

**ENFORCEMENT AND COMPOUNDING COMMITTEE
MEETING MATERIALS
DECEMBER 14, 2015**

Amy Gutierrez, PharmD, Chair, Board President

Greg Lippe, Public Member, Vice Chair

Stan Weisser, Professional Member

Allan Schaad, Professional Member

Rosalyn Hackworth, Public Member

Greg Murphy, Public Member

I. PUBLIC COMMENT FOR ITEMS NOT ON THE AGENDA/AGENDA ITEMS FOR FUTURE MEETINGS

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

II. ENFORCEMENT MATTERS

a. Presentation by the California Department of Health Care Services on California's Drug Utilization Review Program and the Medi-Cal DUR Educational Bulletin on "Morphine Equivalent Daily Dose to Prevent Opioid Overdose"

Attachment 1

There is housed in the California Department of Health Care Services a Drug Utilization Review Committee that supports the state's Medi-Cal program in creating drug benefits. Board Member Allen Schaad has asked that this program provide an overview of its duties and functions to the board's Enforcement and Compounding Committee, this will occur during this meeting. There will be three presentations as part of this segment.

- Pauline Chan, R.Ph., MBA, California Department of Health Care Services
- Shal Lynch, PharmD, CGP, Health Sciences Associate Clinical Professor
UCSF Department of Clinical Pharmacy, School of Pharmacy
- Randall S. Stafford, MD, PhD, Medi-Cal DUR Board Member, Professor of Medicine, Stanford University

The committee will hear a second presentation of the evaluation of morphine equivalent daily dose (MEDD) in patient care. Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers. Recent studies demonstrate that a patient's cumulative MEDD is an indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose. As a result, many state Medicaid Drug Utilization Review (DUR) programs have established recommendations for MEDD or opioid dose limitation.

At this meeting, the California Department of Health Care Services will provide an overview of the Medi-Cal DUR program, and discuss the Medi-Cal DUR educational bulletin “Morphine Equivalent Daily Dose to Prevent Opioid Overdose.” A copy of the article is provided in **Attachment 1**.

b. Legislative Proposal for the Board of Pharmacy to Establish a List of Synthetic Cannabinoids that Would be Illegal for Use in California

Attachment 2

Spice (synthetic cannabinoids) and *bath salts* (synthetic cathinones) refer to two groups of designer drugs that have increased in popularity in recent years. These substances are created with *analogs* of commonly used illicit drugs. An analog is one of a group of chemical compounds that are similar in structure and pharmacology. **Attachment 2** contains a number of fact sheets on these products.

A form of synthetic cannabinoids, commonly referred to as “Spice” or “K2,” is designed to affect the body in a manner similar to marijuana, but is not derived from the marijuana plant. These substances began appearing across the U.S. in 2008, and their popularity grew over the following years mainly because they could be sold legally and not detected in urinalysis drug tests.

These substances contain different ingredients that have been reported to cause a number of physical reactions including agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremors, seizures, hallucinations, paranoid behavior, and no responsiveness. Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new products of this type makes it difficult to detect these chemicals or regulate products that contain these substances.

Although these substances were made illegal nationally in 2012, synthetic cannabinoids and cathinones remain available, generally through black market internet sites, indicating a need for continued education, prevention, and enforcement.

Young adults and youth are often the buyers.

California’s Health and Safety Code as amended effective 1/1/16 provides the following:

11375.5. [Stimulants]

- (a) Every person who sells, dispenses, distributes, furnishes, administers, or gives, or offers to sell, dispense, distribute, furnish, administer, or give, any synthetic stimulant compound specified in subdivision (c), or any synthetic stimulant derivative, to any person, or who possesses that compound or derivative for sale, is guilty of a misdemeanor, punishable by imprisonment in a county jail not to exceed six months, or by a fine not to exceed one thousand dollars (\$1,000), or by both that fine and imprisonment.

- (b) Every person who uses or possesses any synthetic stimulant compound specified in subdivision (c), or any synthetic stimulant derivative, is guilty of *an infraction, punishable by a fine not to exceed two hundred fifty dollars (\$250)*.
- (c) Unless specifically excepted, or contained within a pharmaceutical product approved by the United States Food and Drug Administration, or unless listed in another schedule, subdivisions (a) and (b) apply to any material, compound, mixture, or preparation which contains any quantity of a substance, including its salts, isomers, esters, or ethers, and salts of isomers, esters, or ethers whenever the existence of such salts, isomers, esters, or ethers, and salts of isomers, esters, or ethers is possible, that is structurally derived from 2-amino-1-phenyl-1-propanone by modification in one of the following ways:
- (1) By substitution in the phenyl ring to any extent with alkyl, alkoxy, alkylenedioxy, haloalkyl, or halide substituents, whether or not further substituted in the phenyl ring by one or more other univalent substituents.
 - (2) By substitution at the 3-position with an alkyl substituent.
 - (3) By substitution at the nitrogen atom with alkyl or dialkyl groups, or by inclusion of the nitrogen atom in a cyclic structure.
- (d) This section shall not prohibit prosecution under any other provision of law.

And

11357.5. [Synthetic Cannabinoids]

- (a) Every person who sells, dispenses, distributes, furnishes, administers, or gives, or offers to sell, dispense, distribute, furnish, administer, or give, or possesses for sale any synthetic cannabinoid compound, or any synthetic cannabinoid derivative, to any person, is guilty of a misdemeanor, punishable by imprisonment in a county jail not to exceed six months, or by a fine not to exceed one thousand dollars (\$1,000), or by both that fine and imprisonment.
- (b) Every person who uses or possesses any synthetic cannabinoid compound, or any synthetic cannabinoid derivative, is guilty of an infraction, punishable by a fine not to exceed two hundred fifty dollars (\$250).
- (c) As used in this section, the term “synthetic cannabinoid compound” refers to any of the following substances:
- (1) Adamantoylindoles or adamantoylindazoles, which includes adamantyl carboxamide indoles and adamantyl carboxamide indazoles, or any compound structurally derived from 3-(1-adamantoyl)indole, 3-(1-adamantoyl)indazole, 3-(2-adamantoyl)indole, N-(1-adamantyl)-1H-indole-3-carboxamide, or N-(1-adamantyl)-1H-indazole-3-carboxamide by substitution at the nitrogen atom of the indole or indazole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the indole or indazole ring to any extent and whether or not substituted in the adamantyl ring to any extent, including, but not limited to, 2NE1, 5F-AKB-48, AB-001, AKB-48, AM-1248, JWH-018 adamantyl carboxamide, STS-135.

- (2) Benzoylindoles, which includes any compound structurally derived from a 3-(benzoyl)indole structure with substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent, including, but not limited to, AM-630, AM-661, AM-679, AM-694, AM-1241, AM-2233, RCS-4, WIN 48,098 (Pravadoline).
- (3) Cyclohexylphenols, which includes any compound structurally derived from 2-(3-hydroxycyclohexyl)phenol by substitution at the 5-position of the phenolic ring by alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the cyclohexyl ring to any extent, including, but not limited to, CP 47,497, CP 55,490, CP 55,940, CP 56,667, cannabicyclohexanol.

And more of this follows in the section.

At this meeting, the committee will review and discuss a legislative concept that would be authored as 2016 legislation by Senator Hernandez to have the Board of Pharmacy establish a list of synthetic cannabinoids and stimulants that would be illegal for use in California until incorporated formally as statutory modifications into Health and Safety Code sections 11375.5 and 11357.5. Currently the Senator's office is working on the language.

c. Update by the University of California, San Diego on Its Pilot Program to Permit Patients to Access Medication from an Automated Storage Device not Immediately Adjacent to a Pharmacy

Attachment 3

At the Board of Pharmacy's April 2015 Board Meeting, the board approved an 18-month pilot study under the auspices of the UCSD School of Pharmacy involving use of an automated storage device for prescription medication for which staff and their families of a Sharp Hospital in San Diego, who opt in, may pick up their outpatient medications from this device located in a hospital, instead of having to go to the community pharmacy. Consultation will be provided via telephone before medication can be dispensed to a patient.

This study was planned to start in June or July, 2015; however, at the September 9, 2015 Enforcement Committee meeting, Dr. Jan Hirsch, BS Pharm, PhD, spoke via telephone and anticipated the pilot study would not begin until December.

At this meeting, Dr. Hirsch will provide an update via telephone and respond to questions from the committee. A copy of her presentation is included in **Attachment 3**.

Reports on this study will be provided at each quarterly Enforcement and Compounding Committee while the study is underway.

d. Sunset Review Proposals

The board's 2016 Sunset Report was submitted to the Legislature when it was due on December 1, 2015. Below are several issues highlighted in the report. This committee will have an opportunity to discuss these items.

1. Regulation of Outsourcing Facilities by the Board

In 2012, medication contaminated by fungal material that was compounded by a Massachusetts pharmacy killed 65 and injured approximately 700 individuals in various states. In response, the California Board of Pharmacy initiated a review of its then sterile injectable compounding requirements that had been enacted in 2001. Among other actions, the board sponsored legislation in 2013 to increase licensure requirements for sterile compounding pharmacies (SB 294, Chapter 565, Emmerson). The legislation expanded the definition of sterile compounding to include injectable medications, inhalation products and medication applied in the eyes. The law also eliminated accreditation by outside agencies as an alternative to licensure with annual board inspections, and the board began a massive upgrading of its sterile compounding regulations, a process that is nearing completion in late 2015.

The November 2013 enactment of the federal Drug Quality and Security Act (DQSA) responded to the 2012 compounding tragedy in a new way: this legislation created a new type of entity authorized to compound medications – the outsourcing facility. These generally large-scale production facilities are authorized to compound large quantities of medications for use by other entities, whereas a pharmacy generally compounds pursuant to a patient-specific prescription. Medications prepared by outsourcing facilities must be done under current good manufacturing practices (or cGMPs), which are more stringent than compounding requirements for sterile compounding pharmacies, since many patients in multiple locations can receive these medications that are not usually linked to patient-specific prescriptions.

Currently California is licensing as sterile compounding pharmacies federally licensed outsourcing facilities located within or shipping medication into California. This is increasingly losing its viability as a regulatory solution. First, it does not recognize the federal outsourcing requirements that permit large scale compounding. Second multiple states are moving to establish regulatory frameworks to license outsourcing facilities as separate entities, and some bar licensure of these facilities in their home states as sterile

compounding pharmacies. This is currently an issue in Mississippi, will and be an issue in July in New Jersey. Several other states have pending legislation in this area as well.

In 2015, the board sponsored legislation (SB 619, Morrell) to license outsourcing facilities as separate entities both within and outside California to ship into the state. This bill was held in suspense by the Senate Appropriations Committee. In 2016, the board seeks to resume pursuing regulation of outsourcing facilities as separate entities. The Senate Business and Professions Committee will evaluate outsourcing facilities as part of its evaluation of the impact of the DQSA during our sunset review. A legislative solution is likely to come as part of this review.

At this meeting, the committee will discuss pursuing legislation to establish licensing programs for outsourcing facilities located within and outside California.

2. Registration of Automated Delivery Devices in Use

Pharmacies are able to operate automated dispensing machines or devices in various settings away from the licensed pharmacy. This includes in:

- Skilled nursing homes and other health care facilities licensed under Health and Safety Code section 1250 (c), (d) or (k) (the devices are authorized under section 1261.6 of the Health and Safety Code, authority for pharmacies to do this in specific locations is specified in Business and Professions Code section 4119.1)
- Clinics licensed under section 4180 of the Business and Professions Code (the devices are authorized under section 4186) – these include licensed, nonprofit community or free clinics defined under Health and Safety Code 1204(a)(1), a clinic operated by a federally recognized Indian tribe or tribal organization referred to in Health and Safety Code section 1206(b), a clinic operated by a primary care community or free clinic operated on a separate premises from a licensed clinic and that is open no more than 20 hours per week as referred to in Health and Safety Code section 1206(h), a student health center clinic operated by a public institution of higher education such as college health center as referred to in Health and Safety Code section 1206(j).
- Hospitals may use Pyxis or Pyxis-type machines throughout a hospital to store medication under application of provisions in Title 22 that allow drugs to be stored in nursing stations. The Pyxis and like devices are considered secured storage units for drugs.

The board has no idea how many of these machines are in use, where they are in use, or which pharmacy is responsible for any machine.

