(s) furnished and advise the patient to consult an appropriate health care professional of the patient's choice.

(9) Referrals and Supplies: If self-administered hormonal contraception services are not immediately available or the pharmacist declines to furnish pursuant to a conscience clause, the pharmacist shall refer the patient to another appropriate health care provider.

The pharmacist shall comply with all state mandatory reporting laws, including sexual abuse laws.

(10) Product Selection: The pharmacist, in consultation with the patient, may select any hormonal contraceptive listed in the current version of the USMEC for individuals identified as Category 1 or 2, based on the information reported in the self-screening tool and the blood pressure (if recorded by the pharmacist). The USMEC shall be kept current and maintained in the pharmacy or health care facility, and shall be available on the Board of Pharmacy's website.

Generic equivalent products may be furnished.

(11) Documentation: Each self-administered hormonal contraceptive furnished by a pharmacist pursuant to this protocol shall be documented in a patient medication record and securely stored within the originating pharmacy or health care facility for a period of at least three years from the date of dispense. A patient medication record shall be maintained in an automated data processing or manual record mode

such that the required information under title 16, sections 1717 and 1707.1 of the California Code of Regulations is readily retrievable during the pharmacy or facility's normal operating hours.

(12) Training: Prior to furnishing self-administered hormonal contraception, pharmacists who participate in this protocol must have completed a minimum of one hour of a board-approved continuing education program specific to self-administered hormonal contraception, application of the USMEC, and other CDC guidance on contraception. An equivalent, curriculum-based training program completed on or after the year 2014 in an accredited California school of pharmacy is also sufficient training to participate in this protocol.

(13) Patient Privacy: All pharmacists furnishing self-administered hormonal contraception in a pharmacy or health care facility shall operate under the pharmacy or facility's policies and procedures to ensure that patient confidentiality and privacy are maintained.

(14) Self-Screening Tool Questions

HORMONAL CONTRACEPTION SELF-SCREENING TOOL QUESTIONS

1	What was the first date of your last menstrual period?	/ /	
2a	Have you ever taken birth control pills, or used a birth control patch, ring, or shot/injection? (If no, go to question 3)	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2b	Did you ever experience a bad reaction to using hormonal birth control?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2c	Are you currently using birth control pills, or a birth control patch, ring, or shot/injection?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3	Have you ever been told by a medical professional not to take hormones?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4	Do you smoke cigarettes?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
5	Do you think you might be pregnant now?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
6	Have you given birth within the past 6 weeks?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
7	Are you currently breastfeeding an infant who is less than 1 month of age?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8	Do you have diabetes?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
9	Do you get migraine headaches, or headaches so bad that you feel sick to your stomach, you lose the ability to see, it makes it hard to be in light, or it involves numbness?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
10	Do you have high blood pressure, hypertension, or high cholesterol?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
11	Have you ever had a heart attack or stroke, or been told you had any heart disease?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12	Have you ever had a blood clot in your leg or in your lung?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
13	Have you ever been told by a medical professional that you are at a high risk of developing a blood clot in your leg or in your lung?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
14	Have you had bariatric surgery or stomach reduction surgery?	Yes <input type="checkbox"/>	No <input type="checkbox"/>

15	Have you had recent major surgery or are you planning to have surgery in the next 4 weeks?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
16	Do you have or have you ever had breast cancer?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
17	Do you have or have you ever had hepatitis, liver disease, liver cancer, or gall bladder disease, or do you have jaundice (yellow skin or eyes)?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
18	Do you have lupus, rheumatoid arthritis, or any blood disorders?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
19a	Do you take medication for seizures, tuberculosis (TB), fungal infections, or human immunodeficiency virus (HIV)?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
19b	If yes, list them here:		
20a	Do you have any other medical problems or take regular medication?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
20b	If yes, list them here:		

Authority: Sections 4005 and 4052.3, Business and Professions Code.

Reference: Sections 733, 4052, 4052.3 and 4103, Business and Professions Code.



Virginia Herold
Executive Officer
California State Board of Pharmacy

Attachment 6

FDA News Release

FDA proposes new, risk-based enforcement priorities to protect consumers from potentially harmful, unproven homeopathic drugs

FDA continues to find that some homeopathic drugs are manufactured with active ingredients that can create health risks while delivering no proven medical benefits

For Immediate Release

December 18, 2017

Summary

FDA is proposing a new, risk-based enforcement approach to homeopathic drug products that have the greatest potential to cause risk to patients.

Release

[Español \(/NewsEvents/Newsroom/ComunicadosdePrensa/ucm589885.htm\)](#)

Today, the U.S. Food and Drug Administration proposed a [new, risk-based enforcement approach \(/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM589373.pdf\)](#) to drug products labeled as homeopathic. To protect consumers who choose to use homeopathic products, this proposed new approach would update the FDA's existing policy to better address situations where homeopathic treatments are being marketed for serious diseases and/or conditions but where the products have not been shown to offer clinical benefits. It also covers situations where products labeled as homeopathic contain potentially harmful ingredients or do not meet current good manufacturing practices.

Under the law, homeopathic drug products are subject to the same requirements related to approval, adulteration and misbranding as any other drug product. However, prescription and nonprescription drug products labeled as homeopathic have been manufactured and distributed without FDA approval under the [agency's enforcement policies \(/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074360.htm\)](#) since 1988.

“In recent years, we’ve seen a large uptick in products labeled as homeopathic that are being marketed for a wide array of diseases and conditions, from the common cold to cancer. In many cases, people may be placing their trust and money in therapies that may bring little to no benefit in combating serious ailments, or worse – that may cause significant and even irreparable harm because the products are poorly manufactured, or contain active ingredients that aren’t adequately tested or disclosed to patients,” said FDA Commissioner Scott Gottlieb, M.D. “Our approach to regulating homeopathic drugs must evolve to reflect the current complexity of the market, by taking a more risk-based approach to enforcement. We respect that some individuals want to use alternative treatments, but the FDA has a responsibility to protect the public from products that may not deliver any benefit and have the potential to cause harm.”

The FDA’s proposed approach prioritizes enforcement and regulatory actions involving unapproved drug products labeled as homeopathic that have the greatest potential to cause risk to patients. Under this approach, many homeopathic products will likely fall outside the risk-based categories described in the new draft guidance and will remain available to consumers. The FDA intends to focus its enforcement authorities on the following kinds of products:

- products with reported safety concerns;
- products that contain or claim to contain ingredients associated with potentially significant safety concerns;
- products for routes of administration other than oral and topical;
- products intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions;
- products for vulnerable populations; and
- products that do not meet standards of quality, strength or purity as required under the law.

Examples of products that may be subject to the enforcement priorities in the draft guidance are infant and children’s products labeled to contain ingredients associated with potentially significant safety concerns, such as belladonna and nux vomica; and products marketed for serious conditions, such as cancer and heart disease.

While the FDA considers comments to the draft guidance, the FDA intends to examine how the agency is implementing its current compliance policy. Given the concerns about the proliferation of potentially ineffective and harmful products labeled as homeopathic, the FDA will consider taking additional enforcement and/or regulatory actions, consistent with the current enforcement policies, which also align with the risk-based categories described in the draft guidance, in the interest of protecting the public.

Homeopathy is an alternative medical practice developed in the late 1700s, based on two main principles: that a substance that causes symptoms in a healthy person can be used in diluted form to treat illness (known as “like-cures-like”); and the more diluted the substance, the more potent it is (known as the “law of infinitesimals”). Homeopathic drug products are prepared from a variety of sources, including plants, minerals, chemicals and human and animal excretions or secretions. These products are typically sold in pharmacies, retail stores and online.

Until relatively recently, homeopathy was a small market for specialized products. Over the last decade, the homeopathic drug market has grown exponentially, resulting in a nearly \$3 billion industry that exposes more patients to potential risks associated with the proliferation of unproven, untested products and unsubstantiated health claims. During this time, the FDA has seen a corresponding increase in safety concerns, including serious adverse events, associated with drug products labeled as homeopathic. In addition, the agency has also found an increasing number of poorly manufactured products that contain potentially dangerous amounts of active ingredients that can create additional risks.

In September 2016, the FDA warned against the use of [homeopathic teething tablets and gels](#) ([/NewsEvents/Newsroom/PressAnnouncements/ucm523468.htm](#)) containing belladonna, a toxic substance that has an unpredictable response in children under two years of age, after the products were associated with [serious adverse events](#) ([/Drugs/DrugSafety/InformationbyDrugClass/ucm523936.htm](#)), including seizures and deaths, in infants and children. An [FDA lab analysis](#) ([/Drugs/DrugSafety/InformationbyDrugClass/ucm538669.htm](#)) later confirmed that certain homeopathic teething tablets contained elevated and inconsistent levels of belladonna. A similar issue occurred in 2010 when [Hyland's Teething Tablets](#) ([/ForConsumers/ConsumerUpdates/ucm230762.htm](#)) were found to contain varying amounts of belladonna. An FDA inspection of that product's manufacturing facility indicated substandard control of the product's manufacturing.

The FDA has issued warnings related to a number of other homeopathic drug products over the past several years. These include certain homeopathic [zinc-containing intranasal products](#) ([https://wayback.archive-it.org/7993/20170113083935/http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm166931.htm](#)) that may cause a loss of sense of smell, [homeopathic asthma products](#) ([https://wayback.archive-it.org/7993/20170112131529/http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm439014.htm](#)) that have not been shown to be effective in treating asthma and various homeopathic drug products labeled to contain potentially toxic ingredients, like nux vomica, which contains [strychnine](#) ([/ICECI/EnforcementActions/WarningLetters/2017/ucm586501.htm](#)) (a highly toxic, well-studied poison often used to kill rodents).

"Homeopathic products have not been approved by the FDA for any use and may not meet modern standards for safety, effectiveness and quality," said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research. "The draft guidance is an important step forward in the agency's work to protect patients from unproven and potentially dangerous products."

In [April 2015 \(ssLINK/UCM430539\)](#), the FDA held a public hearing to obtain input from stakeholders about the current use of drug products labeled as homeopathic, as well as the agency's regulatory framework for these products. The FDA sought broad public feedback on its enforcement policies related to drug products labeled as homeopathic. As a result of the agency's evaluation, which included consideration of the information obtained from the public hearing and the more than 9,000 comments received to the agency's public docket, the FDA has determined that it is in the best interest of the public health to issue a new draft guidance that proposes a comprehensive, risk-based enforcement approach to drug products labeled as homeopathic and marketed without FDA approval.

The FDA is not alone in reexamining its approach to homeopathy. In November 2016, the Federal Trade Commission (FTC) announced a new [enforcement policy](#) ([https://www.ftc.gov/news-events/press-releases/2016/11/ftc-issues-enforcement-policy-statement-regarding-marketing](#)) explaining that they will hold efficacy and safety claims for over-the-counter homeopathic drugs to the same standard as other products making similar health claims. Notably, the FTC said that companies must have competent and reliable scientific evidence for health-related claims, including claims that a product can treat specific conditions.

The FDA encourages public comments on the draft guidance during the 90-day comment period.

The agency also encourages health care professionals and patients to report adverse events or quality problems experienced with homeopathic or any drug products to the FDA's MedWatch program:

- Complete and submit the report online at [www.fda.gov/medwatch/report.htm](#) ([https://www.fda.gov/medwatch/report.htm](#)); or
- Download and complete the [form](#) ([/downloads/AboutFDA/ReportsManualsForms/Forms/UCM349464.pdf](#)), then submit it via fax at 1-800-FDA-0178.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

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Consumers

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Related Information

- [FDA: Homeopathic Products \(/Drugs/DrugSafety/InformationbyDrugClass/ucm589282.htm\)](/Drugs/DrugSafety/InformationbyDrugClass/ucm589282.htm)
- [Draft Guidance on Drug Products Labeled as Homeopathic: Draft Guidance for FDA Staff and Industry \(PDF - 78KB\) \(/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM589373.pdf\)](/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM589373.pdf)
- [NIH/NCCIH: Homeopathy \(https://nccih.nih.gov/health/homeopathy\)](https://nccih.nih.gov/health/homeopathy)

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Drug Products Labeled as Homeopathic Guidance for FDA Staff and Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ 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 Dockets Management Staff (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 the Center for Drug Evaluation and Research (CDER) at 301-796-2089 or the Office of Communication, Outreach and Development (CBER), 800-835-4709 or 240-402-8010.

**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)**

**December 2017
Compliance**

Drug Products Labeled as Homeopathic Guidance for FDA Staff and Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
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Email: druginfo@fda.hhs.gov

*<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
and/or*

Office of Communication, Outreach and Development

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<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)**

**December 2017
Compliance**

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41 symptoms and illnesses (known as “like-cures-like”); and (2) the more diluted the substance, the
42 more potent it is (known as the “law of infinitesimals”). Proponents claim that a significantly
43 diluted aqueous solution, consisting mainly of water molecules, retains therapeutic properties
44 due to a “memory” of the substance diluted in it. Historically, homeopathic drugs have been
45 identified through “provings,” in which substances are administered to healthy volunteers in
46 concentrations that provoke overt symptoms. Symptoms experienced by volunteers are recorded
47 to indicate possible therapeutic uses for the substances. In other words, if a substance elicits a
48 particular symptom, individuals experiencing that symptom would be treated with a diluted
49 solution made from that substance.

50
51 In 1938, when the Federal Food, Drug, and Cosmetic Act (FD&C Act) was enacted, the bill’s
52 senatorial sponsor, Dr. Royal Copeland, himself a homeopathic practitioner, added a provision to
53 the law recognizing the Homeopathic Pharmacopoeia of the United States (HPUS) alongside its
54 counterparts, the U.S. Pharmacopeia and the National Formulary.³ Recent years have seen an
55 increase in the sale of products labeled as homeopathic. In the past, these products were mostly
56 prepared by homeopathic physicians for individual patients. Today they are frequently mass
57 manufactured and widely marketed as over-the-counter (OTC) products.

58
59 The definition of “drug” in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)) includes
60 articles recognized in the HPUS or any of its supplements. As such, homeopathic drugs are
61 subject to the same regulatory requirements as other drugs. Generally, a drug, including a
62 homeopathic drug, is considered a “new drug” if it is not generally recognized as safe and
63 effective (GRAS/E) by qualified experts for use under the conditions prescribed, recommended,
64 or suggested in the labeling (section 201(p) of the FD&C Act) (21 U.S.C. 321(p)). FDA makes
65 GRAS/E determinations for OTC drugs marketed under the OTC Drug Review.⁴ The FDA has
66 not reviewed any drug products labeled as homeopathic under the OTC Drug Review, because
67 the Agency categorized these products as a separate category and deferred consideration of them.
68 (37 FR 9464, 9466 (May 11, 1972)). Under section 505(a) of the FD&C Act (21 U.S.C. 355(a)),
69 before any “new drug” is marketed, it must be the subject of an approved application filed
70 pursuant to section 505(b) or section 505(j) of the FD&C Act; however, a biological product
71 with an approved license under section 351(a) of the Public Health Service Act (PHS Act) (42
72 U.S.C. 262(a)) is not required to have an approved application under section 505 of the FD&C
73 Act. Accordingly, absent a determination that a drug product labeled as homeopathic is not a
74 “new drug” under section 201(p), all drug products labeled as homeopathic are subject to the
75 premarket approval requirements in section 505 of the FD&C Act or section 351 of the PHS Act.
76 There are no drug products labeled as homeopathic that are approved by FDA.

77
78 The FDA’s evidence-based systems for the review of drugs under new drug applications
79 (NDAs), biologics license applications (BLAs), and the OTC Drug Review play an essential role
80 in ensuring that drugs are both safe and effective.⁵ Drugs marketed without required FDA
81 approval may not meet modern standards for safety, effectiveness, quality, and labeling. The

³ Section 201(g)(1) of the FD&C Act.

⁴ See 21 CFR part 330.

⁵ For instance, during the new drug application approval process the applicant must demonstrate that its manufacturing processes can reliably produce drug products of expected identity, strength, quality, and purity. 21 CFR 314.50(d)(1)(ii)(a).

82 continued marketing of products that have neither been approved by FDA nor found to be
83 GRAS/E is a public health concern.

84

85 **A. Compliance Policy Guide 400.400**

86

87 In May 1988, the Center for Drug Evaluation and Research issued Compliance Policy Guide
88 400.400 entitled “*Conditions Under Which Homeopathic Drugs May be Marketed.*” As stated in
89 the 1988 CPG, it delineates the conditions, including ones regarding ingredients, labeling,
90 prescription status, and current good manufacturing practice, under which homeopathic drug
91 products may ordinarily be marketed.

92

93 **B. FDA’s Reexamination of its Enforcement Policies**

94

95 In light of the growth of the industry and passage of more than 2 decades since the issuance of
96 the 1988 CPG, FDA announced on March 27, 2015, that it was evaluating its regulatory
97 framework for these products.⁶ In April 2015, FDA held a public hearing to obtain information
98 and comments from stakeholders about the current use of drug products labeled as homeopathic,
99 as well as the Agency’s regulatory framework for such products.⁷ FDA sought broad public
100 input on its enforcement policies related to drug products labeled as homeopathic in an effort to
101 better promote and protect the public health. As a result of the Agency’s evaluation, including
102 consideration of the information obtained as a result of the public hearing, FDA has determined
103 that it is in the best interest of public health to issue a new guidance that applies a risk-based
104 enforcement approach to drug products labeled as homeopathic and marketed without the
105 required FDA approval, consistent with FDA’s risk-based regulatory approaches generally.

106

107 **C. FDA’s Risk-based Approach**

108

109 In many instances, FDA uses a risk-based approach to carry out its mandates. For
110 example, FDA has generally employed a risk-based enforcement approach with respect to
111 marketed unapproved new drugs.⁸ The Agency historically has prioritized compliance
112 actions involving unapproved new drug products that have potential safety risks, lack
113 evidence of effectiveness, are health fraud products, present challenges to the new drug
114 approval or OTC drug monograph systems under the OTC Drug Review, are violative of
115 the FD&C Act in other ways, or that are reformulated to evade an FDA enforcement
116 action.

117

118 The Agency generally intends to apply a risk-based enforcement approach to the manufacturing,
119 distribution, and marketing of drug products labeled as homeopathic, as described below.

120

⁶ 80 FR 16327, *Homeopathic Product Regulation: Evaluating the Food and Drug Administration’s Regulatory Framework After a Quarter-Century.*

⁷ Docket No. FDA-2015-N-0540; available at <https://www.regulations.gov/docket?D=FDA-2015-N-0540>.

⁸ See *Marketed Unapproved Drugs - Compliance Policy Guide*, Section 440.100, September 19, 2011. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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III. FDA's ENFORCEMENT POLICY

The issuance of this guidance, when finalized, is intended to provide notice that any product labeled as homeopathic that is being marketed illegally is subject to FDA enforcement action at any time. FDA is not required, and generally does not expect, to give special notice that a drug product may be subject to enforcement action. However, in the listing that follows, we clarify our approach to prioritizing our enforcement actions with regard to drug products labeled as homeopathic and marketed in the United States without the required FDA approval.

Enforcement and Regulatory Priorities

In developing a risk-based approach, FDA has identified certain categories of drug products labeled as homeopathic and marketed without the required FDA approval as potentially posing higher risks to public health. FDA intends to prioritize enforcement and regulatory actions involving drug products labeled as homeopathic and marketed without the required FDA approval in the following categories:

- ***Products with reported safety concerns.*** For example, MedWatch reports or other information submitted to the Agency can indicate or signal a potential association between the product and an adverse event, medication errors, or other safety issues.
- ***Products that contain or purport to contain ingredients associated with potentially significant safety concerns.*** For example, potentially significant safety concerns are raised by products that contain or purport to contain:
 - An infectious agent with the potential to be pathogenic;
 - A controlled substance, as defined in the Controlled Substances Act, 21 U.S.C. 812;
 - Multiple ingredients that, when used in combination, raise safety concerns due to possible interactions, synergistic effects, or additive effects of the various ingredients; and,
 - Ingredients that pose potential toxic effects, particularly when those ingredients are concentrated or in low dilution presentations (e.g., 1X, 2X, or 1C), or are not adequately controlled in the manufacturing process.
- ***Products for routes of administration other than oral and topical.*** For example, unapproved injectable drug products and unapproved ophthalmic drug products pose a greater risk of harm to users due to their routes of administration (e.g., bypassing some of the body's natural defenses, differences in absorption) and the potential risk of harm from contamination.
- ***Products intended to be used for the prevention or treatment of serious and/or life-threatening diseases and conditions.*** Unapproved products for serious and/or life-threatening diseases and conditions raise public health concerns, in part, because they may cause users to delay or discontinue medical treatments that have been found safe and

166 effective through the NDA or BLA approval processes.

167

168 • ***Products for vulnerable populations.*** For example, patient populations such as
169 immunocompromised individuals, infants and children, the elderly, and pregnant women
170 may be at greater risk for adverse reactions associated with a drug product, even if it
171 contains only small amounts of an ingredient, due to their varying ability to absorb,
172 metabolize, distribute, or excrete the product or its metabolites. These populations may
173 also be at greater risk of harm as a result of foregoing the use of medical treatments that
174 have been found safe and effective through the NDA or BLA approval processes or under
175 the OTC Drug Review.

176

177 • ***Products deemed adulterated under section 501 of the FD&C Act.*** For example, if a
178 product purports to be or is represented as a product recognized in an official
179 compendium but its strength, quality, or purity differs from the standards set forth in that
180 official compendium (defined by 21 U.S.C. 321 as the official United States
181 Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official
182 National Formulary, or any supplement to any of them), or if there are significant
183 violations of current good manufacturing practice requirements.

184

185

Attachment 7

Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**November 2017
Clinical/Medical**

Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry

Additional copies are available from:

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<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**November 2017
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Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry¹

This guidance represents 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. 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist pharmaceutical sponsors in the evaluation of the effects of psychoactive drugs on the ability to operate a motor vehicle. Specifically, this guidance addresses the FDA's current thinking regarding FDA-regulated drugs for which such evaluation may be needed² and the types of studies that such an evaluation entails during clinical trials.

This guidance does not address the specific methods or instruments used to collect data on driving ability; rather, this guidance outlines the general principles and goals of such studies. Experience suggests that a number of methods may be suitable for providing the necessary data. For specific drug development programs, sponsors should discuss with the appropriate review division the study methods to be used.

This guidance also does not address the effects on driving ability from underlying disease, normal aging, or other factors unrelated to regulated drugs (e.g., distracted driving, aggressive driving). Although psychoactive drugs are the focus of this guidance, nonpsychoactive drugs may affect driving ability through effects on function, including intended effects and secondary effects (e.g., impaired consciousness from a hypoglycemic reaction to a glucose-lowering drug, impaired vision from a mydriatic drug). Therefore, the need to consider possible effects on driving ability is not limited to psychoactive drugs, and the approach to evaluating risk for nonpsychoactive drugs, which may differ substantially from the approaches described in this guidance, should be guided by drug-specific effects.

¹ This guidance has been prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

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.

II. BACKGROUND

Driving is a complex activity involving a wide range of cognitive, perceptual, and motor activities. Reducing the incidence of motor vehicle accidents (MVAs) that occur because of drug-impaired driving is a public health priority. A systematic effort to identify drugs that increase the risk of MVAs is a critical component of assessing drug risk and designing strategies to reduce this risk.

Drugs that impair driving ability may also impair an individual's ability to judge the extent of his or her impairment. Therefore, in general, patient self-perception is not adequate for evaluating the presence or degree of driving impairment or for mitigating risk. Instead, objective information about how a drug affects driving ability may be needed to enable safe use.

III. THE NEED TO EVALUATE DRIVING IMPAIRMENT

When determining whether to evaluate the effect of a drug on driving ability, sponsors should first consider the conditions for use of the drug and the intended patient populations. Drugs intended for chronic (including chronic-intermittent) outpatient use by adults are most likely to need evaluation of effects on driving ability. In contrast, drugs limited to use in young children or to use in hospital inpatient settings would not need such evaluation. FDA recommends that sponsors engage in early discussions with the appropriate review division to determine whether studies are needed in any given development program to evaluate drug effects on driving ability.

Drugs that have pronounced central nervous system (CNS) impairing effects and are intended to be administered primarily at night (e.g., drugs for insomnia and other sleep disorders) are of concern because residual daytime effects can impair driving ability.

In some cases, psychoactive drugs may appear to have the potential to *improve* driving performance, for example by decreasing somnolence (an established risk factor in MVAs). However, such drugs can have additional effects that increase the likelihood of driving impairment; for example, CNS stimulants may increase risk-taking (e.g., aggressive driving). Consequently, sponsors of psychoactive drugs should consider additional data on other functions important for safe driving.

Sponsors also may need to conduct driving studies if an active moiety approved for a particular use is proposed for a different indication, at a different dose or dosing schedule, or in a new patient population in which there is insufficient information about how the drug may affect driving ability. For example, drugs with well-known CNS depressant activity, such as

barbiturates and benzodiazepines, have been used in wide ranges of doses and schedules for a number of indications, from anxiety to insomnia to general anesthesia. Potential effects on driving ability may differ among the various uses and patient populations.

The driving impairment studies described in this guidance may be impossible to conduct in the intended patient population or may need modification for drugs associated with serious safety risks that prevent enrollment of healthy subjects. Depending on the specific circumstances, the risk of driving impairment might be adequately addressed using data that were feasible to collect combined with labeling that addresses remaining uncertainty. Sponsors should discuss such approaches with the relevant review division during drug development.

IV. TIERED APPROACH TO EVALUATING DRUG EFFECTS ON DRIVING ABILITY

A drug's effect on driving ability cannot be assessed using the risk of actual MVAs because using MVAs as endpoints in randomized controlled trials would be unethical. Instead, sponsors should use studies that assess the effects of a drug on CNS functions necessary for safe driving and, if necessary, driving tests to determine the potential for causing MVAs.

The FDA recommends evaluating impaired driving using a *tiered assessment*³ consisting of pharmacology/toxicology, epidemiology, and clinical/standardized behavioral assessments. With this approach, sponsors can use drug information obtained early in development to guide the need to collect data later in development related to driving impairment potential. This can ensure that resources are not unnecessarily expended on evaluating drugs with little to no potential for impairment or on tests of drugs that are so clearly impairing when used as indicated that a detailed study is unnecessary (e.g., drugs used for surgical anesthesia). Early in drug development, assessments should have high sensitivity for detecting impairment. Later in development, studies should be designed to characterize the clinical relevance of earlier findings. The following broad functional domains are important for driving ability and should be assessed with increasingly focused studies if accumulating data suggest a risk of clinically meaningful driving impairment:

- Alertness/arousal/wakefulness
- Attention and processing speed
- Reaction time/psychomotor functions
- Sensory-perceptual functioning
- Executive functions

³ Kay, GG and BK Logan, 2011, Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving, DOT HS 811 438, Washington, DC: National Highway Traffic Safety Administration.

A. Pharmacology/Toxicology

The chemical structure or receptor binding profile of a drug can suggest the potential to affect driving ability. For example, drugs with a benzodiazepine structure or that promote binding of gamma-aminobutyric acid to the drug's receptors are likely to have CNS depressant effects and will need close attention to depressant effects in clinical trials. However, structure and receptor binding alone may not be sufficient to conclude that a drug does *not* impair driving ability because cortical functions such as judgment are not well assessed in structure/binding studies. Similarly, the primary mechanism of action may not be adequate to provide reassurance about safety because unanticipated off-target actions can cause adverse effects.

The pharmacokinetic properties of a drug can be critical for evaluating the driving impairment risk that a drug may cause. Plasma or, if more relevant, brain tissue half-life is particularly important for drugs when the patient is expected to be active at night or at other times when the patient is typically not expected to be driving. Another important factor may be the extent of blood-brain barrier penetration, as illustrated by differences in somnolence caused by first- versus second-generation H₁ antihistamines related in part to differences in blood-brain barrier penetration.

Nonclinical studies may provide data useful for anticipating the potential for a drug to impair driving ability. In general, nonclinical studies for evaluating potential for impaired behavior should include an *in vitro* binding panel to assess on- or off-target pharmacologic targets of the drug, assays to assess the pharmacologic activity at the targets, and an *in vivo* CNS safety pharmacology study with careful assessment of signs potentially indicative of impaired CNS function. Sponsors should consider the pharmacological activity and pharmacokinetics of major circulating metabolites in humans, as well as the effect of the parent compound.

B. Use of Epidemiological Data

Evidence from drugs of the same or similar class, or with similar activity profiles, may raise concern about the effects of a drug on driving ability. Epidemiological data can also be useful for understanding how various factors related to actual clinical use (e.g., drug-disease interactions, drug-drug interactions, dosing errors) may impact the effect of a new drug on driving ability.

Epidemiological data may show an association between a specific illness (e.g., narcolepsy, obstructive sleep apnea) or a driver subset (e.g., young men) and an increased risk for MVA.⁴ Although the focus of this guidance is limited to drug effects on driving ability, taking epidemiological information about possible vulnerability to drug problems into consideration may be important when designing or interpreting driving studies.

Epidemiological data, however, are generally poorly suited to provide convincing evidence that a drug or drug class does or does *not* increase the risk of MVAs. MVAs are common, and even in

⁴ LeRoy, AA and ML Morse, 2008, Multiple Medications and Vehicle Crashes: Analysis of Databases, DOT HS 810-858, Washington, DC: National Highway Traffic Safety Administration.

patients with clinically meaningful impairment, many other factors contribute to the occurrence of a collision, decreasing the power of epidemiological studies to reliably identify increased risk from drug use, which is at worst only one factor among many increasing risks. Patient population and other disease-specific factors can also have a large effect on MVA risk.

Similarly, postmarketing adverse event reports are of limited use for identifying drugs that do or do not impair driving ability. First, there is limited ability to verify critical circumstances of use such as dose, timing, and concomitant use of other drugs or alcohol. In addition, the high background rate of MVAs and the recognized relation of MVAs to age, sex, driving experience, and many other factors are poorly documented in spontaneous reports. Finally, underreporting may occur if patients and providers are not aware that impairment from a drug may have contributed to an MVA.

C. Clinical/Behavioral Assessment

1. Phase 1 Drug Development Trials

Beginning with first-in-human trials, all drugs, including drugs intended for non-CNS indications, should be evaluated for adverse effects on the CNS (e.g., somnolence, agitation, dizziness). The occurrence of concerning adverse CNS events at clinically relevant exposures in even a small number of phase 1 subjects might indicate the need for more focused studies of CNS-impairing effects. However, if few adverse events are observed for a drug with no biologic plausibility of CNS effects, additional studies may not be warranted.

Early testing for CNS-impairing effects should generally emphasize sensitivity over specificity. Psychomotor and neuropsychological tests, including measures of reaction time, divided attention, selective attention, and memory may be appropriate. Early trials often include higher doses than will be used in later efficacy trials, which provides an opportunity to explore CNS-impairing effects at higher exposures. For drugs designed to affect sleep and wakefulness, directed studies such as the multiple sleep latency test or maintenance of wakefulness test may help to inform about both drug safety and efficacy. Subjective evaluation of CNS-impairing effects (e.g., by visual analogue scale) can contribute important information with respect to the strength of the correlation between subjective and objective impairment.

If there is initial evidence of impairing effects, additional studies should examine CNS impairment over the full range of drug exposures that may occur in phase 2 and 3 trials. Studies should include consideration of active metabolites and increased exposure in subpopulations such as those with genetic polymorphisms that lead to decreased levels of metabolizing enzymes or those with renal or hepatic insufficiency.

In studies primarily intended to examine CNS impairment, a positive control is critical for study interpretability. In general, negative studies in the absence of demonstrated assay sensitivity are not interpretable. Even for studies that show impairment, a positive control is useful to understand the magnitude and duration of impairment. Commonly used positive controls include ethanol, sedating antihistamines, and benzodiazepine-like drugs. Other positive controls may be appropriate and should be discussed with the FDA.