The demand for additional use of devices is growing. As scheduled earlier at this meeting, a pilot study is underway that if proven valuable, would allow patients to pick up medication from machines not specifically located in a pharmacy.

At the September 9, 2015, Enforcement Committee meeting, staff suggested that a simple registration be established for pharmacies that operate each of these machines that identifies their locations, as a beneficial step in board oversight and enforcement. The list could be updated as needed via form submission to the board by a pharmacy adding, moving or removing a machine. This registration could operate much like the off-site storage waivers for records waivers. Then at annual renewal of the pharmacy, the pharmacy would update or confirm the list of machines it operates and where each is located. Staff noted that a regulation or statutory amendment is likely needed to establish this requirement.

At this meeting, the committee will discuss pursuing legislation to establish a registration requirement to link automated delivery systems to the pharmacy that owns and is responsible for the medications stored and released from the delivery device.

e. Proposal for Routine Inspections of Pharmacies every Four Years

The board’s charge to regulate the pharmacy profession necessitates routine inspections of licensed facilities to confirm adherence to or identify failures in adherence to the requirements of pharmacy law. Failure to perform such inspections means that the board’s enforcement program is reactive rather than proactive and relies solely on being advised of a potential violation of pharmacy law via a complaint or other information that would trigger an investigation.

For a number of years the board has wanted to inspect all facilities every three or four years. The board has been unable to complete these routine inspections of all facilities with any regularity, and in recent years has had to substantially reduce such inspections. While inspections are completed, inspections occur generally as part of the investigative process, prior to issuance or renewal of a sterile compounding license or as part of probation monitoring.

All Inspections FY11-12 thru FY14-15 by Visit Type					
# of Inspections					
Inspection Type	FY11-12	FY12-13	FY13-14	FY14-15	Total
Routine	1730	1010	287	342	3369
Investigation	743	896	875	926	3440
Probation/PRP	258	228	139	227	852
Sterile Compounding	268	276	996	1067	2607
Other	34	39	32	26	131
Grand Total	3033	2449	2329	2588	10399

Mandatory inspections on a routine but random basis would enable the board to perform compliance inspections to educate licensees about pharmacy law as well as identify problems early to prevent more serious consumer issues from developing. Like all inspections, such inspections would be unannounced.

Compliance inspections provide an opportunity for board staff to answer questions about pharmacy law and to complete follow up inspections of facilities previously issued either citations or letters of admonishment to confirm compliance.

Mandatory inspections once every four years would be an alternative to our current practice of conducting inspections principally to investigate problems (or inspect sterile compounders).

The board currently has 6,572 community pharmacies licensed in California. Some of these pharmacies have never been inspected by the board. The creation of a statutory mandate directing the board to perform inspections of all pharmacies every four years would require approximately 1650 routine inspections annually. Over the last two years, the board completed an average of 1,215 inspections annually (routine plus investigation inspections).

f. Discussion on Items in the News:

1. "Preventing Diversion in the ED" from www.pppmag.com, November 2015

Attachment 4

The article in **Attachment 4** has been added to the agenda by Board President and Committee Chair Gutierrez. In the article, the author asserts that drug diversion by health care workers is quite common. The article reviews the techniques health care workers use to divert drugs and suggests multifaceted approaches for preventing and identifying diversion.

2. Settlement Agreement Between the Drug Enforcement Administration and Massachusetts General Hospital for Drug Diversion

Attachment 5

Earlier this fall, the U.S. Drug Enforcement Administration alleged that Massachusetts General Hospital failed to make and keep records required by the Controlled Substances Act, and failed to provide effective controls and procedures to guard against theft and loss of controlled substances from October 4, 2011 through April 1, 2015. On September 28, 2015, Massachusetts General Hospital agreed to pay a settlement amount of \$2,300,000.

A copy of the settlement is provided in **Attachment 5**.

The settlement agreement provides information about drug diversion from a prestigious US hospital.

g. Review of Controlled Substances Losses Reported to the Board

Board discussions in recent meetings have discussed drug thefts from automated drug dispensing machines. Board staff was recently asked to tabulate how many controlled substances losses have been reported to the board from automated dispensing machines.

While there is no category listed on the DEA 106 report to capture this specific type of data, board staff reviewed all loss reports since July 1, 2015 and identified the following losses that had been identified to automated dispensing machines. When reviewing the data keep in mind that:

1. The amount of controlled substances reported lost is usually lower than the actual amount of loss determined at the end of an investigation, and
2. Without a reporting category for this type of loss, some losses from automated dispensing machines could be reported under other categories.

Reports of Losses Related to Automatic Dispensing Machines (ADMs: Pyxis, Omnicell, Acudose, etc.) January 1, 2015 - November 30, 2015	Total # Reports	ADM Losses - Percent of Total Reports	Total Dosage Units Lost
180	2,267	8%	6,714

*total dosages (mLs converted into 5mL dosage units and added to solids)

Board of Pharmacy License Type for ADM Losses	# of Reports
Hospitals	177
Pharmacies	3
Total	180

Type of loss	# of Reports
Pilferage/Possible Pilferage or Not following proper procedures by nurse(s)	97
Unknown cause	78
Lost in transit to/from Automatic Dispensing Machine	2
Automatic Dispensing Machine error	1
Possible Pilferage by Pharmacy Technician	1
Possible Theft by patient	1
Total	180

The board will begin reporting all controlled substances losses reported to the board at each Enforcement and Compounding Committee Meeting.

h. Update on the CURES 2.0 Prescription Monitoring Program

Attachment 6

The California Department of Justice is continuing to work on upgrading the CURES system. On June 30, the DOJ had a “soft launch” of CURES 2.0 as the new system is called. Since then the DOJ has been working to pilot test the new system and install upgrades that will permit conversion to the new, enhanced system.

The DOJ’s press release that was prepared in late June on the soft launch of CURES 2.0 is provided in **Attachment 6**.

At the September 9, 2015, Enforcement Committee Meeting, staff from the California Department of Justice provided an update on the transition to the new CURES 2.0 system and advised the committee that CURES 2.0 should be available to users by January 2016. It was stated that 18,487 pharmacists, less than 50 percent of California’s licensed pharmacists, had registered for CURES 2.0.

Meanwhile, the board continues to register pharmacists at CE events it hosts.

At this meeting, Executive Officer Herold, who sits on the DOJ/DCA Change Control Board for CURES, will provide an update on CURES 2.0 program.

In another area of program change, the board advised licensees in the most recent *The Script*, of legislation that moved the CURES mandatory registration date for prescribers and dispensers to July 2016.

i. Enforcement Options for Patient Consultation Violations

Attachment 7

Nearly 25 years ago, the Board of Pharmacy promulgated regulations to require pharmacists to consult with patients every time they receive a medication for the first time. The board included in the regulation additional occasions where a pharmacist must consult a patient – where the patient has questions or the pharmacist believes a medication warrants consultation. A copy of the requirement is provided in **Attachment 7**.

Sometimes California's requirements are confused with national requirements enacted about the same time by CMS for Medicare patients in what was known as "OBRA 90." However, California's requirements were actually adopted before OBRA 90's requirements. The OBRA 90 requirements provided that Medicare patients be offered consultation when they receive medication for the first time. So California's requirements, requiring the pharmacist to initiate consultation, were stronger and broader than the OBRA 90 requirements in that they pertained to all patients, not just those whose medications were paid for by Medicare, establishing one standard of care for all patients in California.

After approval of California's patient consultation requirements, the board also delayed implementation of patient consultation at the request of the profession because pharmacists stated they could not provide consultation without the aid of pharmacy technicians. So the approved patient-consultation regulation was delayed so that the board could secure statutory authority and then promulgate regulations to establish the licensure of pharmacy technicians to "free" the pharmacist to provide consultation.

California's requirement is for the pharmacist to consult the patient – not to offer to consult. When doing the consultation rulemaking, the board emphasized that consultation was to be initiated by the pharmacist, and that any denial of the consultation must be made directly to the pharmacist, other staff (e.g., pharmacy technicians or ancillary staff) were not to screen for consultation by asking if the patient wanted to speak to the pharmacist or had questions about the medication. Consultation was required whenever the patient or the patient's agent was present in the pharmacy to receive the consultation.

Over the years, the board has added other enhancements to help ensure patients receive meaningful consultation, including a notice to consumers poster that must be posted in a pharmacy that specifically states the pharmacist must consult with each patient about his or her new medication, and lists the 5 questions a patient should understand before taking a prescription medication.

More recently in promulgating the requirements for patient-centered labels, the board required that oral consultation services be available in 12 languages to aid limited-English speaking patients in better understanding how to take their prescription medication.

Over the years, the board has enforced its patient consultation requirements in various ways. Initially it was one of the first violations for which the board used its citation and fine authority. In recent years, the board has typically assessed fines of approximately \$1,000 when it observes failure to consult during an inspection. Where a medication error has occurred and consultation was not provided, the board generally issues a higher fine.

In 2011, board staff began working on a project with three California district attorneys' offices to aid in the board's enforcement of patient consultation. Using the state's unfair business practices statute in Business and Professions Code section 17200, the DAs' offices were able to assess higher fines for failure to consult. Additionally, the DAs' offices used undercover investigators to pass prescriptions, an action the board has not done.

The DAs' investigations have resulted in more substantial fines to three pharmacy chains where investigations have been completed – CVS (2013, \$658,500), Rite Aid (2014, \$498,250) and recently Walgreens (2015, \$502,000).

At the September 9, 2015, committee meeting, the committee heard questions and comments from the public regarding whether the board can prohibit the use of a system that requires a patient to accept or decline patient consultation in advance of payment. The committee requested that the Communication and Public Education committee focus on consumer education and why patient consultation is important.

This item is on the agenda in the event the committee wishes to discuss sanctions for failure to consult, or to wait for the Communication and Public Education Committee to complete its work on review consultation matters before discussing sanctions.

j. Discussion and Update to the Board's Emergency Response Policy

Attachment 8

On September 15, 2015, the board held an Emergency Board Meeting in response to the wildfires in Lake and Napa counties. In light of the recent use of the policy it is being brought to the board for evaluation and assessment to determine if changes to the policy are necessary.

At the October 28-29, 2015 board meeting, this item was referred to the enforcement committee for discussion.

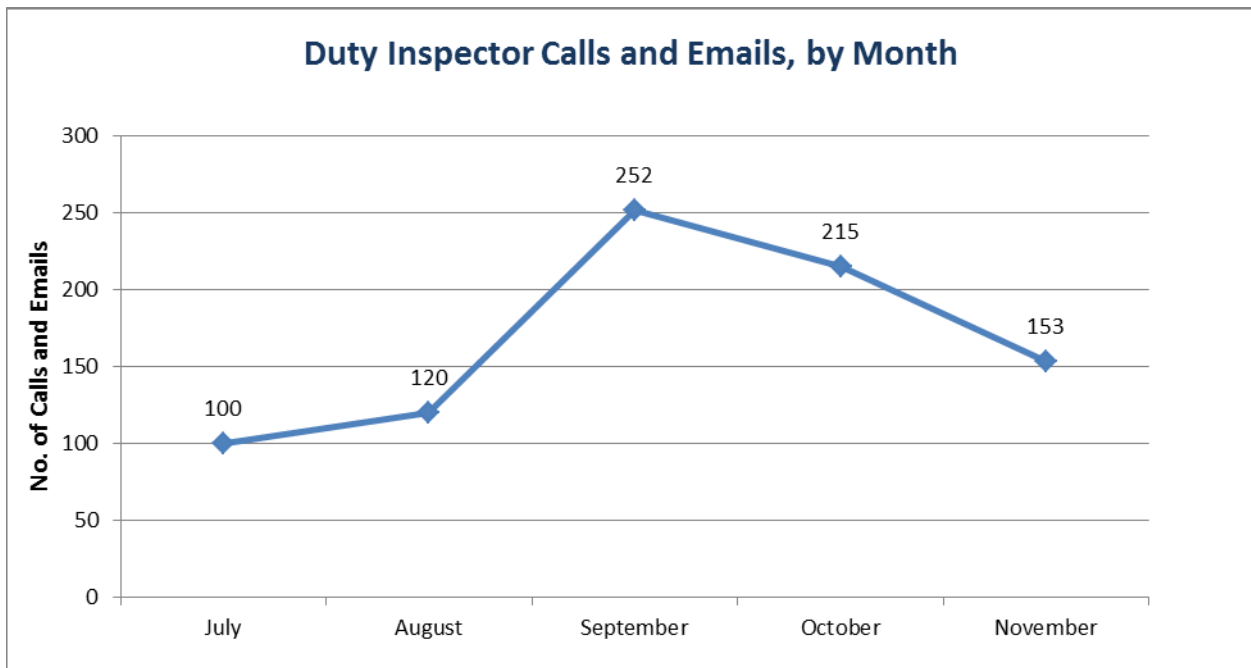
Attachment 8 contains the board's current emergency response policy, an excerpt of the board meeting minutes where the policy was adopted and a copy of Business and Professions Code section 4062.

k. Review of Duty Inspector Activities

Attachment 9 shows the number of pharmacy inspector calls handled by the board’s Complaint Unit during the first half of the 2015-2016 fiscal year.