2. *Phase 2 and 3 Trials*

For drugs with potential effects on driving ability (e.g., drugs with sedating properties, drugs in early testing suspected of impairing CNS functions necessary for driving), it is particularly important that drug blood levels, including major active metabolites, should be measured during phase 2 and 3 trials. Sponsors should document factors that affect blood levels, such as time of dosing, food effects, and concomitant treatments (see IV. C.1., Phase I Drug Development Trials). The number and timing of blood concentration measurements should be adequate to support examination of exposure-response relationships. We recommend that sponsors share and discuss with the appropriate review division analysis plans to explore relationships between drug and active metabolite concentrations and potential effects on driving ability to confirm the adequacy of the analyses.

For drugs identified in early development as having a high potential to cause impairment, patients should be monitored at appropriate intervals during phase 2 and 3 trials for signs and symptoms that could place individuals at unacceptable risk. While this monitoring should be guided by adverse effects elicited in earlier-phase testing (e.g., somnolence, dizziness, depressed level of consciousness, disturbance in attention, hypersomnia, lethargy, mental impairment, stupor, altered state of consciousness, and drugged feeling), monitoring should be broad enough, as discussed below, to detect effects that might not have been previously identified, such as impaired executive function or memory (e.g., amnesia, memory impairment, retrograde amnesia, amnesic disorder, global amnesia).

Investigators should use both open-ended and targeted questions regarding adverse effects. Specific patient-reported outcomes that measure relevant symptoms, such as sleepiness scales, can help to quantify severity. Investigators should ask patients (and family members when appropriate) about their perceived driving ability; negative responses provide limited reassurance of safety, but positive reports of difficulty staying awake while driving or collision near misses are informative. Sponsors should specifically query patients about the occurrence of CNS symptoms such as inattention, sleepiness, and impaired judgement experienced while driving. In studies during phase 2 and 3 trials, sponsors should document to the degree possible the time of day and duration of adverse effects on the CNS because this information can characterize temporal effects on the risk of driving impairment.

Objective tests of psychomotor function, as described in section IV.C.1., Phase 1 Drug Development Trials, may also be needed to protect patient safety adequately. During phase 2 and 3 trials, sponsors should document to the degree possible the time of day and duration of adverse effects on the CNS because this information can characterize temporal effects on the risk of driving impairment. Sponsors should specifically query patients about the occurrence of adverse drug effects experienced while driving. The FDA encourages sponsors to collect data on actual MVAs and traffic violations in phase 3 trials, although such events are generally infrequent.

3. *Driving Studies*

If accumulating data suggest a potential for driving impairment, dedicated driving studies with higher specificity than more general tests of CNS function may be needed to refine assessment of the clinical effect of impairment. Sponsors can conduct such studies with either actual motor vehicles or driving simulators. Sponsors should consider the advantages and disadvantages of selected approaches and discuss any relevant issues with the appropriate review division. For instance, if the sponsor is conducting a driving study with a simulator, the sponsor should consider whether thresholds for impairment have been established and, if not, how to approach the establishment of a meaningful threshold.

Driving is a multifaceted activity and any given test of driving ability may not be capable of characterizing all of the different types of drug effects that can impair driving ability. For example, sustained ability to maintain driving lane position in a monotonous driving environment has been used to assess drug-related somnolence but may be substantially less informative with respect to executive functions, which may be better tested in driving scenarios presenting new or more demanding situations, such as those that might call for anticipatory adaptation of vehicle speed or go/no-go decisions. Sponsors should explain the rationale to support their selections of administered tests.

Sponsors should include positive control and placebo groups in dedicated driving studies. The positive control should be selected based on its ability to confirm assay sensitivity at the threshold of concern for clinically meaningful driving impairment. An important, but not the only, benchmark for sponsors to consider when selecting a positive control is the impairment caused by ethanol at various blood levels, including levels that are per se illegal for driving. An example of a positive control may be a drug that the FDA approved with detailed labeling regarding driving impairment.

Enrolling subjects in driving studies who are from the population likely to use the drug, including the elderly, is important for providing information about disease-drug interactions. In some cases, however, it might be possible to conclude that differences between healthy subjects and patients are sufficiently small to allow healthy subjects to be studied.

Generally, sponsors should conduct driving studies to evaluate both the effects of initial drug exposure and effects after chronic exposure. Drugs or active metabolites with a long half-life can result in markedly higher blood levels after multiple doses than occur after a single dose causing greater impairment with chronic, as compared to initial, use. Conversely, initial exposure to a drug may be more impairing than chronic exposure because there may be development of pharmacological tolerance or habituation over time. Testing of driving ability should take place when maximal levels of parent and/or active metabolite(s) are achieved. Even if tolerance develops, it is often incomplete and may only develop after an extended duration of exposure. Therefore, determining the time course and extent of any tolerance that develops can be important for instructing patients adequately about safe use.

Studies of driving impairment should include an assessment of drug effects at the highest relevant exposures expected to be encountered in clinical use. Therefore, sponsors should study

drug exposures at the highest therapeutic doses and possibly at doses above the intended therapeutic dose to account for increased levels in subsets of patients, such as patients taking concomitant medications that cause drug-drug interactions leading to higher blood levels or increased pharmacodynamic effects or patients with specific genetic traits or other characteristics (e.g., renal hepatic disease) that could lead to higher exposures.

For certain drugs intended to be dosed at night, including drugs for sleep disorders, effects on the CNS, which have an intended effect at night, *cannot* be assumed to be absent at the lower blood levels expected during the following day, especially in the morning. Focused studies of residual CNS-impairing effects may be needed to characterize the risk of driving impairment.

4. Randomization

A randomization scheme is described below for testing both the acute (1 dose) and later (1 week in this example) effects of a drug on driving ability.

The example design is a randomized, double-blind, double-dummy, placebo and active-controlled multiple oral dose, four-period crossover study. In treatment periods 1 through 4, subjects are randomized to receive the following treatments in a double-dummy fashion (with a well-matched placebo):

- A. High dose test drug for 8 days
- B. Low dose test drug for 8 days
- C. Positive control, day 1 and day 8
- D. Placebo

The investigational drug is given for 8 consecutive days to determine whether tolerance/desensitization develops; the finding of less impairment on day 8 than day 1 would indicate the development of tolerance. The positive control is given only on days 1 and 8 so that there is no opportunity for the development of tolerance that could confound interpretation of the study.

A minimum 5 half-life washout period occurs between each treatment dosing period for any given subject. Driving tests are conducted at both the beginning of each study period (after the first dose or few doses) and at the end of the study period.

Table 1 shows the treatment assignments for each period.

Table 1. Treatment Assignments

N	Period 1 (8 Days)	Washout	Period 2 (8 Days)	Washout	Period 3 (8 Days)	Washout	Period 4 (8 Days)
	A		C		D		B
	B		D		C		A
	C		B		A		D
	D		A		B		C

For drugs that have considerably long half-lives, parallel study design may need to be considered. Otherwise, if less than a 5 half-life washout period is proposed, sponsors should provide justification with discussion of whether a carry-over effect exists.

5. *Endpoint Analysis*

Although analysis of safety endpoints based on mean effect can be informative, exposure (e.g., maximum plasma concentration, area under the curve, tissue levels) from many drugs varies among subjects by an order of magnitude or more. Thus, clinically meaningful impairment in subjects at the high end of drug exposure may not be predicted by mean changes. Differences in pharmacodynamic sensitivity among subjects may also result in meaningful impairment in individual subjects that may not be predicted by aggregate measurements. Therefore, sponsors should examine the entire distribution of a measure of impairment, rather than just its mean, paying special attention to values that indicate clinically meaningful impairment.

6. *Exposure-Response Modeling*

Establishing the relationship of drug concentrations (exposure) to driving ability test endpoints (response) may be useful in interpreting driving studies. The exposure-response relationship may provide insight into dosing regimens not studied directly, predict the effect of various intrinsic/extrinsic factors on driving study endpoints, suggest dose adjustments in subpopulations, and inform labeling. Therefore, sponsors should collect time-matched data on appropriate drug and metabolite exposure and driving ability test endpoints. Sponsors should use regression techniques to analyze the relationship between drug or metabolite concentrations and changes in the endpoints. General considerations for exposure-response analysis can be found in the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.⁵

V. LABELING

Studies to evaluate an important safety endpoint such as driving impairment should be described in the CLINICAL STUDIES section of labeling, including a brief description of the design (e.g., population studied, endpoints, statistical analysis methods) and pertinent results.⁶ Safety information from driving studies should be included in other sections of labeling as appropriate, including but not limited to, WARNINGS AND PRECAUTIONS, PATIENT COUNSELING INFORMATION, and FDA-approved patient labeling (e.g., patient information, Medication Guide).

⁵ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁶ See the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

Title 16. Board of Pharmacy

Order of Adoption

To Amend Section 1744 of Article 5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1744. Drug Warnings

Pursuant to Business and Professions Code Section 4074, a pharmacist shall inform the patient or his or her representative of the harmful effects of certain drugs dispensed by prescription.

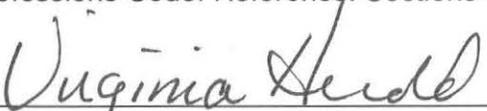
(a) ~~Because~~ the following classes of drugs may impair a person's ability to drive operate a motor vehicle or vessel, operate machinery when taken alone or in combination with alcohol a pharmacist shall include a written label on the drug container indicating that the drug may impair a person's ability to operate a vehicle or vessel:

- (1) Muscle relaxants.
- (2) ~~Analgesics with central nervous system depressant effects.~~
- (3) ~~Antipsychotic drugs with central nervous system depressant effects including phenothiazines.~~
- (4) ~~Antidepressants with central nervous system depressant effects.~~
- (5) ~~Antihistamines, motion sickness agents, antipruritics, antinauseants, anticonvulsants and antihypertensive agents with central nervous system depressant effects.~~
- (6) ~~All Schedule II, III, IV and V agents with central nervous system depressant effects, or narcotic-controlled substances as set forth in Health and Safety Code at Section 11055 et seq. prescribed in doses which could have an adverse effect on a person's ability to operate a motor vehicle.~~
- (7) ~~Anticholinergic agents and other drugs which that may impair vision.~~
- (7) Any other drug which, based on the pharmacist's professional judgment, may impair a patient's ability to operate a vehicle or vessel.

(b) ~~Because~~ the following are examples classes of drugs pose a substantial risk to the person consuming the drug when taken in combination with alcohol, a pharmacist shall include a written label on the drug container to alert the patient about possible potentiating effects: which may have harmful effects when taken in combination with alcohol. These may or may not affect a person's ability to operate a motor vehicle.

- (1) Disulfiram and other drugs (e.g., chlorpropamide, metronidazole) which may cause a disulfiram-like reaction.
- (2) Mono amine oxidase inhibitors.
- (3) Nitrates.
- (4) Cycloserine.
- (5) Antidiabetic agents including insulin and sulfonylureas (due to risk of hypoglycemia).
- (6) Any other drug which, based upon a pharmacist's professional judgment, may pose a substantial risk to the person consuming the drug when taken in combination with alcohol.

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4022, 4055 and 4074, Business and Professions Code.


Virginia Herold, Executive Officer
California State Board of Pharmacy

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RESEARCH

Enhancing the educational value of direct-to-consumer advertising of prescription drugs

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ABSTRACT

Objectives: The educational value of direct-to-consumer advertising (DTCA) of prescription drugs hinges on its ability to convey important benefit and risk information to consumers. However, the literacy level required to understand some of the information presented in print advertisements may hinder DTCA's ability to educate consumers. The objective of this study was to compare the comprehension and retention of benefit and risk information between consumers who viewed an original print DTCA and those who viewed an advertisement modified according to health literacy principles.

Design: An experimental design was used to conduct the study. Participants were randomly assigned to view a modified print advertisement (experimental group) or the original print advertisement (control group) for an antidepressant medication.

Setting and participants: Study participants were recruited from the University of Wisconsin Kidney Clinic.

Outcome measures: Ten true-false and 10 multiple-choice questions were developed to assess participants' comprehension and retention of benefit and risk information.

Results: A total of 120 participants were randomized to view either the original or the modified version of the advertisement. Regarding the comprehension and retention of only the benefit information, no significant differences were observed between the 2 groups. Significant differences were observed for comprehension and retention of only the risk information. The experimental group had significantly higher scores in comprehension ($U = 1224$; $P < 0.01$) and retention ($U = 965$; $P < 0.01$) of the risk information compared with the control group. These differences were also significant in multivariate analyses controlling for extraneous variables that were found to have associations with comprehension and retention of information.

Conclusion: Study results demonstrated that the health literacy techniques used to modify the advertisement were successful in enhancing both consumers' comprehension and their retention of information presented in a print DTCA. This was especially apparent for the risk information.

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Direct-to-consumer advertising (DTCA), or “pharmaceutical company–sponsored advertising of prescription medicines that directly targets consumers via the mass media,”¹ has increased. As pharmaceutical companies increase the use of

DTCA, the debate about potential benefits and risks of DTCA to the public and the health care system persists.² Proponents of DTCA argue that the advertisements provide consumers with valuable educational information. Advocates state that DTCA informs consumers about available treatment options and new therapies that may provide consumers with more autonomy in weighing available treatment options.^{1,3,4} Advocates also state that DTCA motivates consumers to seek care and pursue earlier screening for disease that may otherwise go unnoticed, which can ultimately bring financial and health-related benefits in the long term.^{3,4}

On the other hand, opponents of DTCA argue that the advertisements provide consumers with incomplete and biased information that may generate unnecessary visits and

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Key Points**Background:**

- FDA guidelines stress the importance of a fair balance of benefit and risk information in DTCA. Policy makers think that consumers are more likely able to make informed and conscious evaluations and decisions when they are presented with both sides of the information.
- Although both benefit and risk information are presented in DTCA, the amount of benefit and risk information consumers are able to comprehend and retain is questionable owing to the differences in how the 2 types of information are presented.
- Previous researchers have modified only the benefit or only the risk information in an attempt to enhance consumers' understanding; no previous study has modified both benefit and risk information in print DTCA. To the best of the authors' knowledge, this is the first study to modify both the benefit and risk information in a print DTCA for an antidepressant and compare the comprehension and retention of the information between consumers who viewed the original advertisement and those who viewed the modified advertisement.

Findings:

- Participants who viewed the modified version of the advertisement had higher scores for both comprehension and retention of information compared with participants who viewed the original advertisement. This was especially apparent for the risk information, which suggests that risk information in the original ad was presented in an overwhelming manner.
- This experimental study's results demonstrate that the health literacy techniques used to modify the advertisement were successful in enhancing both consumers' comprehension and their retention of the information presented in a print DTCA.

inappropriate requests for medications,^{1,4} as well as encourage consumers to take new drugs that may bring risks that they had not anticipated.¹ The critics also think that these ad-driven behaviors ultimately create unnecessary physician–patient encounters where consultation time is spent re-educating patients who have been misinformed by the advertisements.^{1,4}

In the midst of these debates, the Food and Drug Administration (FDA) created regulations and guidelines to control prescription drug advertisements by pharmaceutical companies. The presentation of a fair balance between benefit and risk information is considered to be a fundamental part of the regulation, because FDA thinks that consumers are more likely able to make informed and conscious evaluations and decisions when they are presented with both sides of the information.^{5,6} Advertisements that do not present risk information in at least the same scope, depth, or detail as the benefit information may be considered to be misleading.⁷

Although presenting a balance of benefit and risk information is regarded as one of the important components of the FDA guidelines, how the information gets presented to consumers should also be considered. Even though both benefit and risk information are present in DTCA, they are presented differently.⁸ Benefit information is more likely to be presented in larger font sizes,^{9,10} usually requires lower readability skills,¹¹ and rarely quantifies the information.¹² Therefore, it is easier for consumers to read, understand, and form their own opinion about the benefit information. On the other hand, risk information is usually presented in smaller font sizes that can be easily ignored¹³ and composed of long lists where it is hard to recognize clinically important and unimportant information,¹⁴ and is often missing key pieces of information, such as numeric descriptors for the incidence level of each adverse effect.⁸ The format in which risk information is presented makes it difficult for consumers to comprehend.¹⁵ Therefore, although both benefit and risk information are presented in the advertisements, as the FDA guidelines require, the amount of benefit and risk information that consumers are able to comprehend and process is questionable due to the differences in how the 2 types of information are presented.