Since July 1, 2015, Pharmacy Board inspectors have responded to 840 calls, an average of 168 calls each month. Our highest month was September, with 252 calls. July was our lowest month, with 100 calls.

Chart: All Inspector Calls, Trends by Month



In September, we expanded our inspector answer program in two ways. First, we tripled the hours inspectors take phone calls from six hours each week to 16 hours. Second, we added the “Ask.Inspector” email box. Board inspectors respond to emails five days a week. Additionally, in September, we sent our licensees a Subscriber Alert to let them know of our expanded inspector hours.

The addition of the added call hours and the email box has resulted in a significant increase in activity. In September, our inspector requests more than doubled from August. There were 120 calls in August and 252 in September, an increase of 115 percent. In September and October, our inspectors handled more than 200 calls each month. In October and November, the number of calls declined but not yet back to the August levels.

The September spike in inspector calls may be temporary, but it is too soon to be certain. Our office was closed for three days in November for holiday observances. It is possible these closures contributed to the declines.

We will continue to provide these statistics at future meetings.

The board's new public information officer is beginning to work to establish an online resource directory FAQ. The goal is to put many questions and answers online so individuals may find their own answers. The public information officer is just beginning training to do this.

More data is provided in **Attachment 9**.

III. COMPOUNDING MATTERS

a. 2015 FDA Intergovernmental Meeting on Drug Compounding and Drug Supply Chain Security Held in November 2015

Attachment 10

On November 16 and 17, the FDA convened the 2015 Intergovernmental Working Meeting on Drug Compounding and Supply Chain Security. This meeting had representatives from about 45 states and was intended to exchange information with states as the 2013 Drug Quality Security Act is being implemented.

Executive Officer Herold and a deputy director from the California Department of Public Health were California's attendees.

The purpose of the meeting was to update states on emerging FDA policy regarding sterile compounding, outsourcing facilities and supply chain security requirements (the latter are the provisions that preempted California's e-pedigree requirements).

Most of the meeting focused on compounding/outsourcing requirements, with the last quarter of the meeting focusing on the licensing requirements for wholesalers and third-party logistics providers. Executive Officer Herold provided presentations during both segments.

Attachment 10 contains information on two presentations provided during the two-day meeting. Below is an overview of the agenda:

1. Compounding Regulatory Policy Update
2. Draft Standard Memorandum of Understanding between FDA and the States
3. Information Sharing and Disclosures (between state agencies and FDA)
4. A Comparison of US Pharmacopeial Convention General Chapter 797 to the Current Good Manufacturing Practice Regulations Enforced by DEA
5. Inspections of Sterile compounding Facilities and Enforcement

6. State Handling of Outsourcing Facilities
7. Overview of DSCSA Implementation
8. Wholesaler Distributor and 3PL Provider Licensing
9. FDA and State Collaboration

During this committee meeting Ms. Herold will discuss information provided from several other presentations.

During this committee meeting, Executive Officer Herold will highlight some of the specific information.

b. Development of a Waiver Process from Building Standards Requirements Contained in Proposed Title 16 California Code of Regulations Sections 1751 et seq.

During the October 2015 board meeting, the board discussed and took action on proposed changes to compounding requirements. As part of this discussion, the board discussed the need to establish a waiver requirement for some of the structural requirements. Suggested components to facilitate such a process were included in the most recent modifications to the proposed regulation (where the comment period ended December 5). As proposed in the regulation (as subdivision 1735.6(f) and in 1751.4(l)), the waiver request shall:

1. be made in writing
2. identify the provision(s) requiring physical construction, alteration, or improvement
3. contain a timeline for any such change

Consistent with the proposed language which was noticed for comment, board staff will work on development of a specific format upon adoption of the language by the board. Board review of the last proposed modifications to the compounding regulation will be scheduled for the next board meeting.

c. Review of “USP <800>: Key Considerations and Changes for Health Systems,” Hospital Pharmacy 2015; 501(1):941-949

Attachment 11

This topic has been added to the agenda by President Gutierrez.

On March 28, 2014, the United States Pharmacopeia and the National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3). USP <800> serves as a new standard to guide the handling of hazardous drugs in order to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, and administration and disposal of both sterile and nonsterile products and preparations. According to this review, “Although

complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way. “

The paper in **Attachment 11** explores some of the more important aspects of the regulations in USP <800>.

The final version of the chapter will be published on Feb 1, 2016 and USP states it will become enforceable on July 1, 2018.

IV. MEETING DATES FOR 2016

The Enforcement Committee will meet on the following dates during 2016:

- March 2, 2016
- June 1, 2016
- August 31, 2016

Attachment 1



Clinical Review: Morphine Equivalent Daily Dose to Prevent Opioid Overuse

Learning Objectives:

- Define morphine equivalent daily dose (MEDD) and how it is being used to indicate potential dose-related risk for prescription opioid overdose.
- Describe high-risk prescribing of prescription opioids within the Medi-Cal fee-for-service program.
- Summarize best practices for responsible opioid prescribing.

Key Points:

- While there is no completely safe dose of opioids, MEDD can be used as an indicator of potential dose-related risk for adverse drug reactions, including overdose.
- While there are differing opinions as to the maximum MEDD threshold that should trigger additional action by clinicians, the Medical Board of California (MBC) recommends proceeding cautiously once the MEDD reaches 80 mg.
- In the Medi-Cal fee-for-service population, the vast majority (87%) of paid claims for opioids were well under the 80 mg MEDD threshold recommended by the MBC for a yellow flag warning.
- Online MEDD calculators are available to help clinicians determine morphine milligram equivalency. These calculators are not intended for dosage conversion from one product to another, but can be used to assess the comparative potency of opioids using a morphine equivalency standard.
- All providers who prescribe opioids need to enroll in and access California's prescription drug monitoring program, available on the [Controlled Substance Utilization Review and Evaluation System \(CURES\)](#) Web page of the Office of the Attorney General website. In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers.

Background

Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers.¹ The Centers for Disease Control and Prevention (CDC) describes the following groups as particularly vulnerable to prescription opioid overdose: 1) people who obtain multiple controlled substance prescriptions from multiple providers; 2) those who take high daily dosages of prescription painkillers and those who misuse multiple abuse-prone prescription drugs, especially other CNS depressants, such as benzodiazepines, carisoprodol, or other sedatives; 3) low-income people and those living in rural areas; and 4) people with mental illness and/or those with a history of substance abuse.²

Morphine Equivalent Daily Dose (MEDD)

Recent studies demonstrate that a patient's cumulative MEDD is an indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose.^{3,4} The terminology for daily morphine equivalency may vary depending on the resource used, and may be described as MEDD, morphine equivalent dose (MED), or morphine milligram equivalents (MME). **Daily morphine milligram equivalents are used to assess comparative potency, but not to convert a particular opioid dosage from one product to another.** The calculation to determine morphine milligram equivalents includes drug strength, quantity, days' supply and a defined conversion factor unique to each drug. By converting the dose of an opioid to a morphine

equivalent dose, a clinician can determine whether a cumulative daily dose of opioids approaches an amount associated with increased risk.

Online calculators are available to estimate MEDD. **It should be noted again that these calculators are not intended for dosage conversion from one product to another, but only to assess the comparative potency of opioids.** Furthermore, calculated morphine equivalency may vary between tools for certain drugs, depending on the algorithm used. Commonly used websites that offer MEDD calculators include the following:

- [Washington State Agency Medical Directors' Group](#)
- [Prescription Drug Monitoring Program Training and Technical Assistance Center \(PDMP TTAC\)](#)
- [The New York City Department of Health and Mental Hygiene](#)

Equianalgesic dose ratios are only approximations and do not account for genetic factors, incomplete cross-tolerance between various opioids, and variable pharmacokinetics that may affect relative potency. If used to estimate a conversion, it is recommended that after calculating the appropriate conversion dose, the prescribed dose be reduced by 25 – 50% to assure patient safety.⁴

Compared with patients receiving an MEDD of 1 – 20 mg, who had a 0.2% annual overdose rate, patients receiving an MEDD of 100 mg or more had almost nine times as much risk of overdose and a 1.8% annual overdose rate as compared to the lowest doses.³ The CDC review of opioid prescribing and overdose found that among patients who are prescribed opioids, an estimated 80% are prescribed low doses (<100 mg MEDD) by a single provider, and these patients account for an estimated 20% of all prescription drug overdoses. Another 10% of patients are prescribed high doses (≥100 mg MEDD) of opioids by single prescribers and account for an estimated 40% of prescription opioid overdoses. The remaining 10% of patients seek care from multiple doctors, are prescribed high daily doses, and account for another 40% of opioid overdoses.⁵

While there are differing opinions among experts and organizations as to the maximum MEDD threshold that should trigger additional action by clinicians (Table 1), the MBC recommends proceeding cautiously (a yellow flag warning) once the MEDD reaches 80 mg.⁶ There is no completely safe opioid dose.

Table 1. Selected Organizations' MEDD Thresholds and Recommended Actions

Year	Organization	MEDD Threshold (mg/day)	Recommended Action at MEDD Threshold
2010	American Academy of Pain Medicine ⁷	>200	Increase frequency and intensity of monitoring
2010	Utah State Clinical Guidelines ⁸	>120 – 200	Increase clinical vigilance
2010	Veterans Affairs/Department of Defense ⁹	>200	Refer or consult
2010, 2015	Washington State Agency Medical Directors' Group ⁴	>120	Consult from pain management expert
2011	Canadian Guidelines ¹⁰	>200	Reassess or monitor
2011, 2014	American College of Occupational and Environmental Medicine ¹¹	≥50	Follow up frequently; document improved function
2011	New York City Department of Health and Mental Hygiene ¹²	>100	Reassess pain status or consider other approaches
2012	American Society of Interventional Pain Physicians ¹³	>91	Consider pain management consultation
2012	Centers for Medicare and Medicaid Services ¹⁴	>120	Consider case management
2014	Medical Board of California ⁶	≥80	Proceed cautiously and consider referral to specialist when higher doses are contemplated
2015	California Division of Workers' Compensation ¹⁵	≥80	Increase clinical monitoring, consider specialty referral, attempt to wean to lower dose.

In addition, as of federal fiscal year 2013 (FFY 2013), nine state Medicaid programs reported having an established policy with a recommended maximum MEDD (Table 2).¹⁶

Table 2. State Medicaid Drug Use Review (DUR) Programs with Established Recommendations for Maximum MEDD

State	MEDD Threshold (mg/day)	Additional Information
Delaware	120	All long-acting opioids require prior authorization. The total dose for all narcotic therapy must be <120 mg MEDD.
Kansas	200	
Massachusetts	360	Individual dose limits for each opioid were determined based on utilization trends.
Maine	30	Prior authorization is required for any dose over 30mg; maximum allowable dose 300 mg
Michigan	30	
North Carolina	750	Maximum allowable dose
Oregon	120	
Washington	120	Based on Agency Medical Directors Association Interagency Guidelines
Wyoming	120	

Both Massachusetts and Washington have described in detail the impact of implementing an established policy and predetermined maximum MEDD threshold for triggering a detailed patient review.^{17,18} Massachusetts defined a specific maximum MEDD for oxycodone, fentanyl, morphine,

and methadone (they selected two standard deviations outside the mean dose noted in their drug utilization review). In addition to requiring prior authorization for the specified dose, a multidisciplinary team including a physician, pharmacist, and behavioral specialist reviewed high-dose utilization profiles every two weeks. The team participated in phone interventions for clarification of prior authorization requests, treatment care plans, or specific restrictions. Over a three-year period (2002 – 2005), the number of unique utilizers decreased by 17.8% (p <0.0001) and the number of claims by 4.1% (p <0.0001).¹⁷ Claims for oxycodone decreased by 34.9% and claims for fentanyl decreased by 25%.¹⁷

In 2007, the Washington State Agency Medical Directors' Group, which represents all public payers in Washington, developed a collaborative interagency guideline on opioid dosing (updated in June 2015).⁴ The guideline recommends that at an MEDD of 120 mg providers must obtain consultation from a pain medicine expert for patients whose pain and function have not substantially improved as a result of opioid treatment. An evaluation of the impact of the guideline was conducted through 2010, and showed the number of prescriptions for Schedule II opioids plateaued during 2006 – 2008, then declined sharply in 2009 and 2010.⁷ The total number of paid prescriptions for Schedule III opioids had peaked in 1999 (93,550), then declined through 2008 (79,882), 2009 (63,808) and 2010 (52,499).⁷ The average MEDD among beneficiaries declined from a peak of 144.7 in 2002 to 105 in 2010.¹⁸

MEDD in the Medi-Cal Fee-For-Service Population

A retrospective cohort study was conducted to calculate the MEDD for all paid pharmacy claims for prescription opioid medications in the Medi-Cal fee-for-service population (dates of service between July 1, 2014, and June 30, 2015). The National Drug Code (NDC), days supply, and drug quantity fields were extracted from Medi-Cal pharmacy claims data and matched (via NDC) to the drug strength and MME conversion factor using the Morphine Equivalent Calculator Tool developed by the PDMP TTAC at Brandeis University, in collaboration with the CDC.

The following equation was used to calculate MEDD:

$$\frac{(\text{Drug Strength}) \times (\text{Drug Quantity}) \times (\text{MME Conversion Factor})}{(\text{Days Supply})}$$

All instructions for MEDD calculation were followed using the technical assistance guide provided by the PDMP TTAC.¹⁹

An additional analysis was performed on a subset of Medi-Cal fee-for-service beneficiaries who were continuously eligible in the Medi-Cal fee-for-service program between January 1, 2015, and June 30, 2015, and who had at least one paid claim for a prescription opioid medication between April 1, 2015, and June 30, 2015 (the measurement period). Medical and pharmacy claims data were reviewed for all beneficiaries in the study population with a calculated cumulative morphine equivalent dose >120 mg for at least one day during the measurement period. Data fields specifying diagnostic codes and place of service were extracted from medical claims data and were used to identify those beneficiaries in the study population who had a primary or secondary diagnosis of cancer and/or who were receiving hospice care.

Descriptive statistics were used to summarize MEDD values and claims data. Data analyses were performed using IBM® SPSS®, version 23.0 (Chicago, IL).

Results

Between July 1, 2014, and June 30, 2015, a total of 529,681 paid pharmacy claims for prescription opioid medications were filled by a total of 262,017 Medi-Cal fee-for-service beneficiaries. The summary of paid claims exceeding MEDD thresholds of 80 mg, 100 mg, and 120 mg for all paid claims is shown in Table 3. Also shown in Table 3 is the distribution among a subset of paid claims with a days supply >14 days, as over half (56%) of all paid claims for opioids between July 1, 2014, and June 30, 2015, were for a days supply ≤7 days.

Table 3. Total Paid Claims Exceeding Recommended MEDD Thresholds in the Medi-Cal Fee-For-Service Population (Dates of Service Between July 1, 2014, and June 30, 2015)

	Recommended MEDD Thresholds		
	>80 mg/day	>100 mg/day	>120 mg/day
Total paid claims (n = 529,681)	71,236 (13.4%)	58,741 (11.1%)	47,769 (9.0%)
Total paid claims >14 days supply (n = 237,106)	62,596 (26.4%)	54,060 (22.8%)	43,865 (18.5%)

The vast majority of paid claims for opioids were well under the 80 mg/day threshold recommended by the MBC for a yellow flag warning (87% of all paid claims and 74% of paid claims >14 days supply). However, during one year there were 47,769 paid claims identified that exceeded 120 mg MEDD.

As the CDC identified people who obtain multiple controlled substance prescriptions from multiple providers as one of the high-risk groups for opioid overdose, a summary of the total number of prescribers and pharmacies is shown in Table 4 for all Medi-Cal fee-for-service beneficiaries who had a paid claim for an opioid during that same year.

Table 4. Crosstabulation of Total Prescribers and Total Pharmacies for Opioid Paid Claims in the Medi-Cal Fee-For-Service Population (Dates of Service Between July 1, 2014, and June 30, 2015)

Total Utilizing Beneficiaries (n = 262,017)		Total Pharmacies					
		1	2	3	4	5 – 9	10+
Total Prescribers	1	208,071	8,131	886	129	24	0
	2	18,113	13,079	1,434	269	66	0
	3	2,952	3,104	1,467	288	113	0
	4	648	790	533	249	102	1
	5-9	300	403	365	241	208	7
	10+	2	5	3	5	22	7

The majority of these beneficiaries (n = 208,071; 79%) had only one paid claim for a prescription opioid medication during this one-year period. However, a total of 3,611 beneficiaries (1%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies.

A total of 22,505 beneficiaries were included in an analysis of cumulative MEDD. Each of these beneficiaries was continuously eligible in the Medi-Cal fee-for-service program between January 1, 2015, and June 30, 2015, and had at least one paid claim for a prescription opioid medication between April 1, 2015, and June 30, 2015. This 90-day window was selected in order to identify the distribution of beneficiaries who exceeded a cumulative total of >120 mg MEDD for at least one of those days, and to identify beneficiaries who exceeded >120 mg MEDD for the entire 90 days, which would make this group at high-risk for overdose due to sustained high-dose opioid use over time.

As shown in Table 5, a total of 3,904 beneficiaries (17%) were identified in this group with at least one day out of 90 that exceeded >120 mg cumulative MEDD. Results are stratified by those who had a primary or secondary diagnosis of cancer and/or who were receiving hospice care, and those who did not have a primary or secondary diagnosis of cancer and no indication of hospice care in the medical claims data.

Table 5. Summary of Medi-Cal Fee-For-Service Beneficiaries Days >120 mg Cumulative MEDD (Dates of Service Between April 1, 2015, and June 30, 2015)

Days with MEDD >120 mg	Cancer/Hospice (n = 1,306)	Non-cancer/ Non-hospice (n = 21,199)	Total (n = 22,505)
0	1,078 (83%)	17,523 (83%)	18,601 (83%)
≥1	228 (17%)	3,676 (17%)	3,904 (17%)
≥2	225 (17%)	3,648 (17%)	3,873 (17%)
≥3	223 (17%)	3,593 (17%)	3,816 (17%)
≥10	217 (17%)	3,467 (16%)	3,684 (16%)
≥30	178 (14%)	2,778 (13%)	2,956 (13%)
≥60	120 (9%)	1,900 (9%)	2,020 (9%)
≥90	65 (5%)	963 (5%)	1,028 (5%)

Of the 1,028 beneficiaries that exceeded >120 mg cumulative MEDD for all 90 days, almost half (n = 410; 40%) had only one prescriber and one pharmacy for all opioid claims, while 49 beneficiaries (5%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies. There was no statistically significant difference between the number of days that exceeded >120 mg cumulative MEDD when stratified by cancer/hospice status.

Conclusion/Discussion

While there is no completely safe dose of opioids, the ability to calculate morphine equivalent dose adds an additional assessment tool to combat potential opioid overdose and/or overuse. Federal and state agencies should provide guidelines and instructions for calculation of MEDD and promote case management and, as needed, referrals to appropriate pain specialists as higher doses of opioids are considered. Finally, all providers who prescribe opioids need to enroll in and access California's prescription drug monitoring program, CURES. In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers.

Clinical Recommendations

- Review materials and resources for preventing prescription drug abuse available through the [California State Board of Pharmacy](#), [Medical Board of California](#), and the [California Department of Public Health](#).
- Weigh the benefits and risks of opioid therapy, especially for opioid therapy when alternative treatments are ineffective.
- Discuss with patients the risks and benefits of pain treatment options, including those that do not involve prescription painkillers.
- Follow best practices for responsible opioid prescribing, including:
 - Consult CURES initially and at every subsequent visit
 - Conduct a physical exam, urine drug test, and document pain history prior to prescribing opioids
 - Screen for substance abuse, mental health problems, and other physical conditions that are contraindicated for opioid use
 - Advise against concomitant use of alcohol, sedatives, and hypnotics
 - Implement pain treatment agreements

- Prescribe the lowest effective dose of short-acting opioid producing analgesia and improved function (no more than 80 mg MEDD) in a limited supply with no refills
- Regularly evaluate the role of opioid therapy beyond 3 months for non-cancer chronic pain
 - ❖ Use tapering (not abrupt cessation) to discontinue or reduce dose of opioids
- Track and document levels of pain and function at every visit
- Exercise vigilance at high doses
 - ❖ Consider prescribing naloxone as a rescue medication in the event of a potentially life-threatening overdose and instruct caregivers on proper use and administration. For detailed information on dosing and administration of naloxone, please go to the [Prescribe to Prevent](#) website
- Enroll in and access CURES reports to establish whether or not an individual is receiving controlled substances from multiple prescribers. The CURES report should be requested frequently for patients who are being treated for pain and/or addiction.

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Attachment 2

SPICE, BATH SALTS, AND BEHAVIORAL HEALTH

Spice (synthetic cannabinoids) and *bath salts* (synthetic cathinones) refer to two groups of designer drugs that have increased in popularity in recent years. These substances are created with *analogs* of commonly used illicit drugs. An analog is one of a group of chemical compounds that are similar in structure and pharmacology. This *Advisory* provides introductory information about spice and bath salts for behavioral health professionals who treat people with mental illness, substance use disorders, or both. It is not meant to present comprehensive information about spice or bath salts or treatment of substance use disorders involving their use. See the Resources section of this *Advisory* for links to additional information.

What Are Spice and Bath Salts?

Spice and bath salts are synthetic versions of controlled substances that are produced to avoid existing drug laws. In 2011, the U.S. Drug Enforcement Administration added, on a temporary, emergency basis, spice and bath salts analogs to its list of Schedule I substances. There are many synthetic chemicals that can be used to produce these drugs and their analogs; when federal or state regulations are amended to include new substance prohibitions, the makers of spice and bath salts turn to other synthetic analogs to produce these designer drugs. Both spice and bath salts are marketed online and sold in drug paraphernalia stores. They are attractively packaged and, to further help retailers evade the laws that prohibit possession or sale of designer drugs, may include labels that state “not for human consumption.”^{1,2}

Spice

Spice, also known as *herbal incense*, is dried, shredded plant material treated with a *cannabinoid* analog. Although labels on spice products will list the ingredients as “natural” psychoactive plant products, chemical analyses show that their active ingredients are primarily synthetic cannabinoids added to the plant material.² These synthetic analogs function similarly to the active ingredient in marijuana, Delta-9-tetrahydrocannabinol (Δ^9 -THC).

In this context, studies indicate that the synthetic cannabinoids act on the same receptors as natural cannabinoids, but they can bind with greater affinities and exhibit greater potency compared with natural cannabinoids.^{3,4} For example, many of the synthetic cannabinoids that have been found in spice are between 4 and 100 times more potent than Δ^9 -THC and produce correspondingly stronger psychoactive effects and side effects.³ These synthetics are known to alter various physiological processes, including neurotransmission and cardiovascular functioning, through the same signaling pathways as their natural counterparts.³ In addition, metabolites from some of these synthetic substances retain biologic activity and may account for a subset

Common Product Names for Spice

Arctic Synergy, Black Mamba, Bombay Blue, Cloud Nine, Genie, K2 Blonde, K2 Blueberry, Moon Rocks, Natures Organic, Skunk, Spice Diamond, Spice Gold, Spice Silver, Yucatan Fire, Zen, Zen Organic

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of the physiological changes associated with spice.⁴ It is also important to note that other psychoactive compounds may be added to spice (e.g., synthetic opioids have been found in spicelike blends), further amplifying and expanding its psychotropic effects.^{1,3}

Spice is marketed under more than 140 product names.⁵ Typically, it is smoked like marijuana⁶ or infused as a hot drink.² Spice is marketed as a “safer” alternative to marijuana and is not easily detected in urine or blood drug tests. Furthermore, the analogs that are added to produce the desired effects are constantly changing in response to federal regulations and state laws banning certain types of synthetic cannabinoids.^{4,7}

As a consequence, people who use these substances cannot know the precise array of chemicals that are in them or the serious, if not lethal, outcomes that may result from their use.^{1,8}

Bath salts

Bath salts, sometimes known as *plant food*, are usually produced as white, tan, or brown powders or crystals, but they are sometimes sold in tablets. Bath salts usually are ingested nasally as a powder, taken orally, injected, or smoked.⁹

Bath salts are synthetic cathinones. *Cathinone* is a naturally occurring substance found in the leaves of the *Catha edulis* plant, better known as *khat*. *Khat* is widely used for its stimulant effects, particularly in parts of Africa. Synthetic cathinones are derivatives of this

Common Product Names for Bath Salts

Bliss, Bloom, Blue Silk, Cloud Nine, Crazy Train, Drone, Energy-1, Hurricane Charlie, Ivory Wave, Lunar Wave, Ocean Snow, Purple Wave, Red Dove, Scarface, Snow Leopard, Stardust, Vanilla Sky, White Lightning, Zoom

compound and have effects similar to those of cocaine, amphetamine, or MDMA (3,4-methylenedioxy-N-methylamphetamine, or “ecstasy”).