In addition, previous research indicates that the literacy level required to understand the main text body of DTCA (where most of the benefit information is) is at a high school reading level; the brief summary section (where most of the risk information is) is at a college reading level.¹³ According to the National Assessment of Adult Literacy (NAAL), more than one-third of America's adult population has a basic or below-basic health literacy level, which is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.”¹⁶ When considering that more than one-third of the adult U.S. population has a basic or below-basic health literacy level, DTCA information presented in a high school or college reading level can be challenging for the average consumer to process and understand. The educational value of DTCA, as the proponents stress, is at stake if consumers are challenged with understanding the presented information. Therefore, to enhance the educational value of DTCA and ensure that consumers are able to comprehend information from the advertisements, a study that examines how best to present both benefit and risk information in DTCA is necessary.

Theoretic framework

The McGuire information processing model (1969) provides a framework for understanding consumers' processing of the information presented in DTCA. The information processing model includes comprehension and retention components.¹⁷ For a message to have any influence, consumers must comprehend the message that they are viewing or hearing. Consumers should comprehend information in DTCA to begin the cognitive processes needed to act. For DTCA, the expectation of advertisers is not for the message to have an immediate effect on consumers, but rather on a purchasing decision (e.g., communicating with a physician about the advertised medication) to be made some time thereafter. This expectation requires that consumers retain the information

received as well as further process the initially comprehended material. In the present study, we modified an existing DTCA for a prescription medication based on previous literature and examined the impact of those modifications on consumers' comprehension and retention of benefit and risk information.

Objectives

The objective of this study was to compare the comprehension and retention of information between consumers who viewed an original advertisement and those who viewed an advertisement that was modified according to health literacy principles.

Methods

An experimental design was used to conduct the study. Study participants were randomly assigned to view the modified print advertisement (experimental group) or the original print advertisement (control group) for an antidepressant medication. Randomization was conducted before potential participants were recruited. Study materials were placed in envelopes. A random number generator was used to assign each envelope to the experimental or the control group. A note was placed inside each envelope to indicate the assignment. The assignment of the randomization was blinded to the researcher. The researcher opened the envelope in the numbered order only after a potential participant agreed to participate in the study. The study received approval from the Health Sciences Institutional Review Board at the University of Wisconsin–Madison.

Study sample

Study participants were recruited from the University of Wisconsin Kidney Clinic. There were 4 study inclusion criteria: 1) a diagnosis of chronic kidney disease (CKD), 2) 18 years of age or older, 3) ability to communicate in English, and 4) no previous or current prescription for Pristiq (a prescription antidepressant medication). CKD patients were chosen because of the potential comorbidity of depression.^{18,19} The researcher approached CKD patients individually in the patient waiting area at the clinic. The researcher briefly introduced the study to the patient. If the patient was interested in participating in the study, the researcher took the patient to a private room, reviewed information about the study, answered any questions about the study, and conducted the informed consent procedures.

Data collection

After the participant provided informed consent, the researcher opened an envelope that contained the study materials. First, the researcher asked the participant to read the randomly assigned print advertisement (original or modified version). Two copies of the same issue of a magazine were used in presenting the advertisements. The original advertisement was placed in 1 issue and the modified advertisement was placed in another. The advertisements were placed in magazines to present the advertisements as seen in real-life settings. After the participant read the advertisement, she or

he was asked to complete an in-clinic survey that contained 20 questions (described below) to assess the comprehension of the information presented in the advertisement (without having access to the advertisement). Next, the participant was asked to indicate 3 good times when she or he could be reached on the telephone to conduct a second survey.

Within 48 hours of completing the in-clinic survey, each participant received a telephone call to participate in the second survey. The telephone survey assessed participants' retention of the information presented in the advertisement (same items used in the in-clinic survey), demographic information, health literacy level, and self-rated global health. The telephone survey took approximately 20 minutes. Participants who completed both parts of the data collection procedure (in-clinic and telephone survey) were sent a \$10 gift certificate by mail to thank them for their participation.

Advertisement modification

The advertisement was modified based on health literacy principles (e.g., the enhancement of the readability and comprehension of written health information), the Explanatory Structure Building Model, and findings from previous studies.²⁰⁻²⁸ A graphic designer helped with the modification of the format and presentation of the information in the advertisement. In summary, the modified advertisement used simple plain language by avoiding technical or medical words; was constructed with sentences that have 10 or fewer words; contained paragraphs with fewer than 10 lines; used the active voice; used headers, bullets, and table boxes to organize information; used at least 12-point-size font; and contained written information at or below an eighth grade reading level. The modified advertisement was reviewed for its compliance with federal regulations for DTCA by a regulatory affairs professional. The specific methodology applied in creating the modified advertisement and figures showing the original and modified advertisements have been published previously.²⁹

Study variables

Ten true-false and 10 multiple-choice questions were developed to assess participants' comprehension and retention of the information presented in the advertisement. Previous studies that assessed recall of information in DTCA were used as guidance in developing the questions.³⁰⁻³² Among the 20 comprehension questions, 8 focused on benefit or general information and 12 on risk information. A total score was generated by adding the number of correctly answered items, with a theoretic range of 0-20. Subscores were also created for the benefit and risk information components by summing the respective items; thus, comprehension (and retention) of benefit information scores could theoretically range from 0 to 8 and of risk information scores from 0 to 12. Additional information about the development and pilot testing of the comprehension and retention questions has been published elsewhere.²⁹

Control variables

Control variables consisted of participants' demographic information (age, gender, race, place of birth, most

comfortable language, education), past and current health-related job status (yes/no), time since CKD diagnosis, diagnosis of depression (yes/no), use of an antidepressant medication (yes/no), previous exposure to Pristiq advertisement (yes/no), family or friend use of Pristiq (yes/no), health literacy level, and self-rated quality of life according to the Global Quality of Life Scale. Participants' health literacy was measured with the Short Test of Functional Health Literacy in Adults (S-TOFHLA). The S-TOFHLA measures an individual's comprehension of written material rather than only her or his ability to read and correctly pronounce a list of words.³³ The original TOFHLA takes up to 22 minutes to administer, which may cause respondent fatigue. To overcome this barrier, the S-TOFHLA was developed; S-TOFHLA takes approximately 7 minutes to administer.^{33,34} S-TOFHLA items are scored a "1" for correct or a "0" for incorrect. The total score for the S-TOFHLA is calculated by adding up the correctly answered items. The S-TOFHLA score is divided into 3 categories of health literacy: inadequate health literacy (scores from 0 to 16), marginal health literacy (scores from 17 to 22), and adequate health literacy (scores from 23 to 36).

Analysis

Data were analyzed with the use of SPSS (version 19) and Stata (version 12). Descriptive statistics were conducted to characterize all study variables. Independent-sample *t* tests, chi-square analyses, and Mann-Whitney *U* tests (when appropriate) were conducted to examine between-group differences regarding the control variables after randomization. To address the research objectives, Mann-Whitney *U* tests were conducted to examine between-group differences on comprehension and retention of information (both variables did not meet the assumptions for using a *t* test). In addition, multivariate analyses were conducted to examine the differences in comprehension and retention between the 2 groups while controlling for extraneous variables. Bivariate analyses were conducted to examine the associations between the control and dependent variables. Results from bivariate analyses informed the construction of multivariate models: control variables with associations of $P < 0.20$ were included in the models, as suggested to construct the most parsimonious model.³⁵ Owing to the potential impact of violating distributional assumptions for the dependent variables, we estimated model standard errors and 95% confidence intervals (CIs) with the use of a bias-corrected bootstrapping approach.^{36,37}

Results

Participation rate and response rate

A total of 120 participants were enrolled into this study; 214 patients were solicited for participation. The 2 main reasons for declining participation included no desire to participate or inability to complete the telephone survey (because of hearing problems or lack of telephone accessibility). Out of 120 participants, 109 (53 in the control group and 56 in the experimental group) completed both the in-clinic and telephone survey parts of the study. This resulted in a participation rate of 51%. The remaining 11 participants were not able to

be reached by telephone within 48 hours of completing the in-clinic survey.

Sample description

The majority of the 109 participants were white (88%) and female (51%). The mean age was 60 years (SD 17 years). Although approximately 7% of the participants were not born in the U.S., all of them indicated English as their most comfortable language. Regarding participants' education level, the majority indicated high school graduation (35%), some college (27%), or college graduation (23%). The mean number of years since CKD diagnosis was 5 years, 6 months (SD 8 years). Approximately one-half of the participants (52%) stated that they were exposed to a Pristiq advertisement before participating in the study. The majority of the participants (86%) had an adequate health literacy level. Detailed information on participant characteristics can be found in Table 1.

There were no statistical differences in the demographic characteristics between the control (participants who viewed the original version of the advertisement) and the experimental (participants who viewed the modified version of the advertisement) groups except for their education level. The control group (those who viewed the original advertisement) had a significantly higher education level compared with the experimental group ($P = 0.045$).

Comprehension of information

Regarding the comprehension of the information obtained in the advertisement, the control group had a minimum score of 4 and a maximum score of 20 and the experimental group a minimum score of 7 and a maximum score of 20. The difference between the 2 study groups was tested with the use of a 2-tailed Mann-Whitney *U* test (Table 2). Results indicated that the experimental group obtained a significantly higher comprehension score compared with the control group ($P < 0.01$). Regarding the comprehension of only the benefit information, both groups had a minimum score of 4 and a maximum score of 8. No significant differences were observed between the 2 groups. Regarding the comprehension of only the risk information, the control group had a minimum score of 0 and a maximum score of 12 and the experimental group a minimum score of 3 and a maximum score of 12. The Mann-Whitney *U* test revealed that the experimental group had a significantly higher score in comprehension for the risk information compared with the control group ($P < 0.01$). Details of these results are presented in Table 2.

Retention of information

Regarding the retention of information scores, the control group had a minimum score of 6 and a maximum score of 20 and the experimental group a minimum score of 9 and a maximum score of 20. The difference between the 2 study groups was tested with the use of a 2-tailed Mann-Whitney *U* test (Table 3). Test results indicated that the experimental group significantly retained more information compared with the control group ($P < 0.01$). Regarding the retention of only the benefit information, both groups obtained similar scores (no significant differences). Regarding the retention of only the

Table 1
Participant demographics

Variable	Overall (n = 109)	Control (n = 53)	Experimental (n = 56)	Comparison
Age, y, mean ± SD	60 ± 17	57 ± 19	63 ± 15	
Gender				$\chi^2 = 2.09; P = 0.148$
Female	56 (51.4%)	31 (58.5%)	25 (44.6%)	
Male	53 (48.6%)	22 (41.5%)	31 (55.4%)	
Race				
White	96 (88.1%)	45 (84.9%)	51 (91.1%)	
Black	7 (6.4%)	3 (5.7%)	4 (7.1%)	
Other	6 (5.5%)	5 (9.4%)	1 (1.8%)	
Place of birth				
United States	101 (92.7%)	48 (90.6)	53 (94.6)	
Other	8 (7.3%)	5 (9.4%)	3 (5.4%)	
Most comfortable language English	109 (100%)	53 (100%)	56 (100%)	
Education				$U = 1165; P = 0.045^*$
Less than high school	2 (1.8%)	0	2 (3.6%)	
High school graduate	38 (34.9%)	17 (32.1%)	21 (37.5%)	
Some college, no degree	29 (26.6%)	12 (22.6%)	17 (30.3%)	
College graduate	25 (22.9%)	12 (22.6%)	13 (23.2%)	
Graduate or professional degree	15 (13.8%)	12 (22.6%)	3 (5.4%)	
Past health-related job				$\chi^2 = 0.073; P = 0.787$
Yes	28 (25.7%)	13 (24.5%)	15 (26.8%)	
No	81 (74.3%)	40 (75.5%)	41 (73.2%)	
Currently hold health-related job				
Yes	7 (6.4%)	5 (9.4%)	2 (3.6%)	
No	102 (93.6%)	48 (90.6%)	54 (96.4%)	
Time since CKD diagnosis	5 y 6 mo ± 8 y	6 y 6 mo ± 9 y	4 y 6 mo ± 7 y	$U = 1307; P = 0.284$
Diagnosis with depression				$\chi^2 = 690; P = 0.406$
Yes	27 (24.8%)	15 (28.3%)	12 (21.4%)	
No	82 (75.2%)	38 (71.7%)	44 (78.6%)	
Use of depression medication				$\chi^2 = 1.161; P = 0.281$
Yes	24 (22.0%)	14 (26.4%)	10 (17.9%)	
No	85 (78.0%)	39 (73.6%)	46 (82.1%)	
Previous exposure to Pristiq ad				
Yes	57 (52.3%)	30 (56.6%)	27 (48.2%)	
No	52 (47.7%)	23 (43.4%)	29 (51.8%)	
Family or friend use of Pristiq				$\chi^2 = 0.768; P = 0.381$
Yes	1 (1.0%)	1 (1.9%)	0	
No	108 (99.0)	52 (98.1)	56 (100)	
S-TOFHLA				$U = 1404.5; P = 0.421$
Inadequate health literacy	8 (7.3%)	2 (3.8%)	6 (10.7%)	
Marginal health literacy	7 (6.4)	4 (7.5)	3 (5.3%)	
Adequate health literacy	94 (86.2%)	47 (88.7%)	47 (84.0%)	
Quality of life, mean ± SD	7 ± 2	8 ± 2	7 ± 2	

Abbreviations used: CKD, chronic kidney disease; S-TOFHLA, Short Test of Functional Health Literacy in Adults.

* $P < 0.05$.

risk information, the control group had a minimum score of 2 and a maximum score of 12 and the experimental group a minimum score of 4 and a maximum score of 12. The Mann-Whitney U test revealed that the experimental group had a significantly higher score in the retention of risk information compared with the control group ($P < 0.01$). Details of these results are presented in Table 3.

Multivariate analyses: Comprehension and retention of information

Bivariate analyses were used to inform the construction of multivariate models. With the use of the $P < 0.20$ criteria, findings indicated significant associations between comprehension and past health-related job ($t = -1.580; P = 0.117$),

Table 2
Difference between the study groups in information comprehension scores

Variable	Study group	Mean ± SD	Median	Min.	Max.	IQR	Comparison
Overall comprehension score	Control (n = 59)	14.4 ± 3.35	15	4	20	3.75	$U = 1253; P = 0.004$
	Experimental (n = 60)	16 ± 2.83	16	7	20	4	
Benefit comprehension score	Control (n = 60)	6.85 ± 1.19	7	4	8	2	$U = 1601; P = 0.269$
	Experimental (n = 60)	7.12 ± 0.99	7	4	8	1	
Risk comprehension score	Control (n = 60)	7.53 ± 2.55	8	0	12	3	$U = 1224; P = 0.002$
	Experimental (n = 60)	8.88 ± 2.21	9	3	12	3.75	

Abbreviation used: IQR, interquartile range.