Three of the most common compounds found in bath salts are mephedrone, methylone, and MDPV (3,4-methylenedioxypropylone). All three of these compounds have dopaminergic (among other) effects. Mephedrone appears to stimulate release of dopamine, whereas MDPV and methylone appear to increase dopamine levels by inhibiting dopamine reuptake.^{10,11,12} Synthetic cathinones have been found to increase dopamine levels equal to or more than those produced by the stimulant drugs they mimic.¹²

These three compounds are now illegal, but a wide range of other synthetic cathinones are now being used to create bath salts. Bath salts may contain any combination of unknown chemicals with unknown effects, making these substances more dangerous.¹³ In addition, the chemicals in bath salts are also often sold as ecstasy or other drugs, so they may be taken unintentionally.

Can People Become Dependent on Spice or Bath Salts?

People start using designer drugs for many of the same reasons people use other drugs—to experiment or because friends pressure them to use the drugs. Once they start using designer drugs, people may continue to use them to relieve stress, alleviate pain, function better, have fun, or cope with mental disorders.

Spice and dependence

Although there have been few studies to date on withdrawal and addiction liability, anecdotal evidence suggests that people who regularly use spice experience withdrawal and addiction symptoms.²

Bath salts and dependence

Both anecdotal and experimental evidence suggest that bath salts are highly addictive and produce an intense craving.¹⁴ One study of laboratory mice found that mephedrone achieved a brain stimulation reward similar to that achieved by cocaine, underscoring mephedrone's potential for abuse.¹⁵ A 2013 review article concluded that the increase in dopamine transmission created by the cathinones in bath salts likely creates a high potential for addiction.¹⁰

Who Uses Spice and Bath Salts?

Spice

Spice appears to be popular among young people. The 2012 Monitoring the Future (MTF) survey¹⁶ found that, aside from alcohol and tobacco, spice was the second most widely used substance among 10th and 12th graders, after marijuana; it was the third most widely used illicit drug among 8th graders, after marijuana and inhalants. The survey indicated that 11.3 percent of high school seniors, 8.8 percent of 10th graders, and 4.4 percent of 8th graders in the United States reported using spice in the past year.

The 2013 MTF survey¹⁷ reported that annual prevalence rates declined in all three grades, but the decline was significant only among 12th graders (7.9 percent annual prevalence, down from 11.3 percent). The 2013 rates for 10th and 8th graders were 7.4 percent and 4.0 percent, respectively.

Bath salts

Fewer young people use bath salts than use spice. The 2012 MTF survey¹⁶ found annual prevalence rates of 0.8 percent for grade 8, 0.6 percent for grade 10, and 1.3 percent for grade 12. Data from the 2013 MTF¹⁷ showed a slight increase in use in 8th and 10th grades (annual prevalence of 1.0 percent and 0.9, respectively) and some decline in 12th grade use (0.9 percent annual prevalence).

Calls to Poison Control Centers

Calls to U.S. poison control centers about spice increased from 2,906 in 2010 to 6,968 in 2011;¹⁸ they decreased to 5,230 in 2012 and to 2,663 in 2013.¹⁹

Bath salts-related calls to U.S. poison control centers increased dramatically between 2010 and 2011, from 304²⁰ to 6,137²¹ calls. Calls decreased to 2,691 in 2012 and to 996 in 2013.²¹

One investigation of 35 Michigan emergency department episodes involving adverse reactions to bath salts use found that, although people of all ages and both genders presented at the emergency department with symptoms related to bath salts use, 63 percent were ages 20 to 29, and 54 percent were male.²²

Included in the marketing of spice and bath salts are the claims that these products cannot be detected through routine drug screening. This makes these drugs popular with individuals who are subject to workplace or other mandatory drug testing (e.g., clients involved in drug court programs or otherwise in mandatory treatment, individuals on probation, members of the military). Although testing *is* available for some of the psychoactive compounds that have been found in spice and bath salts, these chemicals are typically not included in routine drug screens.

Is the Use of Spice or Bath Salts Related to Mental Disorders?

Spice

A growing body of evidence suggests an association between using spice and having an acute episode of psychosis in individuals with no history of psychosis or triggering a psychotic episode among individuals with a history of psychosis.^{23,24,25} However, current evidence has not established a definitive, causal link; additional research in this area is important.

Marijuana contains the compound *cannabidiol*, which has antipsychotic properties. Spice, however, does *not* contain an analog for cannabidiol. That lack, combined with spice's high potency, appears to increase the risk of psychosis.²⁶

Evidence underscores the relationship between spice and other adverse psychoactive effects. For example, individuals who are intoxicated on spice can exhibit an array of cognitive changes (e.g., difficulty thinking clearly, confusion, amnesia), behavioral disturbances (e.g., agitation, restlessness, aggression), mood changes (e.g., anxiety, negative mood), or sensory and perceptual changes (e.g., paranoia, delusions, hallucinations).²⁷ Because spice use is relatively new, the long-term effects remain unknown.

Bath salts

Bath salts intoxication can produce symptoms that resemble those of mental disorders.²⁸ Symptoms include:^{5,28,29}

- Aggression and violent behavior.
- Confusion.
- Delirium.
- Delusions.
- Anxiety.
- Hallucinations.
- Panic attacks.
- Extreme paranoia.
- Acute psychosis.
- Agitation.

Adolescents and adults with mental illness are at greater risk of abusing drugs and developing a substance use disorder than are people without mental illness.³⁰ An investigation of emergency room episodes in Michigan found that 46 percent of the individuals who presented with bath salts intoxication were people with a history of mental illness (e.g., bipolar disorder, schizophrenia, depression).²²

What Are the Adverse Physical Effects of Spice and Bath Salts?

Spice

Spice can produce anticholinergic effects (dry mouth, dehydration), nausea, and seizures.⁵ Spice can also have cardiovascular effects, including tachycardia (rapid heart rate) and hypertension (increased blood pressure). In a few cases, the designer drug has been associated with heart attacks.² Because spice is a relatively new drug, it is not known whether it causes negative long-term physical effects.

Bath salts

Bath salts can also produce adverse physical effects, including hypertension, tachycardia, headaches, teeth grinding, overactive or overresponsive reflexes, nausea, vomiting, and seizures.⁵ As with ecstasy, there is heightened risk of hyperthermia and dehydration. In one study of emergency department episodes, the most commonly observed clinical symptom was tachycardia (56 percent).³¹ Less common clinical symptoms included twitching and other movement disorders (19 percent), hypertension (17 percent), and chest pain (17 percent).

What Are the Implications for Behavioral Health Services Providers?

It is likely that behavioral health services providers will encounter clients who use spice, bath salts, or both; practitioners should educate themselves about these substances and the ways in which they are advertised (see Resources).

Treatment for substance use disorders that involve the use of spice or bath salts does not differ significantly from treatment for substance use disorders that involve similar substances (e.g., marijuana or stimulants, respectively), although further research is needed.

However, there are a few substance-specific considerations, including assessment, education about the risks of use, and monitoring abstinence.

Assessment

Behavioral health services providers should include specific questions about spice and bath salts use when assessing clients at intake and periodically throughout treatment. Clients may not think to mention their use of these substances. Providers also need to remain mindful that clients sometimes switch from an initial drug of choice to spice or bath salts to avoid positive toxicology tests.

Because spice and bath salts can trigger psychosis or produce symptoms that resemble those of mental disorders, it is critical that practitioners provide careful assessment to distinguish between substance-induced symptoms and those of a preexisting mental illness.

Education about risk of use

Spice tends to be marketed as a natural, safe, and legal alternative to marijuana, and many individuals who use it believe those claims to be true. The 2013 MTF survey found that only 24 to 26 percent of 8th, 10th, and 12th grade students perceived “great risk” in using spice once or twice.¹⁷

Bath salts, although not marketed as natural botanical products, are marketed as legal alternatives to illicit substances. Consumers who use these substances may assume that “legal” means “safer.” For both spice and bath salts, it is important that behavioral health services providers offer specific education about the risks associated with use of these substances. Key points include the following:

- People who purchase spice or bath salts cannot know what psychoactive compounds or fillers were used to produce them. Products marketed with the same name may contain active ingredients different from or in addition to those stated on the packaging.

- The only “natural” ingredients in spice are the nonpsychoactive fillers. The psychoactive chemicals added to the fillers are synthetic, and they are much stronger than marijuana and carry higher risks of adverse effects, including psychosis.
- Spice and bath salts produce a wide range of both psychiatric and physical adverse effects that may be worse than those produced by the substances they mimic.
- The evidence suggests that spice and bath salts may be just as likely to produce addiction as the substances they mimic.

Monitoring abstinence

The compounds used in developing spice and bath salts are not typically included in routine toxicology screens. However, many laboratories have the capability to test for the most commonly used analogs in both spice and bath salts. Providers need to communicate with the laboratories they regularly use about providing testing for these substances.

As with marijuana, the commonly found compounds in spice have a long window of detection; one study reported the tested compounds to be detectable in urine for up to 102 days following self-reported cessation of use.³² For this reason, providers should monitor concentration levels over time rather than just the presence or absence of the compound.

Conclusion

Designer drugs are not new, and they are not a passing fad. Spice and bath salts are currently popular alternative drugs, but providers can expect that development of new psychoactive compounds specifically designed to evade substance regulations will continue, evolving as necessary to stay ahead of federal and state laws. Although substance use disorder treatment in instances where spice and bath salts are involved is not likely to vary from treatment involving similar substances, providers need to remain alert and informed to best help their clients.

Resources

The DAWN Report: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids, Substance Abuse and Mental Health Services Administration

<http://www.samhsa.gov/data/2k12/DAWN105/SR105-synthetic-marijuana.pdf>

DrugFacts: Spice (“Synthetic Marijuana”), National Institute on Drug Abuse (NIDA)

<http://www.drugabuse.gov/publications/drugfacts/spice-synthetic-marijuana>

DrugFacts: Synthetic Cathinones (“Bath Salts”), NIDA

<http://www.drugabuse.gov/publications/drugfacts/synthetic-cathinones-bath-salts>

Drugs of Abuse, U.S. Drug Enforcement Administration (Spice, p. 62; Bath Salts, p. 74)

http://www.justice.gov/dea/pr/multimedia-library/publications/drug_of_abuse.pdf

NIDA’s Emerging Trends Web Page

<http://www.drugabuse.gov/drugs-abuse/emerging-trends>

Synthetic Drugs (factsheet), Office of National Drug Control Policy

http://www.whitehouse.gov/sites/default/files/page/files/synthetic_drugs_fact_sheet_455_2_15_12.pdf

Understanding the “Spice” Phenomenon, European Monitoring Centre for Drugs and Drug Addiction

<http://www.emcdda.europa.eu/publications/thematic-papers/spice>

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SAMHSA Advisory

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The DAWN Report

December 4, 2012

Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids

Synthetic cannabinoids are substances that are designed to affect the body in a manner similar to marijuana but that are not derived from the marijuana plant.¹ Because they can be purchased with no age restrictions, their popularity among young people has grown.²

Synthetic cannabinoids are known by a variety of names, such as “Spice” or “K2,” and sometimes are referred to as “synthetic marijuana” or “fake marijuana” because they are marketed with claims that their effects mimic those of marijuana. Synthetic cannabinoids are typically sprayed onto herbal products, many of which are listed as inactive on the product packaging.²

Although certain synthetic cannabinoids and/or specific chemicals contained in these preparations were made illegal in some States, a comprehensive national ban was not enacted until July 2012.³ Therefore, products containing synthetic cannabinoids were frequently marketed as “legal” and “not for human consumption” and could be purchased online and in legal retail outlets such as convenience stores.¹

Because products marketed as synthetic cannabinoids contain different ingredients from each other, it is difficult to identify which physical effects are caused by synthetic cannabinoids.⁴ They have been reported to cause agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremor, seizures, hallucinations, paranoid behavior, and nonresponsiveness.^{2,5} These products are relatively new, and related clinical and public health outcomes have not been fully examined. Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new products of this type makes it difficult to detect these chemicals or regulate these products.

The Drug Abuse Warning Network (DAWN) first detected a measurable number of emergency department (ED) visits involving synthetic cannabinoids in 2010, and this report presents data related to these visits.⁶ DAWN is a public health surveillance system that monitors drug-related ED visits in the United States. To be a DAWN



IN BRIEF

In 2010, an estimated 11,406 emergency department (ED) visits involved a synthetic cannabinoid product, sometimes referred to as “synthetic marijuana” and commonly known by street names such as “Spice” or “K2”

Three fourths of these ED visits involved patients aged 12 to 29 (75 percent), of which 78 percent were male

The majority (76 percent) of these ED visits did not receive follow-up care upon discharge from the ED

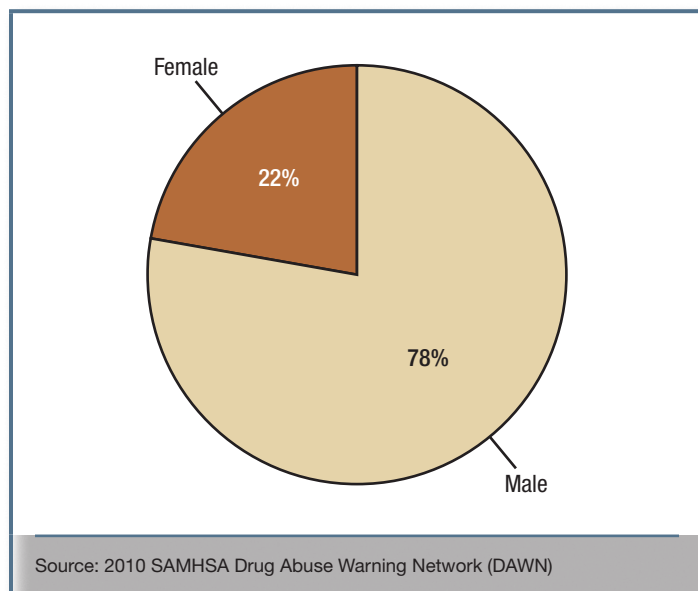
case, an ED visit must have involved a drug, either as the direct cause of the visit or as a contributing factor.

Of the approximately 2,300,000 ED visits that involved drug misuse or abuse in 2010, synthetic cannabinoids were specifically linked to an estimated 11,406 visits. This issue of *The DAWN Report* examines ED visits involving synthetic cannabinoid products in 2010 among patients aged 12 to 29. The report focuses on this age group because ED visits involving synthetic cannabinoids are concentrated in this age range (8,557 visits, or 75 percent of all visits involving synthetic cannabinoids, were made by patients aged 12 to 29 in 2010).

Gender and Age

For patients aged 12 to 29, males made more than three quarters (78 percent) of ED visits involving synthetic cannabinoids in 2010 (Figure 1). The rates of visits per 100,000 population for patients aged 12 to 17, 18 to 20, and 21 to 24 were similar (14.9, 13.9, and 11.8 visits per 100,000 population, respectively) (Table 1). However, the rate for those aged 25 to 29 (4.1 visits per 100,000 population) was lower than those for patients aged 12 to 17 (14.9 visits per 100,000 population) and those aged 18 to 20 (13.9 visits per 100,000 population).

Figure 1. Emergency Department (ED) Visits Involving Synthetic Cannabinoids among Patients Aged 12 to 29, by Gender: 2010



Drug Combinations

In the majority (59 percent) of ED visits involving synthetic cannabinoids for patients aged 12 to 29, no other substances were involved (Figure 2). This differs from ED visits involving other illicit drugs or nonmedical use of pharmaceuticals, in which the majority of visits involved multiple drugs.⁷ Synthetic cannabinoids were used in combination with one other substance in 36 percent of visits related to their use, but were rarely used in combination with two or more substances (6 percent). The types of drugs most frequently used in combination with synthetic cannabinoids were marijuana (17 percent), pharmaceuticals (17 percent), and alcohol (13 percent).

Disposition of ED Visits

Among ED visits involving synthetic cannabinoids made by patients aged 12 to 29 in 2010, it appears that the majority (76 percent) did not receive follow-up care (admission to the hospital, transfer to another health care facility, or referral to a detoxification/treatment program). Most of the 2,077 visits resulting in follow-up care involved synthetic cannabinoids in combination with other substances (75 percent).

Table 1. Emergency Department (ED) Visits Involving Synthetic Cannabinoids among Patients Aged 12 to 29, by Age Group: 2010

Age Group	Estimated Number of ED Visits	Rate per 100,000 Population*
Total, Aged 12 to 29	8,557	11.1
Aged 12 to 17	3,780	14.9
Aged 18 to 20	1,881	13.9
Aged 21 to 24	2,022	11.8
Aged 25 to 29	873	4.1

* Rates take into consideration the population size of each group; therefore, groups of different sizes may have varying numbers of ED visits but have similar population rates.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN).

Synthetic Cannabinoids Compared with Marijuana-Related ED Visits

Because synthetic cannabinoids have been marketed as a legal alternative to marijuana, this section will provide a brief comparison of the patient characteristics of ED visits between marijuana and synthetic cannabinoids. Marijuana-related ED visits outnumber synthetic cannabinoid-related visits (461,028 vs. 11,406 visits). The average patient age for marijuana-related visits was 30 years and the average patient age for synthetic cannabinoid-related visits was 24 years. The age distribution also differed between the two drugs. Synthetic cannabinoid-related visits were concentrated in the younger age groups: 75 percent of the visits involved patients aged 12 to 29, with 33 percent of the patients aged 12 to 17. In comparison, 58 percent of marijuana-related visits involved patients aged 12 to 29, with 12 percent in the 12 to 17 age group (Figure 3).

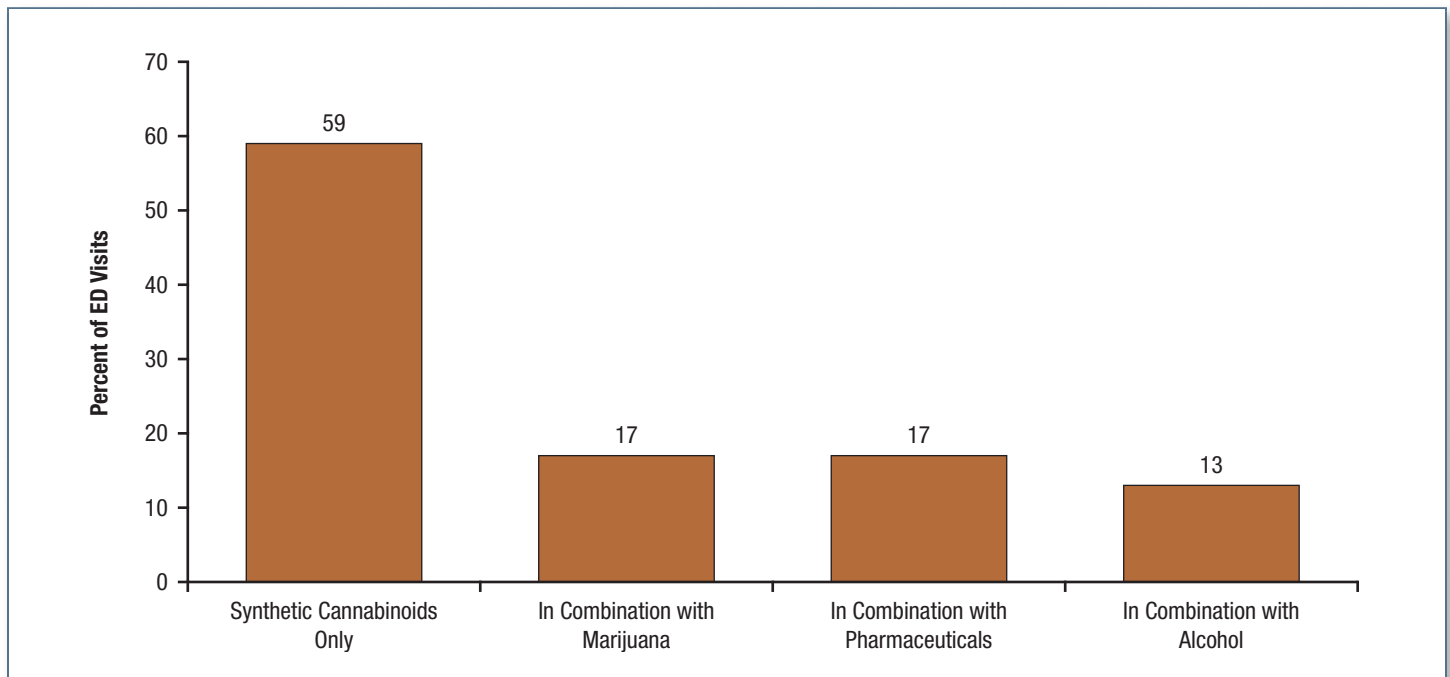
When patients in the 12 to 29 age range were compared, synthetic cannabinoid-related ED visits

were more likely to involve male patients than were marijuana-related visits (78 vs. 66 percent) (Figure 4). Further, synthetic cannabinoids were more likely to be the only drug implicated in the visit, whereas marijuana was more frequently combined with other drugs (59 vs. 31 percent, respectively; data not shown).

Discussion

As synthetic cannabinoids have become more available, the number of ED visits involving synthetic cannabinoids has increased. The higher proportion of ED visits in younger age groups, especially in patients aged 12 to 17, combined with results from a national survey of high school seniors revealing that 11 percent reported using “synthetic marijuana” in 2011, is cause for concern.⁸ Because it is difficult to regulate these products that are easily available online, synthetic cannabinoids may be more accessible to young people than marijuana.⁹ Educators can help prevent use of synthetic cannabinoids by addressing use of these

Figure 2. Emergency Department (ED) Visits Involving Synthetic Cannabinoids Only or in Combination with Other Substances* among Patients Aged 12 to 29: 2010



* Because multiple drugs may be involved in each visit, percentages add to more than 100 percent.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN).

substances in programs designed to prevent use of illicit drugs. Parents can also discuss the dangers of these drugs with their children and use parental controls for online purchases.

Because of limited availability of tests for synthetic cannabinoids, data collection efforts in the ED may have missed visits in which they were involved. However, even in the absence of positive drug test results, health care providers can remain alert to symptoms that may be attributed to synthetic cannabinoids and, when appropriate, inquire about their use.⁴ Further monitoring will be necessary to determine whether synthetic cannabinoid-related health problems continue to be reported. This monitoring can help improve awareness among health care professionals of the possible adverse health effects of these substances. Because most synthetic cannabinoid-related ED visits result in discharge from the ED, a patient's time in the ED is a valuable opportunity for intervention and education.