Table 3
Difference between the study groups in information retention scores

Variable	Study group	Mean \pm SD	Median	Min.	Max.	IQR	Comparison
Information retention score	Control (n = 53)	14.70 \pm 3.33	15	6	20	4	$U = 1030; P = 0.006$
	Experimental (n = 56)	16.38 \pm 2.60	17	9	20	3	
Benefit retention score	Control (n = 53)	6.98 \pm 1.19	7	3	8	1	$U = 1379; P = 0.496$
	Experimental (n = 56)	7.20 \pm 0.90	7	4	8	1	
Risk retention score	Control (n = 53)	7.72 \pm 2.48	8	2	12	3.50	$U = 965; P = 0.001$
	Experimental (n = 56)	9.18 \pm 2.05	9	4	12	3	

Abbreviation used: IQR, interquartile range.

retention of information and past health-related job ($t = -1.738; P = 0.085$), and retention of information and quality of life ($t = -1.329; P = 0.187$). Multivariate analyses were used to examine the effect of the advertisement modifications on the comprehension and retention of information, controlling for the associated variables found in the bivariate analyses. In addition, education level was added to the models owing to the significant difference found between the experimental and control groups after randomization. The Shapiro-Wilk test indicated non-normality for both dependent variables, comprehension ($z = 3.680; P = 0.000$) and retention of information ($z = 2.855; P = 0.002$), and so model standard errors and 95% CIs were estimated with the use of a bias-corrected bootstrapping approach. Results from the multivariate analysis revealed that the experimental group scored approximately 2 points higher in comprehension than the control group ($z = 3.32; P = 0.001$). Regarding the retention of information, the multivariate analysis indicated that the experimental group scored 1.7 points higher than the control group ($z = 2.96; P = 0.003$). Details of these results are presented in Table 4.

Discussion

The educational value of DTCA depends on consumers' ability to process and understand the information presented in advertisements. The present randomized experiment examined the impact of health literacy–based modifications to a print antidepressant advertisement on participants' comprehension and retention of information. Participants who viewed the modified version of the advertisement had higher scores for both comprehension and retention of information than participants who viewed the original advertisement. These differences were also significant in the multivariate analyses that controlled for extraneous variables found to have associations with the comprehension and retention of information scores.

Previous researchers who studied consumers' understanding of information from DTCA found that consumers recall less of the risk-related information.^{31,38,39} Furthermore, in a survey conducted by the FDA, physicians thought that patients understood the possible benefit and positive effects of advertised drugs better than the possible risks and negative effects.⁴⁰ This could be due to the intentional framing of risk versus benefit information in DTCA (i.e., unbalanced presentation), which may be constructed to make advertised drugs appear less harmful.¹⁵ If risk information is presented to consumers in an easier, digestible format, then their perceptions of the advertised drug could be less positive and appealing. From a marketing strategy, pharmaceutical companies may want to make the benefit information more accessible and the risk information less accessible to avoid negative perceptions.

In the spirit of FDA's DTCA regulation regarding the fair balance of information, both benefit and risk information should be presented in at least the same scope, depth, or detail regardless of the pharmaceutical companies' wishes.⁷ In the present study, the modified advertisement was constructed following health literacy principles (e.g., simple plain language, sentences with 10 or fewer words, organized information in boxes with the use of headers and bullets) in an effort to bolster consumers' understanding of both benefit and risk information.²⁹ Simple plain language and short sentences are commonly promoted as key techniques for communicating written health information to consumers with low health literacy levels.^{21–23,25–27} These 2 techniques may have played an important role in influencing participants' comprehension and retention of information in the present study, especially among those participants with lower educational attainment.

Previous researchers also found that consumers considered information organized in boxes to be easy to read and understand.^{32,41} Whereas our modified advertisement organized risk information in a box format with the use of headers and bullets, the original advertisement presented information in 1 long paragraph. The strategy of organizing information in a box format may have influenced participants to read not only the benefit information that was presented in larger font size but also the risk information, resulting in greater comprehension and retention of risk information. Findings from this study suggest that health literacy principles may enhance consumers' processing of drug information presented in DTCA.¹⁷ Future research should conduct qualitative research, such as in-depth interviews or focus groups with consumers, to gain insights into how different modifications in advertisements affect their processing and understanding of

Table 4
Multiple regression for comprehension and retention of information score

Variable	Coefficient	95% CI
Comprehension^a		
Group (experimental)	1.939***	0.794–3.083
Education	0.538	0.103–0.972
Past health-related job	1.048	–0.191 to 2.286
Retention^b		
Group (experimental)	1.710**	0.577–2.843
Education	0.263	–0.201 to 0.726
Past health-related job	1.022	–0.170 to 2.214
Quality of life	–0.150	–0.428 to 0.129

Abbreviation used: CI, confidence interval.

** $P < 0.01, R^2 = 0.114$.

*** $P < 0.001; R^2 = 0.126$.

^a Regression model included education and past health-related job as covariates.

^b Regression model included education, past health-related job, and quality of life as covariates.

presented drug information. In addition, the majority of participants in the present study (~86%) had adequate health literacy. This may have been due to the geographic region that was chosen for the study, which is composed of individuals who live in neighborhoods (i.e., census blocks) that fall into the highest health literacy quartile in the nation.⁴² Future research should also examine the effect of the modified advertisement with a larger sample size including diverse populations (e.g., varying health literacy levels).

Interestingly, participants who were randomly assigned to the experimental group had a statistically significant lower education level compared with participants who were assigned to the control group. Yet the experimental group had statistically significant higher comprehension and retention scores compared with the control group. The modified advertisement was successful in enhancing participants' comprehension and retention of the information even though the experimental group had lower educational attainment. The experimental-group participants also correctly answered more risk-related comprehension and retention questions than the control group. These findings suggest that using health literacy principles to construct print DTCA may improve its educational value even to those consumers with lower education and literacy skills.

Limitations

The results of this study should be interpreted with consideration of the following limitations. First, the modifications of the advertisement involved alteration of multiple characteristics, including format and wording and expanding it from 1 page to 2 pages. The independent effects of each specific modification were not analyzed in this study. There is a possibility that 1 specific modification influenced the study results. Future research should examine the effects of specific modifications with the use of multiple ads (e.g., 1 modification per ad). Second, this study involved only patients with CKD in 1 clinic setting. Therefore, it is hard to generalize the study findings to a larger population. Finally, various forms of DTCA exist (e.g., television and radio ads) and various classes of medication are promoted through DTCA. However, this study attempted to enhance the educational value of a print DTCA for an antidepressant only. Modifications of other forms and types of DTCA should be evaluated to inform the debate regarding the educational value of DTCA.

Conclusion

The presentation of a fair balance between benefit and risk information is considered to be a fundamental part of FDA's regulations for DTCA. However, it is still apparent that benefit and risk information are presented differently in DTCA; risk information is presented in a manner that is overwhelming for consumers to comprehend. The present experimental study's results demonstrated that health literacy-based techniques used to modify the advertisement were successful in enhancing both consumers' comprehension and their retention of the information presented in a print DTCA. This was especially apparent for the risk information. Therefore, this study suggests that health literacy principles can be used to help achieve a fair balance of benefit and risk information.

Acknowledgment

The authors thank Drs. Betty Chewning, Dave Mott, Dhavan Shah, and Hernando Rojas for their insightful comments in this research; the physicians and staff at the University of Wisconsin Kidney Clinic, especially Drs. Micah Chan and Alexander Yevzlin, for their continuous help in patient recruitment; and Dr. Christine Salzwedel for all of the graphic work involved in this research.

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Attachment -

FORTY-SIXTH ANNUAL REPORT
of the
RESEARCH ADVISORY PANEL
OF CALIFORNIA
2016



PREPARED FOR THE
LEGISLATURE AND GOVERNOR

RESEARCH ADVISORY PANEL OF CALIFORNIA
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2016 PANEL MEMBERS

RESEARCH ADVISORY PANEL OF CALIFORNIA

The Research Advisory Panel of California (RAPC) consists of the Panel chairman, Executive officer, and the Panel members.

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This report represents a consensus among Panel members acting as individual experts. It does not represent policies or positions of the appointing agencies nor have those agencies been consulted by the Panel during its function or during the preparation of this report.

SUMMARY OF 2016 PANEL ACTIVITIES

During 2016 the Panel reviewed thirty-five research study submissions. Thirty-two were approved by the Panel. Among the approved studies, nineteen studies were Academic research studies and thirteen studies were Multi-Center Clinical Drug Trial research studies.

Twenty-eight research studies were completed or, in a few cases, terminated in 2016, and they were closed on the Panel's records.

At the end of 2016 the Panel was monitoring one hundred and eleven research projects. Note Appendices A, B, and C for specific listings.

As part of the Panel's supervisory responsibility, ongoing projects are monitored by means of annual reports, significant adverse event (SAE) reports and site visits. Approval may be withdrawn if the study deviates significantly from the approved protocol.

Table 1 is a list of the studies approved by the Panel in 2016 and Table 2 is a list of the studies closed by the Panel in 2016.

SELECTED RESEARCH FINDINGS

Below are brief summary reports of several Panel approved projects which are of interest and indicative of the types of controlled substance research projects currently ongoing in California:

Dr. Matthew Worley, Ph.D., MPH. and colleagues at University of California, San Diego have provided the Panel with the following summary of academic human research titled "Behavioral Economic Mechanisms of Prescription Opioid Addiction in Chronic Pain"

Over the last 10-15 years prescription opioid abuse has increased dramatically in the United States and other developed nations, and is currently a significant public health problem. Chronic pain patients are particularly vulnerable for opioid misuse, abuse, and addiction as they have greater rates of exposure to chronic opioid treatment and thus have greater risk for prescription opioid addiction than the general population. The syndrome of addiction is also difficult to recognize in this population, because opioid tolerance, persistent pain, and prescription opioid misuse behaviors (e.g., early refills, taking more than prescribed) have significant overlap. Specific neurobehavioral factors or "mechanisms" that influence the onset of prescription opioid addiction in chronic

pain patients have not been identified, which limits the safety and specificity of opioid treatment for pain.

Emerging research in substance use disorders (SUDs) prioritizes the identification of specific biologically driven phenotypes that may be causal mechanisms of SUDs. In pursuit of this goal, a significant body of research grounded in behavioral economics has identified behavioral markers of maladaptive reward valuation and decision-making that are common across SUDs. One such marker is excessive “drug demand”, a tendency for persons with SUDs to allocate excessive amounts of personal resources (such as income or time) to obtain and use substances. Among adults with chronic pain who use prescribed opioid medications, opioids serve as a functional reinforcer as they reduce pain, activate neural reward systems, and can reduce aversive symptoms such as stress and negative affect. Excessive drug demand may also contribute to prescription opioid addiction in chronic pain patients, but behavioral economic methods have not been previously applied to prescription opioid addiction in chronic pain patients, due in part to the absence of valid experimental models of pain-related demand in this population. This project will establish a novel human laboratory model to examine behavioral economic markers of reward-related decision-making in chronic pain patients who use prescribed opioids for pain. The study will recruit adults with chronic pain currently in long-term opioid treatment (≥ 3 months) for pain management. The study will involve a screening visit and two experimental sessions, with procedures including pain testing, behavioral economic measures, and clinical measures of pain and opioid use. The primary objective of the study is to establish a valid model of pain-related opioid demand, by comparing measures of in-vivo opioid reinforcement to opioid demand assessed under hypothetical conditions. Results will validate novel behavioral economic measures of decision-making with specific applications for patients with chronic pain. Resultant data will support future, larger studies on the behavioral economics of prescription opioid use disorders in adults with chronic pain.

Rates of prescription opioid abuse have accelerated drastically in the past 15 years, especially among adults with chronic pain (Jones, Mack, & Paulozzi, 2013). The specific mechanisms that underlie prescription opioid addiction in chronic pain patients are not well-understood. Better understanding of such mechanisms would improve treatment of pain and reduce abuse of prescribed opioid pain medications. In prior research behavioral economics has been used to identify markers of dysfunctional decision-making that may underlie substance use disorders (Bickel, Johnson, Koffarnus, Mackillop, & Murphy, 2014). Typically, persons with substance use disorders exhibit excessive demand for their preferred “reinforcer”, in that they continue to expend excessive amounts of personal resources to obtain and consume the reinforcer (e.g., cigarettes, alcohol) even in the presence of increasing costs or incentives against consumption. This excessive “drug demand” appears to be a translational marker of dysfunctional reward-seeking, with consistent evidence across multiple types of addiction and other reward-related disorders such as gambling disorder and obesity (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012). Drug demand is

therefore a strong candidate mechanism of risk for prescription opioid abuse in chronic pain patients, but no prior studies have examined demand for opioid medications in adults with chronic pain, perhaps in part because no valid experimental models of drug demand for this population exist. The proposed study seeks to test and validate a human laboratory model of pain-related drug demand in chronic pain patients. Findings will establish methodology for future investigations of causal mechanisms of prescription opioid misuse and addiction in this population.

To establish the validity of a human laboratory model for examining the effects of pain on opioid demand in adult users of prescribed opioids with chronic pain. We propose to study approximately 15 adults (age 18 - 65) with chronic pain who are prescribed opioid medications on a chronic basis for pain management. The sample will include individuals who exhibit current misuse of prescribed opioid medications, as assessed by validated screening measures. In cases of early study withdrawal or termination, additional subjects will be recruited to complete the sample.

NIDA, NDAT, CTN has provided the Panel with the following summary of the substance abuse treatment research titled “Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)”

This study was designed to assess the comparative effectiveness of extended release injectable naltrexone (XR-NTX, Vivitrol®), an opioid antagonist indicated for the prevention of relapse to opioid dependence, versus buprenorphine-naloxone (BUP-NX, Suboxone®), a high affinity partial agonist indicated for maintenance treatment of opioid dependence, as pharmacotherapeutic aids to recovery.

Study enrollment began on January 30, 2014 and concluded on May 25, 2016. Overall, 570 participants, both males and females over 18 years of age seeking treatment for opioid dependence (heroin or prescription opioids) were admitted to an inpatient (detoxification and/or short term residential treatment) program for treatment of substance dependence and randomized into the study.

The first participant at the Tarzana Treatment Center was enrolled on July 17, 2014, and the final participant was enrolled at the Tarzana site on May 19, 2016. Overall, a total of 66 participants were enrolled at the Tarzana site. All study dosing is now complete.

Twenty-eight Serious Adverse Events (SAEs) were reported in 2016, none of which were considered related to study drug and therefore were not subject to expedited reporting requirements.

The following publication regarding the design and methods of the X:BOT study was published in 2016, and is provided as Attachment 1 to this report:

- Lee JD, Nunes EV, Novo P, Bailey GL, Brigham GS, Cohen AJ, Fishman M, Ling W, Lindblad R, Shmueli-Blumberg D, Stablein D, May J, Salazar D, Liu D, Rotrosen J.

NIDA Clinical Trials Network CTN-0051, Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT):
Study design and rationale. *Contemporary Clinical Trials*, 2016. 50: 253-264.

Dr. Heinz Moser, Ph.D. and colleagues at the Novartis Institute for Biomedical Research, Emeryville, CA have provided the Panel with the following summary of non-human research titled “Synthesis and Optimization of Novel Therapeutics”

The Novartis research site in Emeryville is dedicating its effort on the identification of novel anti-infective therapeutics to address unmet medical needs such as infections by multi-drug resistant bacteria or a variety of viruses. We typically identify compounds with the desired biological activity convert them in a complex, multi step approach to potential clinical candidates. This process requires the synthesis of hundreds to thousands of compounds to refine a number of parameters (safety, selectivity, potency, efficacy, pharmacokinetic profile, solubility, etc.) of the original hit(s) to generate compounds for preclinical profiling, IND filing with FDA, and eventually clinical examination in humans. The realization of this chemical optimization requires a diverse set of chemical substances as either building blocks (intermediates) or reagents. Each project typically requires hundreds of chemicals during these optimization steps, some of which are controlled substances. The requirement of specific chemicals is impossible to predict as pathways or targets of these drug candidates are often novel and part of our work is to gain insight in how effective inhibitors are constructed. For this purpose we request the use of a subset of Schedule I compounds that are viewed by us as either versatile reagents (such as benzylpiperazine, see below) or building blocks (e.g. a subset of amphetamines and tryptamines). We typically use quantities of 100 mg or less and will only use larger quantities for the synthesis of valuable intermediates of interest. To the best of our possibilities, we will keep the use of Controlled Substances to a minimum but in certain circumstances, it will be difficult to avoid.