Figure 4. Emergency Department (ED) Visits Involving Synthetic Cannabinoids Compared with Visits Involving Marijuana among Patients Aged 12 to 29, by Gender*: 2010

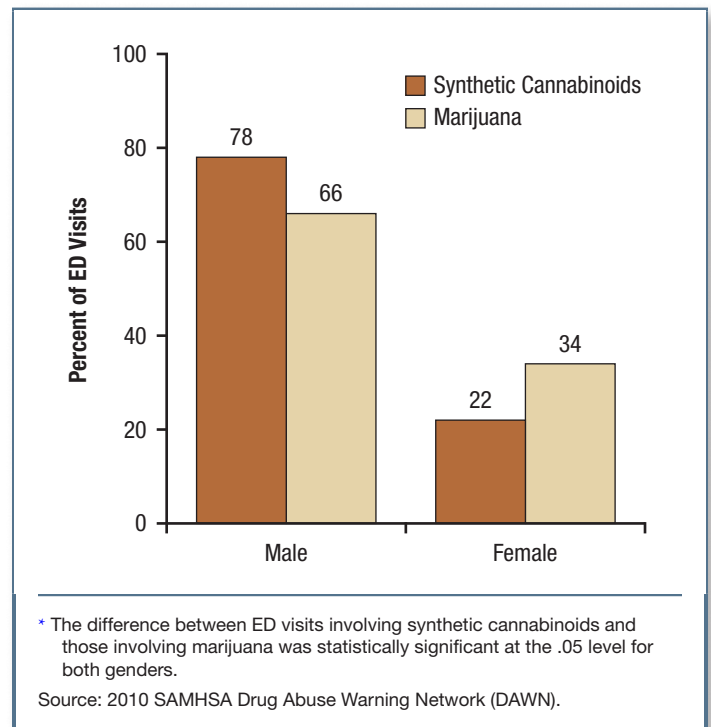
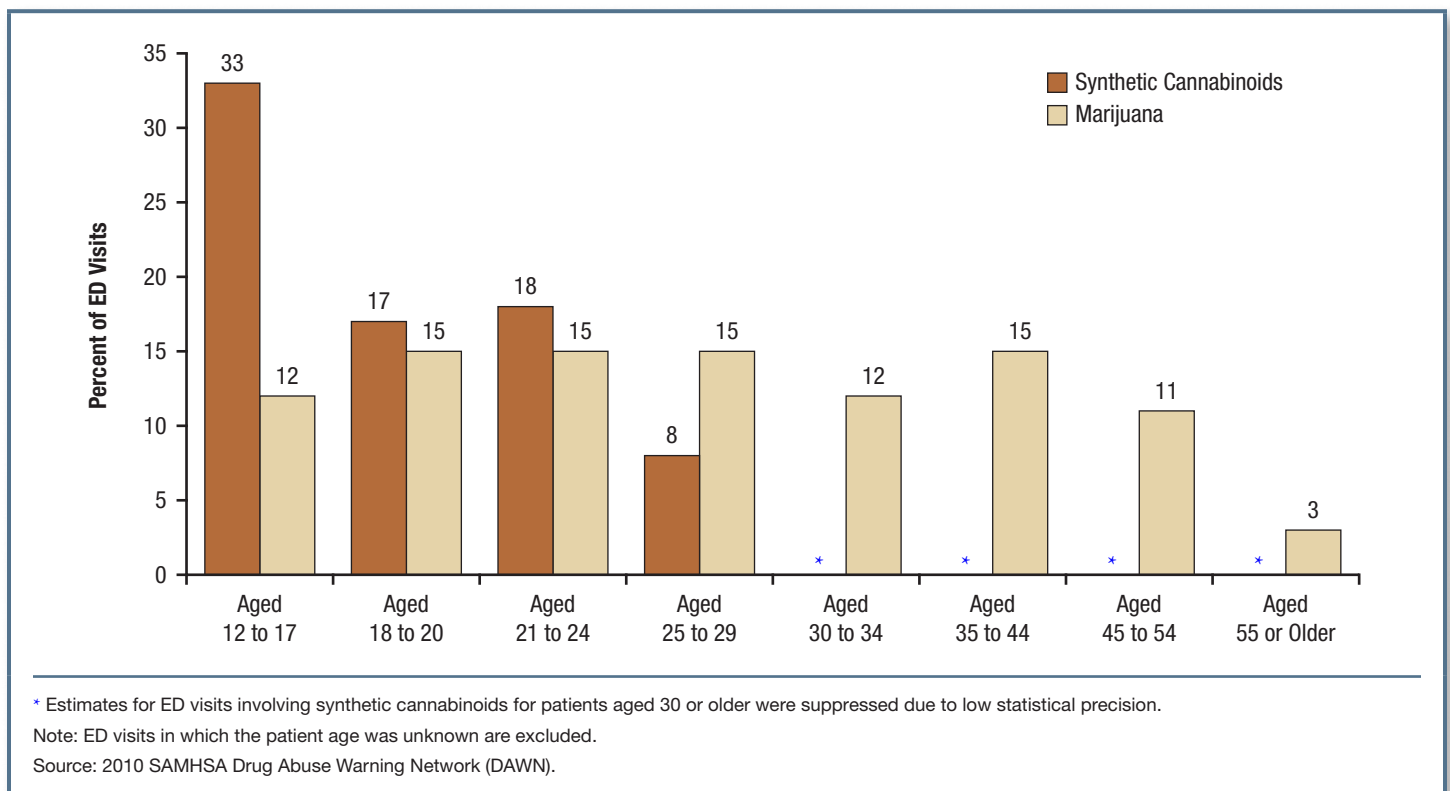


Figure 3. Age Distribution of Synthetic Cannabinoid and Marijuana-Related Emergency Department (ED) Visits: 2010



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Suggested Citation

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The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related morbidity and mortality. DAWN uses a probability sample of hospitals to produce estimates of drug-related emergency department (ED) visits for the United States and selected metropolitan areas annually. DAWN also produces annual profiles of drug-related deaths reviewed by medical examiners or coroners in selected metropolitan areas and States.

Any ED visit related to recent drug use is included in DAWN. All types of drugs—licit and illicit—are covered. Alcohol involvement is documented for patients of all ages if it occurs with another drug. Alcohol is considered an illicit drug for minors and is documented even if no other drug is involved. The classification of drugs used in DAWN is derived from the Multum *Lexicon*, copyright 2010 Lexi-Comp, Inc., and/or Cerner Multum, Inc. The Multum Licensing Agreement governing use of the *Lexicon* can be found at <http://www.samhsa.gov/data/DAWN.aspx>.

DAWN is one of three major surveys conducted by the Substance Abuse and Mental Health Services Administration's Center for Behavioral Health Statistics and Quality (SAMHSA/CBHSQ). For more information on other CBHSQ surveys, go to <http://www.samhsa.gov/data/>. SAMHSA has contracts with Westat (Rockville, MD) and RTI International (Research Triangle Park, NC) to operate the DAWN system and produce publications.

For publications and additional information about DAWN, go to <http://www.samhsa.gov/data/DAWN.aspx>.



U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Substance Abuse & Mental Health Services Administration
Center for Behavioral Health Statistics and Quality
www.samhsa.gov/data

The CBHSQ Report

Short Report

October 16, 2014

UPDATE: DRUG-RELATED EMERGENCY DEPARTMENT VISITS INVOLVING SYNTHETIC CANNABINOIDS

AUTHORS

Donna M. Bush, Ph.D., F-ABFT and David A. Woodwell, M.P.H.

INTRODUCTION

Synthetic cannabinoids are manmade chemicals that are applied (often dissolved in a solvent and sprayed) onto plant material that is not marijuana, marketed as herbal incense products and also as a “legal high.”¹ These herbal products were originally available in 2004 in several European countries with brand names “Spice,” “Spice Diamond,” “Spice Gold,” and “Yucatan Fire.”² By late 2008, synthetic cannabinoids were identified in the United States in “Spice Diamond” and “Spice Artic Energy” products.³ Even though the caution “not for human consumption” is prominently printed on the packaging, these products are used by those seeking a legal high, with smoking as the most common route of administration.^{1,4} They are labeled “not for human consumption” to mask their intended purpose and avoid Food and Drug Administration (FDA) regulatory oversight of the manufacturing process.¹ Users claim that synthetic cannabinoids mimic the effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana.¹

There is an incorrect assumption that synthetic cannabinoids are safe.⁴ Synthetic cannabinoids produce a combination of adverse effects that resemble intoxication from delta-9-tetrahydrocannabinol (delta-9-THC), the psychoactive component of marijuana. However, synthetic cannabinoids appear to be more potent and may stay active in the body longer than delta-9-THC.⁵ The adverse effects of synthetic cannabinoids include severe agitation, anxiety, nausea, vomiting, tachycardia (racing heartbeat), elevated blood pressure, tremors, seizures, hallucinations, paranoid behavior, and nonresponsiveness.^{1,5} After regular consumption, withdrawal signs and symptoms have been observed.⁶ Death after use of synthetic cannabinoids has also been reported.^{4,7}

Because products marketed as synthetic cannabinoids (e.g., “Spice,” “K2,” and hundreds of exotic brand names) contain various amounts of different ingredients or combinations that are different from each other, it is difficult to identify which adverse effects are caused by which synthetic cannabinoid chemicals.^{4,5,8} Additionally, it appears that the chemical structures of the psychoactive components of these products, as well as the composition of the herbal products themselves, is continually changing. There are also unpredictable contaminants in these products since they are manufactured illicitly.^{4,5} Concern about the availability and use of these products has continued to increase, as they are easily purchased online and in small retail outlets, such as “head shops” and convenience stores, without age restrictions.^{1,5}

The U.S. Drug Enforcement Administration (DEA) and nearly all states have taken some degree of regulatory control over synthetic cannabinoids as they are identified.^{4,9} Manufacturers of these compounds have modified their chemical structures, sometimes only very slightly, to evade current laws and regulations to be able to continue marketing these products as “legal highs.”⁴ The ingredients are rarely clearly labeled on the packaging, and the brand names vary widely. Over the past 5 years, the DEA has identified more than 200 designer drugs, many of which are synthetic cannabinoids manufactured in China.¹⁰ Designer drugs are drugs synthesized to be chemically and pharmacologically similar to illicit drugs in order to avoid DEA scrutiny. A list of 27 synthetic cannabinoid chemicals identified in substances secured in law enforcement operations and analyzed by federal, state, and local forensic laboratories was published in a 2014 National Forensic Laboratory Information System (NFLIS)



In Brief

- The number of emergency department (ED) visits involving synthetic cannabinoids increased significantly from 11,406 visits in 2010 to 28,531 visits in 2011.
- The number of ED visits involving synthetic cannabinoids for patients aged 12 to 17 doubled from 3,780 visits in 2010 to 7,584 visits in 2011; for patients aged 18 to 20, visits increased fourfold from 1,881 visits in 2010 to 8,212 visits in 2011.
- Males accounted for about 79 percent (19,923 visits) of the 28,531 ED visits in 2011 involving synthetic cannabinoids; 2011 DAWN estimates indicate a threefold increase in synthetic cannabinoid-related ED visits for females.
- In 2011, synthetic cannabinoids were the only substances involved in about two-thirds of the synthetic cannabinoid-related ED visits for patients aged 12 to 20 years; for those aged 21 or older, almost half of the synthetic cannabinoid-related ED visits involved only those drugs.

Special Report.¹¹ This special report shows that the synthetic cannabinoid chemicals identified in laboratory reports from 2010 are vastly different from those chemicals identified in 2013. Moreover, the availability of synthetic cannabinoids has surged since 2010, as indicated by the number of laboratory reports issued in January through June in 2010 (469) compared to January through June in 2013 (17,241).¹¹ As of June 2014, a number of synthetic cannabinoid chemicals have been either temporarily or permanently placed in Schedule I under the Controlled Substances Act, indicating that these are drugs with no currently accepted medical use and a high potential for abuse.¹¹ Schedule I drugs are among the most dangerous, with the potential for severe psychological or physical dependence.

Public health concerns remain heightened because synthetic cannabinoids have evolved and increased in number over time, even as regulatory action has been taken to ban specifically identified chemicals. The Centers for Disease Control and Prevention (CDC) investigated two severe illness outbreaks in 2013 that were linked to the use of synthetic cannabinoids.^{12,13} The Colorado Department of Public Health and Environment, with the assistance of the CDC, investigated 221 hospital emergency department (ED) reports of severe illness due to ingestion of synthetic cannabinoids.⁴ CDC also reported acute kidney injury associated with the use of synthetic cannabinoids in multiple states.¹⁴

Even with ongoing regulatory action and enforcement, these products continue to be marketed widely, especially to adolescents and those seeking a legal high with a desire to evade detection by current drug testing technologies.⁴ Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new synthetic cannabinoid chemicals makes it difficult to detect them in analysis of bodily fluids (e.g., blood, serum, urine).^{4,8,15,16}

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitored drug-related ED visits in the United States. To be a DAWN case, an ED visit must have involved a drug, either as the direct cause of the visit or as a contributing factor. DAWN first detected a measurable number of ED visits involving synthetic cannabinoids in 2010, and a report was published in 2012.^{17, 18} This report presents updated data for 2011 as well as trends between 2010 and 2011.