Corbus Pharmaceuticals has provided the Panel with the following rationale of multicenter clinical drug trial research titled “A Phase 2, Double-Blind, Randomized, Placebo-Controlled Multicenter Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Efficacy of JBT-101 in Cystic Fibrosis”

JBT-101 has effects on soluble mediators and cell types implicated in the pathogenesis of lung disease in CF, providing evidence that JBT-101 may provide clinical benefit in CF as a novel, orally administered anti-inflammatory and anti-fibrotic treatment. Results from the proposed clinical trial will be used to power a future Phase 2 clinical trial to better characterize the clinical efficacy of JBT-101 in CF.

The hypothesis is that JBT-101 will provide clinical efficacy in CF patients by triggering pathways that resolve adverse innate immune responses and blunt pro-fibrotic processes in the lungs. Based on preclinical data, there is a component of the study to

evaluate the expectation that JBT-101 increases production of pro-resolving lipids, including but not limited to lipoxin A4 and anti-inflammatory eicosanoids PGD2 and PGJ2. Conversely, JBT-101 is expected to decrease production of pro-inflammatory eicosanoids, including leukotriene B4. JBT-101 is expected to inhibit production of pro-inflammatory adhesion molecules, chemokines, and cytokines, neutrophil infiltration of lung tissue, myofibroblast transformation, fibroblast proliferation and the production of extracellular matrix components that leads to tissue fibrosis. Further, JBT-101 is expected to activate apoptosis in activated immune cells and fibroblasts and induce clearance of cellular debris by non-inflammatory macrophages. Through production of lipoxin A4, JBT-101 also may increase mucus fluidity, survival of airway epithelial cells, and reduce pathogen-induced disruption of the airway epithelium. Through these mechanisms, JBT-101 is expected to provide efficacy in CF.

The first-in-CF study, proposed for conduct after results in healthy normal and pain were obtained in humans, is to assess safety, tolerability, PK, efficacy and mechanism of action of JBT-101 in CF subjects. The target population is adults with CF > 18 and < 65 years of age at the time of signing the Informed Consent Form, with FEV1 \geq 40% predicted, corrected. Adults are selected as the target population because neither toxicology studies in juvenile animals nor safety or efficacy assessments in adults with CF have been done yet.

To reduce risk to subjects in this first-in-CF study, subjects will be excluded who have severe organ damage or require intravenous antibiotics in the 14 days prior to first dose. JBT-101 or placebo will be administered as "add-on" to standard of care, allowing subjects to continue to receive what their treating physicians deem most appropriate baseline therapy for their disease, to reduce risk of disease exacerbations. The 84 days duration of dosing is supported by findings in 13-week toxicology studies in rats and dogs. This study will provide data on safety, tolerability, plasma concentrations, and clinical efficacy of JBT-101 over a longer exposure than in a shorter study. The feasibility of enrolling 70 subjects into this study within 12 months at about 24 sites in the EU and US is judged acceptable, based on input from the principal investigators, the Cystic Fibrosis Foundation in the US, and the EU Cystic Fibrosis Society.

The JBT-101 oral doses selected for this study are 1 mg qd, 5 mg qd, 20 mg qd, and 20 mg twice a day (bid). All of these doses are expected have an acceptable safety profile, be well-tolerated, and provide some clinical benefit, based on previous animal or human testing and the nature of the inflammatory components of CF. Based on preclinical data and early higher dose clinical data, it is expected that any safety risk and clinical efficacy of JBT-101 in humans will be related to exposure. To maximize opportunity to detect an early safety signal and clinical efficacy in this study, subjects will receive JBT-101 20 mg bid on Days 29-84. The JBT-101 20 mg bid dose is expected to provide maximal or near maximal levels of clinical benefit, based on extrapolation from animal models of inflammation. Finally, the availability of data from individual subjects who have been exposed to two different doses of JBT-101 or two intervals of dosing increases the robustness of the modeling of relationships between plasma concentrations of JBT-101 and safety outcomes, efficacy outcomes, biomarkers and lipoxin A4 levels.

Parallel dose assignment to JBT-101 in doses up to 20 mg bid is supported by a previous multiple ascending dose study and a Phase 2 study in humans in which JBT-101 doses up to 40 mg bid showed acceptable safety profiles and were well tolerated. Efficacy will be explored with FEV1, LCI, CFQ-R Respiratory Symptoms score, and biomarkers of disease activity. Changes from baseline in these efficacy outcomes are expected to occur and be in the direction of improvement, although the changes are not expected to reach statistical significance after 84 days exposure in this first small pilot trial in CF. Changes in biomarkers of disease activity are expected to happen more quickly than changes in clinical efficacy outcomes, within a few weeks.

The mechanism of action will be evaluated by measuring metabolipidomic profiles, to determine whether JBT-101 increases SPMs, especially lipoxin A4, and anti-inflammatory eicosanoids, both in absolute amounts and relative to pro-inflammatory eicosanoid mediators. The downstream consequences of this activity on biologic pathways relevant to disease pathology in CF will be tested, looking for beneficial effects of JBT-101 on adhesion molecules, cytokines and chemokines, as well as gene transcripts indicating activation of inflammatory pathways. Changes in the metabolipidomic profile are expected within days and changes in these biomarkers of inflammation are expected within days to weeks.

TABLE 1

RESEARCH STUDIES
APPROVED IN 2016

<u>PI / Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Nancy E. Buckley, Ph.D. CA State Polytech University Pomona, CA	Investigating the effect of delta-9-tetrahydrocannabinol (THC) on the susceptibility to systemic C. Albicans infection in mice treated with an anti-cancer drug
Davide Dulcis, Ph.D. UCSD La Jolla, CA	Effects of Neonatal Nicotine Exposure on Dopamine Neurons Affecting Consumption of Substances of Abuse in the Adult
Olivier George, Ph.D. The Scripps Research Institute La Jolla, CA	Animal Models of Addiction: Preliminary Studies of Vaporized THC Self-Administration in a Rat Model
Olivier George, Ph.D. The Scripps Research Institute La Jolla, CA	Animal Models of Addiction: Preliminary Studies for Heroin Dependence and Treatments
Roy Gerona, Ph.D. UCSF, Dept OBGYN San Francisco, CA	Real Time Surveillance of Designer Drug Intoxications using Enhanced High Resolution Mass Spectrometry (HRMS) based Drug Screening and Confirmation
Su Guo, Ph.D. UCSF San Francisco, CA	A novel RNA-Guided Platform for Dissecting Cannabinoid Signaling in Reward Circuit Development

Table 1 Cont.

<u>PI / Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Kim D. Janda, Ph.D. The Scripps Research Institute San Diego, CA	Immunopharmacology Therapy for Methamphetamine Addiction
Gunjan Junnarkar, Ph.D. Jazz Pharmaceuticals Menlo Park, CA	Oxybate Research
Edward Kisak, Ph.D. Tioga Research Inc. San Diego, CA	Research of a Topical Cannabinoid Formulation to Treat Pain and Inflammatory Disorders
David Kokel, Ph.D. UCSF	Behavior Based Neuroactive Drug Discovery in Zebrafish
Thomas Marcotte, Ph.D. UCSD Health Care System San Diego, CA	A Randomized, Controlled Trial of Cannabis in Healthy Volunteers Evaluating Simulated Driving, Field Performance Tests and Cannabinoid Levels
Mark Peterman, Ph.D. OndaVia Hayward, CA	Development of a Rapid and Field-Ready Heroin analysis Tool
Daniele Piomelli, Ph.D. UC Irvine Irvine, CA	1. Effect of Adolescent Cannabis Exposure in Adults Mice and Rats

Table 1 Cont.

<u>PI / Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Daniele Piomelli, Ph.D. UC Irvine Irvine, CA	2. In Vitro and In Vivo Pharmacological Characterization of Acid Phytocannabinoids
Ivan Soltesz, Ph.D. Stanford University Stanford, CA	Investigating the Effect of Naturally-Occurring Cannabinoids on Synaptic Physiology, Cognition and Epilepsy
Matthew L. Springer, Ph.D. UCSF San Francisco, CA	Assessment of Harmful Cardiovascular Effects of Marijuana Secondhand Smoke and Vaporizers
Francesca Telese, Ph.D. UCSD La Jolla, CA	Epigenetic Regulation of Gene Expression in the Brain
Matthew Worley, Ph.D. UCSD La Jolla, CA	Behavioral Economic Mechanisms of Prescription Opioid Addiction in Chronic Pain
Xinmin Simon Xie, Ph.D. Afasci Research Laboratories Redwood City, CA	Pharmacological and Toxicological Effects of Aerosolized Δ^9 -Tetrahydrocannabinol (Δ^9 - THC) on Rodents
Cathy Zhang, M.S. Pfizer La Jolla La Jolla, CA	Induction of Myeloid-Derived Suppressor Cells (MDSC) by Tetrahydrocannabinol (THC)

Table 1 Cont.

<u>PI / Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Brandon Zipp, Ph.D. Vitality Biopharma, Inc. Los Angeles, CA	Cannabinoid-Glycoside Pharmaceutical Prodrug Development and Evaluation
Alkermes Waltham, MA	A Randomized, Double-Blind, Parallel-Group Study in Healthy Subjects to Characterize Insulin Sensitivity and Lipid Metabolism in Response to Treatment with ALKS 3831 and Olanzapine (ALK3831-A108)
Alkermes Waltham, MA	A Phase 3, Multicenter Study to Assess the Long Term Safety and Tolerability of ALKS 3831 in Subjects with Schizophrenia (ALK3831-A304)
Egalet CRO: PPD Wilmington, NC	Panel Approved Research Study

Table 1 Cont.

<u>PI / Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Flamel Ireland CRO: INC Research Austin, TX	A Double-Blind, Randomized, Placebo- Controlled, Two Arm Multi-Center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy (CLFT218-1501)
GW Cambridge, UK	Panel Approved Research Study
INSYS Chandler, AZ	A Phase 2 Multicenter, Randomized, Double- Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain (INS002-16-092)
Opioid PMR Consortium (OPC) CRO: Endo Pharmaceuticals Raleigh, NC	Panel Approved Research Study
Pfizer CRO: ICON New York, NY	Panel Approved Research Study

Table 1 Cont.

<u>PI/ Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Rhodes CRO: MedSource Spokane Valley, WA	A Pharmacokinetic Study of Aptensio XR™ (Methylphenidate Hydrochloride) Extended- Release Capsules in Male or Female Preschool Children 4 to under 6 Years of Age with ADHD in Fed Condition (RP-BP-PK003)
Rhodes CRO: MedSource Spokane Valley, WA	A 12 Month Open Label Safety Study of Methylphenidate Hydrochloride Extended- Release Capsules (Aptensio XR™) in Children Ages 4-5 Years Diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) (RP-BP-EF004)
Trevena King of Prussia, PA	A Phase 3, Multicenter, Randomized, Double- Blind, Placebo- and Active-Controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain After Bunionectomy (CP130-3001)

Table 1 Cont.

<u>PI / Sponsor</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Trevena King of Prussia, PA	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain After Abdominoplasty (CP130-3002)
Trevena King of Prussia, PA	A Phase 3, Open-Label Study to Evaluate the safety of Oliceridine (TRV130) in Patients with Acute Pain for Which Parenteral Opioid Therapy is Warranted (CP130-3003)
Braeburn Princeton, NJ	A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multicenter Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder (HS-11-421)

TABLE 2

RESEARCH STUDIES CLOSED IN 2016

<u>Sponsor / PI</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Donald I. Abrams, M.D. UCSF/SFGH San Francisco, CA	Cannabinoid-Based Therapy and Approaches to Quantify Pain in Sickle Cell Disease
Philip Bickler, MD, PhD Dept of Anesthesia & Perioperative Care UCSF San Francisco, CA	Detecting Apnea in Healthy Volunteers Receiving Opiate or Sedative Medications
Kevin Chu, DO Lotus Clinical Research, LLC Pasadena, CA	A Phase 2, Randomized, Double-Blind, Placebo- and Active-Controlled Study of TRV130 for the Treatment of Acute Postoperative Pain Following Abdominoplasty (CP130-2002)
Kevin Chu, DO Lotus Clinical Research, LLC Pasadena, CA	A Phase 1, Open-Label, Single Ascending Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Fentanyl Sublingual Spray and Fentanyl Citrate Intravenous (IV) in Opioid Naive Subjects (INS002-15-049)
Judith Hellman, Ph.D. UCSF San Francisco, CA	Cannabinoid-Dependent Modulation of the Innate Immune Response to Infection and Injury

Table 2 Cont.

Sponsor / PITitle of Study / Clinical Drug
Trial Protocol

Ardis Ann Moe, M.D.
UCLA
Los Angeles, CA

Phase III, Placebo-Controlled, Double-
Blind Crossover Study of Slow-Release
Methylphenidate (Concerta™) for
Treatment of HIV Dementia

Loren Parsons, Ph.D.
Scripps
La Jolla, CA

Cognitive and Neurochemical Effects of
 Δ^9 -tetrahydrocannabinol and Related
Cannabinoids in Rodents

Joel E. Schlosburg, Ph.D.
The Scripps Research Institute
La Jolla, CA

Treatment of Opiate Dependence Through
Inhibition of Fatty Acid Amide Hydrolase

Matthew L. Springer, Ph.D.
UCSF
San Francisco, CA

Assessment of Impairment of Vascular
Function in Rats by Environmental
Exposure to Marijuana Second Hand
Smoke

Xinmin Simon Xie, Ph.D.
Afasci Research Laboratories
Redwood City, CA

Pharmacological and Toxicological Effects
of Aerosolized Δ^9 -Tetrahydrocannabinols
(Δ^9 -THC) on Rodents

Table 2 Cont.

<u>Sponsor / PI</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Alkermes Waltham, MA	A Phase 3 Multicenter Extension Study of ALKS 5461 to Assess the Long-Term Safety and Tolerability of ALKS 5461 for the Adjunctive Treatment of Major Depressive Disorder in Adults Who Have an Inadequate Response to Antidepressant Therapy (ALK5461-208EXT)
Alkermes Waltham, MA	A Phase 2, Randomized, Multicenter, Safety, Tolerability, and Dose-Ranging Study of Samidorphan, A Component of ALKS 383, in Adults with Schizophrenia Treated with Olanzapine (ALK3831-302)
GW Pharmaceuticals Cambridge, UK	Panel Approved Research Study
GW Pharmaceuticals Cambridge, UK	Panel Approved Research Study
GW Pharmaceuticals Cambridge, UK	Panel Approved Research Study
Ironshore CRO: Rho Chapel Hill, NC	Panel Approved Research Study

Table 2 Cont.

Sponsor / PITitle of Study / Clinical Drug
Trial Protocol

Janssen R&D, LLC
Raritan, NJ

A Randomized, Partially-Blind, Two-Arm, Single-Application, 3-Way Crossover Study to Evaluate the Adherence of 2 Strengths of Newly Manufactured Samples and Aged Samples of a New Formulation (JNJ-35685-AAA-G016 and JNJ-35685-AAA-G021) of Fentanyl Transdermal System Compared with DURAGESIC® Fentanyl Transdermal Patch in Healthy Subjects (FENPAI1025)

Lannett
CRO: Parexel
Waltham, MA

A Phase III Investigation of Topical Application of Cocaine HCl 4% and 10% on Safety and Efficacy in Local (Topical) Anesthesia for Diagnostic Procedures and Surgeries on or Through Accessible Mucous Membranes of the Nasal Cavities (COCA4vs10-001)

Purdue
Pickering, Ontario
Canada

A Randomized, Double-blind Study of the Time Course of Response of PRC-063 in Adults with ADHD in a Simulated Adult Workplace Environment (063-008)

Purdue
Pickering, Ontario
Canada

A Phase III, Randomized, Double-blind, Placebo-controlled, Parallel-arm, Multi-center Study Measuring the Efficacy and Safety of PRC-063 in Adolescent ADHD Patients

Table 2 Cont.

<u>Sponsor / PI</u>	<u>Title of Study / Clinical Drug Trial Protocol</u>
Purdue Pickering, Ontario Canada	A Phase III, Randomized, Double-blind, Placebo-controlled, Parallel-arm, Multi-center Study measuring the Efficacy and Safety of PRC-063 in Adult ADHD Patients (063-010)
Purdue Pickering, Ontario Canada	A Six-month, Open-label, Multi-center Study of the Safety and Efficacy of PRC-063 in Adults and Adolescents with ADHD (063-012)
Shire CRO: Premier Research Philadelphia, PA	A Phase 3, Randomized, Double-blind, Multi-center, Placebo-controlled, Dose-Optimization, Safety and Efficacy Study of SHP465 in Children and Adolescents Aged 6-17 Years with Attention-Deficit Hyperactivity Disorder (ADHD) (SHP465-305)
Shire CRO: Premier Research San Diego, CA	A Phase 3, Multicenter, Open-label Treatment-optimized, Double-blind, Randomized, Placebo-controlled, Forced-withdrawal, parallel Group Study to Evaluate the Safety and Efficacy of Evening Dosed HLD200, a Novel Delayed and Extended Release Formulation (DELEXIS) of Methylphenidate Hydrochloride, in Children Aged 6-12 with Attention Deficit Hyperactivity Disorder (ADHD) in a Laboratory Classroom Setting (HLD200-107)

APPENDIX A

CURRENTLY OPEN (*through December 31, 2016*)
 SCHEDULE I AND SCHEDULE II
 NON-HUMAN AND ACADEMIC HUMAN
 RESEARCH STUDIES

<u>Principal Investigator</u>	<u>Title of Study</u>
Mark A. Agius, M.D. UC Davis Davis, CA	Cannabis for Spasticity in MS: Placebo- Controlled Study
Nancy E. Buckley, Ph.D. CA State Polytech University Pomona, CA	Investigating the effect of THC on the susceptibility to systemic <i>C. Albicans</i> infection in mice treated with an anti-cancer drug
Nicholas Butowski, M.D. UCSF Neurological Surgery San Francisco, CA	CBD Developmental Research Project
Jeremy Caldwell, Ph.D. Genomics Institute Novartis Foundation San Diego, CA	High-Throughput Screening of Known Drugs for Novel Biological Activity in Cell-based Assays
John R. Cashman, Ph.D. Human BioMolecular Research Institute San Diego, CA	Molecular Evolution of Human Cocaine Catalysis
Kent Chu YJ Bio-Products Cordova, CA	Immunochromatographic Test Device for THC and LSD

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Laura Colin Biostride, Inc. Redwood City, CA	Panel Approved Research Study
Nissar A. Darmani, Ph.D. Western University Pomona, CA	Project 1: mechanisms of vomiting induced by chemotherapeutics, related emetics, & GI disorders. Project 2: Dev changes in monoamine function following prenatal & early postnatal exposure to serotonergic altering drugs in mice
Davide Dulcis, Ph.D. UCSD La Jolla, CA	Effects of Neonatal Nicotine Exposure on Dopamine Neurons Affecting Consumption of Substances of Abuse in the Adult
Aaron Ettenberg, Ph.D. UC Santa Barbara Santa Barbara, CA	Dopamine involvement in Opiate and Stimulant Reinforcement
Olivier George, Ph.D. The Scripps Research Institute La Jolla, CA	Animal Models of Addiction: Preliminary Studies of Vaporized THC Self-Administration in a Rat Model
Olivier George, Ph.D. The Scripps Research Institute La Jolla, CA	Animal Models of Addiction: Preliminary Studies for Heroin Dependence and Treatments

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Roy Gerona, Ph.D. UCSF, Dept OBGYN San Francisco, CA	Real Time Surveillance of Designer Drug Intoxications using Enhanced High Resolution Mass Spectrometry (HRMS) based Drug Screening and Confirmation
Mark A. Geyer, Ph.D. Dept of Psychiatry, UCSD La Jolla, CA	Effects of Cannabidiol on Mania-relevant Locomotor and Investigatory Behavior
Su Guo, Ph.D. UCSF San Francisco, CA	A novel RNA-Guided Platform for Dissecting Cannabinoid Signaling in Reward Circuit Development
Kanthi Hettiarachchi, Ph.D. SRI International Menlo Park, CA	Analysis of Controlled Substances
Kim D. Janda, Ph.D. The Scripps Research Institute La Jolla, CA	Vaccines for the Treatment of Opiate Addiction
Kim D. Janda, Ph.D. The Scripps Research Institute San Diego, CA	Immunopharmaco Therapy for Methamphetamine Addiction
Gunjan Junnarkar, Ph.D. Jazz Pharmaceuticals Menlo Park, CA	Oxybate Research

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Jay Keasling, Ph.D. Joint Bioenergy Institute Emeryville, CA	Engineering the Industrial Microbe <i>Saccharomyces Cerevisiae</i> for Biosynthesis of Cannabinoids
Thomas S. Kilduff, Ph.D. SRI International Menlo Park, CA	Neurobiological Studies of Gammahydroxybutyrate (GHB)
Edward Kisak, Ph.D. Tioga Research Inc. San Diego, CA	Research of a Topical Cannabinoid Formulation to Treat Pain and Inflammatory Disorders
Christian Adam Kekoa Koch, MD Lotus Clinical Research, Inc. Pasadena, CA	A Phase I, Multiple Ascending Dose Study to Evaluate the Pharmacokinetics, Pharmaco- dynamics, Safety and Tolerability of Fentanyl Sublingual Spray in Opioid Naive Subjects
David Kokel, Ph.D. UCSF San Francisco, CA	Behavior Based Neuroactive Drug Discovery in Zebrafish
Daniel Levin, Ph.D. S&B Pharma, Inc. Azusa, CA	Panel Approved Research Study
Daniel Levin, Ph.D. S&B Pharma, Inc. Azusa, CA	Panel Approved Research Study

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Daniel Levin, Ph.D. S&B Pharma, Inc. Azusa, CA	Panel Approved Research Study
Daniel Levin, Ph.D. S&B Pharma, Inc. Azusa, CA	Panel Approved Research Study
Walter Ling, M.D. Integrated Substance Abuse Programs, UCLA Los Angeles, CA	Analgesic Response to Opioid Analgesics in Buprenorphine-Maintained Individuals
Robert Malenka, M.D. School of Medicine Stanford University Palo Alto, CA	The Role of Oxytocin in the Pathogenesis of Autism
Thomas Marcotte, Ph.D. UCSD Health Care System San Diego, CA	A Randomized, Controlled Trial of Cannabis in Healthy Volunteers Evaluating Simulated Driving, Field Performance Tests and Cannabinoid Levels
Sean D. McAllister, Ph.D. CPMC Research Institute San Francisco, CA	Panel Approved Research Study

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Sara Mednick, Ph.D. UC Riverside Riverside, CA	The Effects of Zolpidem and Dextroamphetamine on Cognitive Performance
Byung-Sook Moon ARK Freemont, CA	Research and Development of in-Vitro Diagnostic (IVD) Immunoassays for Drug of Abuse Testing
Stephen Morairty, Ph.D. SRI International Menlo Park, CA	Panel Approved Research Study
Heinz Moser, Ph.D. Novartis Institute Emeryville, CA	Synthesis and Optimization of Novel Therapeutics
David E. Olson, Ph.D. UC Davis Davis, CA	Chemical Modulation of Neural Plasticity, Learning and Memory
Jeanne Paz, Ph.D. The J. David Gladstone Institutes San Francisco, CA	The Effects of Developmental Cannabis Exposure on Brain and Behavioral Development in Rats
Mark Peterman, Ph.D. OndaVia Hayward, CA	Development of a Rapid and Field-Ready Heroin analysis Tool

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Daniele Piomelli, Ph.D. UC Irvine Irvine, CA	1. Effect of Adolescent Cannabis Exposure in Adults Mice and Rats
Daniele Piomelli, Ph.D. UC Irvine Irvine, CA	2. In Vitro and In Vivo Pharmacological Characterization of Acid Phytocannabinoids
Florian Rader, M.D. Cedars-Sinai Med Center Los Angeles, CA	Mechanisms and Modulation of Cocaine Effects on Blood Flow to the Heart
Richard Reznichuk, M.D. Harbor-UCLA Los Angeles, CA	Panel Approved Research Study
Douglas Sears, M.D. Encino, CA	A Double-Blind, Placebo-Controlled Study of Combination Therapy in Children with ADHD
Rajkumar J. Sevak, Ph.D. UCLA Los Angeles, CA	Human Methamphetamine Self-Administration in a Progressive-Ratio Paradigm
Rajkumar J. Sevak, Ph.D. UCLA Los Angeles, CA	Safety and Initial Efficacy of Lisdexamfetamine for Modifying the Behavioral Effects of Intravenous Methamphetamine in Humans

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Neil Singla, M.D. Lotus Clinical Research, LLC Pasadena, CA	A Randomized, Open Label, Prospective Study of the Analgesic Efficacy of Oral MNK795 Compared to Generic Oxycodone/APAP in the Treatment of Moderate to Severe Post Operative Pain
Ivan Soltesz, Ph.D. Stanford University Stanford, CA	Investigating the Effect of Naturally-Occurring Cannabinoids on Synaptic Physiology, Cognition and Epilepsy
Matthew L. Springer, Ph.D. UCSF San Francisco, CA	Assessment of Harmful Cardiovascular Effects of Marijuana Secondhand Smoke and Vaporizers
Raymond Stevens, Ph.D. The Scripps Research Institute La Jolla, CA	Structure Determination of the Hallucinogens LSD and Psilocin Bound to the Serotonin Receptor 5-HT _{2B}
Michael Taffe, Ph.D. The Scripps Research Institute La Jolla, CA	Behavioral and Physiological Toxicities of Cannabinoids: Effects of Cannabidiol
Michael Taffe, Ph.D. The Scripps Research Institute La Jolla, CA	Behavioral Toxicities of Amphetamine and Cathinone Stimulant Drugs
Michael Taffe, Ph.D. The Scripps Research Institute La Jolla, CA	Behavioral Toxicities of Amphetamine and Cathinone Stimulant Drugs

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Michael Taffe, Ph.D. The Scripps Research Institute La Jolla, CA	Behavioral and Physiological Toxicities of Cannabinoids: Effects of Cannabidiol
Francesca Telese, Ph.D. UCSD La Jolla, CA	Epigenetic Regulation of Gene Expression in the Brain
Jennifer Thomas, Ph.D. San Diego State University San Diego, CA	The Effects of Developmental Cannabis Exposure on Brain and Behavioral Development in Rats
Stephen Van Dien, Ph.D. Genomatica, Inc. San Diego, CA	Panel Approved Research Study
Ronald Victor, M.D. Cedars-Sinai Med Center Los Angeles, CA	Effects of Cocaine on Blood Flow to the Heart
Friedbert Weiss, Ph.D. The Scripps Research Institute La Jolla, CA	Ethanol Seeking and Relapse: Therapeutic Potential of Transdermal Cannabidiol
Friedbert Weiss, Ph.D. The Scripps Research Institute La Jolla, CA	Implementation of Novel Methodology to Study the Anti-Relapse Potential of Cannabidiol

Appendix A Cont.

<u>Principal Investigator</u>	<u>Title of Study</u>
Timothy Wigal, Ph.D. UC Irvine Irvine, CA	Brain Dopamine Function in Adults with Attention Deficit/Hyperactivity Disorder (ADHD)
Bart Wilsey, M.D. UC Davis Medical Center Sacramento, CA	A Randomized, Cross-Over Controlled Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain
Matthew Worley, Ph.D. UCSD La Jolla, CA	Behavioral Economic Mechanisms of Prescription Opioid Addiction in Chronic Pain
Roya Yumul, MD, PhD Cedars-Sinai Med Center Los Angeles, CA	Intra-operative ketamine and methadone for laminectomy: effect on recovery, post-operative pain, and opioid requirements
Xinmin Simon Xie, Ph.D. Afasci Research Laboratories Redwood City, CA	Pharmacological and Toxicological Effects of Aerosolized Δ^9 -Tetrahydrocannabinols (Δ^9 -THC) on Rodents
Cathy Zhang, M.S. Pfizer La Jolla La Jolla, CA	Induction of Myeloid-Derived Suppressor Cells (MDSC) by Tetrahydrocannabinol (THC)
Brandon Zipp, Ph.D. Vitality Biopharma, Inc. Los Angeles, CA	Cannabinoid-Glycoside Pharmaceutical Prodrug Development and Evaluation

APPENDIX BCURRENTLY OPEN (*through December 31, 2016*)
SCHEDULE II CLINICAL DRUG TRIAL STUDIES

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
Alkermes, Inc. Waltham, MA	A Phase 3 Efficacy & Safety Study of ALK5461 for the Adjunctive Treatment of Major Depressive Disorder (Study I) (ALKS5461-205)
Alkermes, Inc. Waltham, MA	A Phase 3 Efficacy & Safety Study of ALK5461 for the Adjunctive Treatment of Major Depressive Disorder (Study II) (ALKS5461-206)
Alkermes, Inc. Waltham, MA	A Phase 2, Randomized, Double-Blind Study to Evaluate Efficacy, Safety, and Tolerability of ALKS3831 in Subjects with Schizophrenia with Alcohol Use Disorder (ALKS3831-401)
Alkermes, Inc. Waltham, MA	A Phase 3 Efficacy & Safety Study of ALKS5461 for the Adjunctive Treatment of Major Depressive Disorder (the FORWARD-5 Study) (ALKS5461-207)

Appendix B Cont.

SponsorDescription or Title
of Clinical Drug Trial Protocol

Alkermes, Inc.
Waltham, MA

A Phase 3 E & S Study of ALKS5461 for the
Adjunctive Treatment of Major Depressive
Disorder (the FORWARD-5 Study)
(ALKS5461-208)

Alkermes, Inc.
Waltham, MA

A Phase 3 Study to Evaluate Weight Gain of
ALKS 3831 Compared to Olanzapine in
Adults with Schizophrenia
(ALK3831-A303)

Alkermes, Inc.
Waltham, MA

A Phase 3 Study to Determine the
Antipsychotic Efficacy and Safety of ALKS
3831 in Adult Subjects with Acute
Exacerbation of Schizophrenia
(ALK3831-A305)

Alkermes, Inc.
Waltham, MA

A Phase 3, Multicenter Study to Assess the
Long Term Safety and Tolerability of ALKS
3831 in Subjects with Schizophrenia
(ALK3831-A306)

Appendix B Cont.

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
Alkermes, Inc. Waltham, MA	A Randomized, Double-Blind, Parallel-Group Study in Healthy Subjects to Characterize Insulin Sensitivity and Lipid Metabolism in Response to Treatment with ALKS 3831 and Olanzapine (ALK3831-A108)
Alkermes, Inc. Waltham, MA	A Phase 3, Multicenter Study to Assess the Long Term Safety and Tolerability of ALKS 3831 in Subjects with Schizophrenia (ALK3831-A304)
Braeburn Pharmaceuticals Princeton, NJ	A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multi-Center Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8mg or Less of SL Buprenorphine or Buprenorphine/Naloxone to Four Probuphine Subdermal Implants (PRO-814)
CNS Therapeutics CRO: Social & Scientific Systems	Panel Approved Research Study
CNS Therapeutics CRO: Social & Scientific Systems	Panel Approved Research Study

Appendix B Cont.

SponsorDescription or Title
of Clinical Drug Trial Protocol

Cortbus
Norwood, MA

A Phase 2, Double-Blind, randomized,
Placebo-Controlled Multicenter Study to
Evaluate safety, Tolerability, Efficacy, and
Pharmacokinetics of JBT-101 in Cystic
Fibrosis
(BT101-CF-001)

Cortbus
Norwood, MA

A Phase 2, Double-Blind, Randomized,
Placebo-Controlled Multicenter Study to
Evaluate Safety, Tolerability, Efficacy, and
Pharmacokinetics of JBT-101 in Diffuse
Cutaneous Systemic Sclerosis
(JBT101-SSc-001)

Egalet
CRO: PPD
Wilmington, NC

Panel Approved Research Study

Flamel Ireland
CRO: INC Research
Austin, TX

A Double-Blind, Randomized, Placebo-
Controlled, Two Arm Multi-Center Study to
Assess the Efficacy and Safety of a Once
Nightly Formulation of Sodium Oxybate for
Extended-Release Oral Suspension (FT218)
for the Treatment of Excessive Daytime
Sleepiness and Cataplexy in Subjects with
Narcolepsy
(CLFT218-1501)

Appendix B Cont.

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
Grunenthal/Janssen CRO : inVentiv Cary, NC	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study
GW Cambridge, UK	Panel Approved Research Study

Appendix B Cont.

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
INSYS Therapeutics Chandler, AZ	A multicenter, randomized, double-blind, placebo-controlled, interventional study to assess the safety and efficacy of pharmaceutical Cannabidiol Oral Solution as adjunctive therapy for treatment of subjects with inadequately controlled Lennox-Gastaut Syndrome (INS011-14-024)
INSYS Therapeutics Chandler, AZ	A multicenter, randomized, double-blind, placebo-controlled, interventional study to assess the safety and efficacy of pharmaceutical Cannabidiol Oral Solution as adjunctive therapy for treatment of subjects with inadequately controlled Dravet Syndrome (INS011-14-025)
INSYS Therapeutics Chandler, AZ	A multicenter, open-label, flexible dose study to assess the long-term safety of pharmaceutical Cannabidiol Oral Solution as an adjunctive treatment for pediatric and adult subjects with a treatment-resistant seizure disorder who complete INS011-14-024, INS011-14-025, or INS011-14-029 (INS011-14-030)

Appendix B Cont.

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
INSYS Therapeutics Chandler, AZ	A Phase 2 Study to Assess the Efficacy and Safety of Cannabidiol Oral Solution for the Treatment of Refractory Infantile Spasms (NIS011-15-054)
INSYS Therapeutics Chandler, AZ	A Phase I/II Study to Assess the Pharmacokinetics and Safety of Multiple Doses of Pharmaceutical Cannabidiol Oral Solution in Pediatric Subjects with Treatment-Resistant Seizure Disorders (INS011-14-029)
INSYS Therapeutics Chandler, AZ	A Phase 2 Multicenter, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Fentanyl Sublingual Spray for the Treatment of Moderate to Severe Post-Operative Pain (INS002-16-092)
Ironshore CRO: Rho Chapel Hill, NC	Panel Approved Research Study
MAPS Santa Cruz, CA	Panel Approved Research Study

Appendix B Cont.

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
MAPS Santa Cruz, CA	Panel Approved Research Study
Opioid PMR Consortium (OPC) CRO: Endo Pharmaceuticals Raleigh, NC	Panel Approved Research Study
Pfizer CRO: ICON New York, NY	Panel Approved Research Study
Pfizer CRO: ICON New York, NY	Panel Approved Research Study
Rhodes CRO: MedSource Spokane Valley, WA	A Pharmacokinetic Study of Aptensio XR™ (Methylphenidate Hydrochloride) Extended- Release Capsules in Male or Female Preschool Children 4 to under 6 Years of Age with ADHD in Fed Condition (RP-BP-PK003)

Appendix B Cont.

<u>Sponsor</u>	<u>Description or Title of Clinical Drug Trial Protocol</u>
Rhodes CRO: MedSource Spokane Valley, WA	A 12 Month Open Label Safety Study of Methylphenidate Hydrochloride Extended-Release Capsules (Aptensio XR™) in Children Ages 4-5 Years Diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) (RP-BP-EF004)
Shire CRO: PPD San Diego, CA	Panel Approved Research Study
Trevena King of Prussia, PA	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain After Bunionectomy (CP130-3001)
Trevena King of Prussia, PA	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain After Abdominoplasty (CP130-3002)

Appendix B Cont.

Sponsor

Description or Title
of Clinical Drug Trial Protocol

Trevena
King of Prussia, PA

A Phase 3, Open-Label Study to Evaluate the safety of Oliceridine (TRV130) in Patients with Acute Pain for Which Parenteral Opioid Therapy is Warranted (CP130-3003)

APPENDIX C

CURRENTLY OPEN (*December 31, 2016*)
 RESEARCH STUDIES
 ON THE TREATMENT OF CONTROLLED SUBSTANCE ABUSE

<u>Investigator or Sponsor</u>	<u>Description or Title of Research Study</u>
Keith Heinzerling, M.D. UCLA Los Angeles, CA	Randomized Trial of Ibudilast for Methamphetamine Dependence
Steven Shoptaw, Ph.D. UCLA. Los Angeles, CA	Varenicline for Methamphetamine Dependence
Steven Shoptaw, Ph.D. UCLA. Los Angeles, CA	Phase I Safety Interaction Trial of Ibudilast with Methamphetamine
Alkermes Waltham, MA	A Phase 3 Study of Evaluate the Safety, Tolerability, and Efficacy of Naltrexone for use in Conjunction with Buprenorphine in Adults with Opioid Use Disorder Prior to First Dose of Vivitrol (ALK6428-A301)

Appendix C Cont.

Investigator or SponsorDescription or Title
of Research Project

Braeburn
Princeton, NJ

A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multicenter Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder
(HS-11-421)

NIDA
The EMMES Corp.
Rockville, MD

Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT)
(0051)

APPENDIX D

SECTIONS CONCERNING THE RESEARCH ADVISORY PANEL
FROM THE CALIFORNIA HEALTH AND SAFETY CODE

§ 11213. Persons who, under applicable federal laws or regulations, are lawfully entitled to use controlled substances for the purpose of research, instruction, or analysis, may lawfully obtain and use for such purposes such substances as are defined as controlled substances in this division, upon approval for use of such controlled substances in bona fide research, instruction, or analysis by the Research Advisory Panel established pursuant to § 11480 and § 11481.

Such research, instruction, or analysis shall be carried on only under the auspices of the head of a research project which has been approved by the Research Advisory Panel pursuant to § 11480 or § 11481. Complete records of receipts, stocks at hand, and use of these controlled substances shall be kept.

§ 11480. The Legislature finds that there is a need to encourage further research into the nature and effects of marijuana and hallucinogenic drugs and to coordinate research efforts on such subjects.

There is a Research Advisory Panel which consists of a representative of the State Department of Health Services, a representative of the California State Board of Pharmacy, a representative of the Attorney General, a representative of the University of California who shall be a pharmacologist, a physician, or a person holding a doctorate degree in the health sciences, a representative of a private university in this State who shall be a pharmacologist, a physician, or a person holding a doctorate degree in the health sciences, a representative of a statewide professional medical society in this state who shall be engaged in the private practice of medicine and shall be experienced in treating controlled substance dependency, a representative appointed by and serving at the pleasure of the Governor who shall have experience in drug abuse, cancer, or controlled substance research and who is either a registered nurse, licensed pursuant to Chapter 6 (commencing with § 2700) of Division 2 of the Business and Professions Code, or other health professional. The Governor shall annually designate the private university and the professional medical society represented on the Panel. Members of the Panel shall be appointed by the heads of the entities to be represented, and they shall serve at the pleasure of the appointing power.

The Panel shall annually select a chairman from among its members.

Appendix D Cont.

§ 11480. Cont.

The Panel may hold hearings on, and in other ways study, research projects concerning marijuana or hallucinogenic drugs in this state. Members of the Panel shall serve without compensation, but shall be reimbursed for any actual and necessary expenses incurred in connection with the performance of their duties.

The Panel may approve research projects, which have been registered by the Attorney General, into the nature and effects of marijuana or hallucinogenic drugs, and shall inform the Attorney General of the head of the approved research projects which are entitled to receive quantities of marijuana pursuant to § 11478.

The Panel may withdraw approval of a research project at any time, and when approval is withdrawn shall notify the head of the research project to return any quantities of marijuana to the Attorney General.

The Panel shall report annually to the Legislature and the Governor those research projects approved by the Panel, the nature of each research project, and, where available, the conclusions of the research project.

§ 11481. The Research Advisory Panel may hold hearings on, and in other ways study, research projects concerning the treatment of abuse of controlled substances.

The Panel may approve research projects, which have been registered by the Attorney General, concerning the treatment of abuse of controlled substances and shall inform the chief of such approval. The Panel may withdraw approval of a research project at any time and when approval is withdrawn shall so notify the chief.

The Panel shall, annually and in the manner determined by the Panel, report to the Legislature and the Governor those research projects approved by the Panel, the nature of each research project, and where available, the conclusions of the research project.

§ 11603. The Attorney General, with the approval of the Research Advisory Panel, may authorize persons engaged in research on the use and effects of controlled substances to withhold the names and other identifying characteristics of individuals who are the subjects of the research. Persons who obtain this authorization are not compelled in any civil, criminal, administrative, legislative, or other proceedings to identify the individuals who are the subjects of research for which the authorization was obtained.

Appendix D Cont.

§ 11604. The Attorney General, with the approval of the Research Advisory Panel, may authorize the possession and distribution of controlled substances by persons engaged in research. Persons who obtain this authorization are exempt from state prosecution for possession and distribution of controlled substances to the extent of the authorization.

§ 24172. Experimental subject's bill of rights; contents

As used in the chapter, "experimental subject's bill of rights," means a list of the rights of a subject in a medical experiment, written in a language in which the subject is fluent. Except as otherwise provided in § 24175, this list shall include, but not be limited to the subject's right to:

- (a) Be informed of the nature and purpose of the experiment.
- (b) Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.
- (c) Be given a description of any attendant discomforts and risks reasonably to be expected from the experiment.
- (d) Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
- (e) Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.
- (f) Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.
- (g) Be given an opportunity to ask any questions concerning the experiment or the procedures involved.
- (h) Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

Appendix D Cont.

§ 24172. Cont.

- (i) Be given a copy of the signed and dated written consent form as provided for by § 24173 or § 24178.
- (j) Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

§ 24173. Informed consent

As used in this chapter, "informed consent" means the authorization given pursuant to § 24175 to have a medical experiment performed after each of the following conditions have been satisfied:

- (a) The subject or subject's conservator or guardian, or other representative, as specified in § 24175, is provided with a copy of the experimental subject's bill of rights, prior to consenting to participate in any medical experiment, containing all the information required by § 24172, and the copy is signed and dated by the subject or the subject's conservator or guardian, or other representative, as specified in § 24175.
- (b) A written consent form is signed and dated by the subject or the subject's conservator or guardian, or other representative, as specified in § 24175.
- (c) The subject or subject's conservator or guardian, or other representative, as specified in § 24175, is informed both verbally and within the written consent form, in nontechnical terms and in a language in which the subject or the subject's conservator or guardian, or other representative, as specified in § 24175, is fluent, of the following facts of the proposed medical experiment, which might influence the decision to undergo the experiment, including, but not limited to:
 - (1) An explanation of the procedures to be followed in the medical experiment and any drug or device to be utilized, including the purposes of the procedures, drugs, or devices. If a placebo is to be administered or dispensed to a portion of the subjects involved in a medical experiment, all subjects of the experiment shall be informed of that fact; however, they need not be informed as to whether they will actually be administered or dispensed a placebo.

§ 24173. Cont.

(2) A description of any attendant discomfort and risks to the subject reasonably to be expected.

(3) An explanation of any benefits to the subject reasonably to be expected, if applicable.

(4) A disclosure of any appropriate alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.

(5) An estimate of the expected recovery time of the subject after the experiment.

(6) An offer to answer any inquiries concerning the experiment or the procedures involved.

(7) An instruction to the subject that he or she is free to withdraw his or her prior consent to the medical experiment and discontinue participation in the medical experiment at any time, without prejudice to the subject.

(8) The name, institutional affiliation, if any, and address of the person or persons actually performing and primarily responsible for the conduct of the experiment.

(9) The name of the sponsor or funding source, if any, or manufacturer if the experiment involves a drug or device, and the organization, if any, under whose general aegis the experiment is being conducted.

(10) The name, address, and phone number of an impartial third party, not associated with the experiment, to whom the subject may address complaints about the experiment.

(11) The material financial stake or interest, if any, that the investigator or research institution has in the outcome of the medical experiment. For purposes of this section, "material" means ten thousand dollars (\$10,000) or more in securities or other assets valued at the date of disclosure, or in relevant cumulative salary or other income, regardless of when it is earned or expected to be earned.

Appendix D Cont.

§ 24173. Cont.

(d) The written consent form is signed and dated by any person other than the subject or the conservator or guardian, or other representative of the subject, as specified in § 24175, who can attest that the requirements for informed consent to the medical experiment have been satisfied.

(e) Consent is voluntary and freely given by the human subject or the conservator or guardian, or other representative, as specified by § 24175, without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence.

Attachment %\$

Communication and Public Education Communication Plan

The board educates consumers, licensees and stakeholders about the practice and regulation of the profession.

2017-2021

4.1 Develop and implement a communication plan for licensees and consumers to improve communication and keep these stakeholders better informed.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Provide direction and new assignments	Staff	Board, committee requests at meetings	To carry out board, committee requests to communicate with licensees, public	Board, C&PE Committee, Staff	Ongoing
b. Explore ways to engage more directly with licenses	Licensees	Solicit pharmacist input at board meetings, events	Foster dialogue, communication between licensees and board	Board, C&PE Committee, Staff	Ongoing

4.2 Identify and use additional resources for public and licensee outreach services to implement a communication plan.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Website	Licensees and Consumers	Post news, announcements online	Communicate immediate information to licensees, public	Staff	Ongoing
b. Newsletter	Licensees and Consumers	Publish news, announcements in formatted	Communicate to licensees, public	Staff	Quarterly 2018

Communication and Public Education Communication Plan

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		publication			
c. Subscriber alerts	Licensees and Consumers	Notices of recalls, regulations, news, important information	Communicate instantly to licensee, public	Staff	Ongoing 2018
d. News archive	Licensees, Consumers	Website announcements, Script articles	Permanently archive web announcements in easy-to-find place	Staff	Completed January 2017
e. Topic pages	Licensees	Important information for licensees	Organize information by topic on easy-to-find webpages	Staff	Ongoing 2018

4.3 Establish a process to collect email addresses and mobile numbers for text messaging, from all licensees for better ability to improve communications.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Research means to collect email addresses	Licensees	Mechanism to collect email addresses	To distribute information to licensees	Board staff C&PE Committee	Completed spring 2017
b. Research means to collect mobile telephone numbers	Licensees	Mechanism to collect mobile telephone numbers	To distribute information to licensees	Board staff C&PE Committee	TBD

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2017-2021

4.4 Educate licensees about the board's regulations by publishing summaries of all newly issued regulations and explain implementation tactics.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Inform licensees of new regulations	Licensees	Website Subscriber alert Newsletter	Disseminate information about new regulations	Board staff	Ongoing 2018
b. Cohost training forum on drug abuse topics	Licensees	Training at live event	CE for licensees	Staff, DEA, UCSD School of Pharmacy	March, August, October, November 2017; January 2018
c. Produce CE courses	Licensees	Live sessions, webinar	Educate licensees on Pharmacy Law	Staff	Ongoing 2018
d. Update online lawbook	Licensees, public	Website	Inform licensees about new laws and regulations for 2018	Staff	January 2018

4.5 Inspect pharmacies at least once every four years to provide a forum for licensee-inspector communication and education in practice settings.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Inspect pharmacies at least once every four	Licensee – pharmacies	Inspection	Forum for licensee-inspector interaction	Inspectors Board staff	TBD

Communication and Public Education Communication Plan

The board educates consumers, licensees and stakeholders about the practice and regulation of the profession.

2017-2021

years

4.6 Communicate the availability of new or specified pharmacy services and locations so that the public is aware of pharmacies that can meet their needs.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Naloxone availability at pharmacies	Consumers	Website	Inform the public	Board staff	TBD

4.7 Revise consumer-facing materials (e.g., posters, point-to-your-language notices, television messages) to achieve better consumer understanding of their rights and optimal use of medications.

Task	Audience	Content/Methods	Purpose	Responsible Parties	Timing
a. Notice to Consumers	Consumers	Update regulation language	Inform consumers of rights	Board staff C&PE Committee	TBD
b. Point-to-your-language notice	Consumer	Update regulation language	Inform consumers of rights	Board staff C&PE Committee	TBD