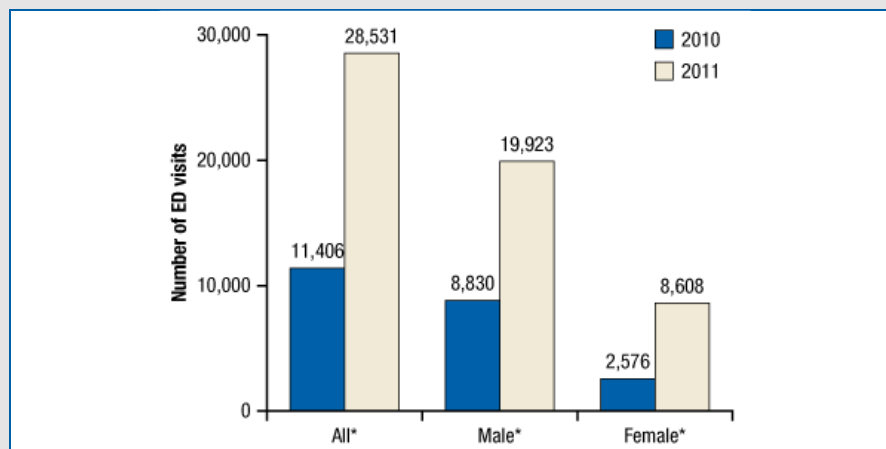
OVERVIEW

Of the approximately 2,460,000 ED visits that involved drug misuse or abuse in 2011, synthetic cannabinoids were specifically linked to an estimated 28,531 ED visits. This was a statistically significant increase from 2010, when 11,406 visits occurred (Figure 1).

TRENDS IN ED VISITS BY GENDER AND AGE

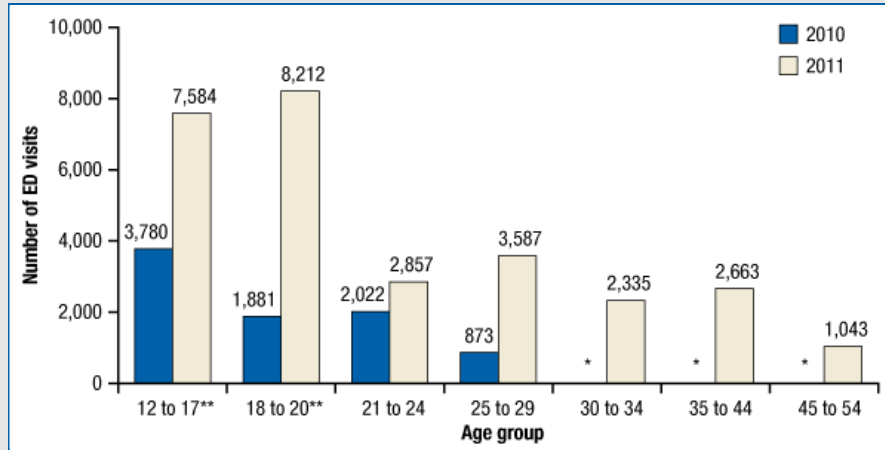
From 2010 to 2011, there were statistically significant increases for both males and females in the number of ED visits involving synthetic cannabinoids. For male patients, ED visits increased significantly from an estimated 8,830 visits in 2010 to an estimated 19,923 visits in 2011 (Figure 1). Visits for female patients tripled from 2,576 visits in 2010 to 8,608 visits in 2011.

Figure 1. Emergency department (ED) visits involving synthetic cannabinoids, by gender: 2010 and 2011



* The difference between 2010 and 2011 was statistically significant at the .05 level.
Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Figure 2. Emergency department (ED) visits involving synthetic cannabinoids, by age group: 2010 and 2011



* Low precision; no estimate reported.

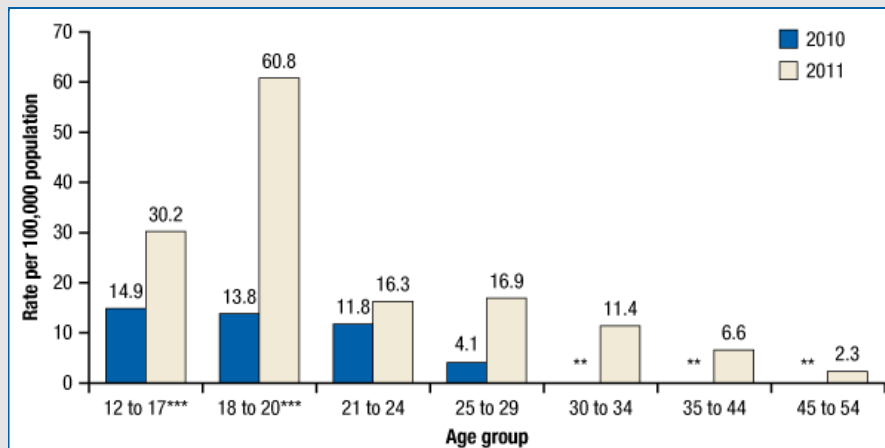
** The difference between 2010 and 2011 was statistically significant at the .05 level.

Source: 2010 and 2011 SAMHSA Drug Abuse Warning Network (DAWN).

When looking at visits made to the ED involving synthetic cannabinoids by age, the number of visits for patients aged 12 to 17 had a statistically significant doubling from 3,780 visits in 2010 to 7,584 visits in 2011 (Figure 2). For patients aged 18 to 20, visits increased fourfold, from 1,881 visits in 2010 to 8,212 visits in 2011. Although the number of visits appears to have increased for patients aged 21 to 24 and aged 25 to 29 between 2010 and 2011, the difference was not statistically significant. For older age groups, 2011 was the first year that visits involving synthetic cannabinoids reached a measurable level. There were 2,335 ED visits involving synthetic cannabinoids by patients aged 30 to 34, 2,663 visits made by patients 35 to 44, and 1,043 visits made by patients aged 45 to 54 (Figure 2).

The rate of ED visits involving synthetic cannabinoids per 100,000 population was calculated in order to compare age groups of different sizes. In 2011, the rate was highest among persons aged 18 to 20, with 60.8 visits per 100,000 population (Figure 3).

Figure 3. Emergency department (ED) visits involving synthetic cannabinoids, rate per 100,000 population,* by age group: 2010 and 2011



* Rates take into consideration the population size of each group; therefore, groups of different sizes may have varying numbers of ED visits but have similar population rates.

** Low precision; no estimate reported.

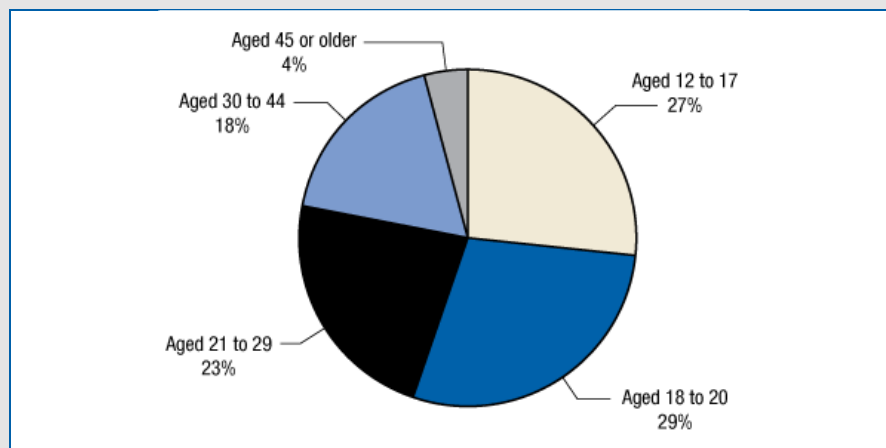
*** The difference between 2010 and 2011 was statistically significant at the .05 level.

Source: 2010 and 2011 SAMHSA Drug Abuse Warning Network (DAWN).

This rate was double the rate among persons aged 12 to 17 (30.2 visits per 100,000 population) and higher than the rate among persons aged 21 or older. Between 2010 and 2011, the rate of ED visits involving synthetic cannabinoids had a statistically significant doubling for patients aged 12 to 17, from 14.9 visits per 100,000 population in 2010 to 30.2 visits per 100,000 population in 2011. The rate per 100,000 population for those aged 18 to 20 had a statistically significant increase of more than four times, from 13.8 visits per 100,000 population in 2010 to 60.8 visits per 100,000 population in 2011. The rate of ED visits involving synthetic cannabinoids did not increase significantly for patients aged 21 or older (Figure 3).

The age distribution of the estimated 28,531 ED visits involving synthetic cannabinoids in 2011 is shown in Figure 4. Approximately a quarter of all visits were made by patients aged 12 to 17 (7,584 visits, or 27 percent), and 29 percent of visits were made by patients aged 18 to 20 (8,212). Summed together, patients aged 12 to 20 made 55 percent (15,796 visits) of all ED visits involving synthetic cannabinoids in 2011. An additional 41 percent of ED visits involving synthetic cannabinoids were made by patients aged 21 to 44. The remaining 4 percent of visits were made by those aged 45 or older (1,090 visits).

Figure 4. Emergency department (ED) visits involving synthetic cannabinoids, by age group*: 2011



*Percentages may not sum to 100 due to rounding.

Source: 2010 and 2011 SAMHSA Drug Abuse Warning Network (DAWN).

DRUGS INVOLVED IN ED VISITS

Among patients aged 20 or younger, no other substances were combined with synthetic cannabinoids in about two-thirds (65 percent) of ED visits related to their use; among patients aged 21 or older, 47 percent of visits involved synthetic cannabinoids only (Table 1).

Table 1. Emergency department (ED) visits involving synthetic cannabinoids only or in combination with other substances, by age group: 2011

Drug combination	Aged 20 or younger		Aged 21 or older	
	Number of ED visits*	Percent of ED visits*	Number of ED visits*	Percent of ED visits*
Total	15,998	100	12,533	100
Synthetic cannabinoids only	10,335	65	5,886	47
Synthetic cannabinoids in combination	5,664	35	6,646	53
Illicit drugs	3,404	21	3,335	27
Other marijuana	2,708	17	**	**
Stimulants***	**	**	1,018	8
Pharmaceuticals	2,531	16	3,243	26
Alcohol	2,438	15	1,368	11

*Because multiple drugs may be involved in each visit, estimates of visits by drug may add to more than the total, and percentages may add to more than 100 percent.

** Low precision; no estimate reported.

*** Includes amphetamines and methamphetamine.

Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

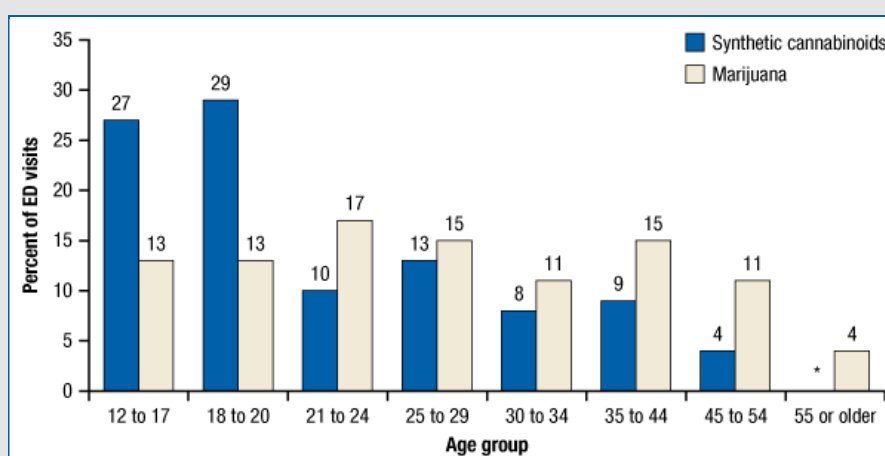
Synthetic cannabinoids were combined with illicit drugs in 21 percent of visits among patients aged 20 or younger and in 27 percent of visits among patients aged 21 or older.

In 2011, synthetic cannabinoids were combined with pharmaceuticals in 16 percent of visits among patients aged 12 to 20 and in 26 percent of visits among patients aged 21 or older.

SYNTHETIC CANNABINOIDS COMPARED WITH MARIJUANA-RELATED ED VISITS

Because synthetic cannabinoids have been marketed as a legal alternative to marijuana, this section will provide a brief comparison of the patient characteristics between ED visits for marijuana and those for synthetic cannabinoids. In 2011, marijuana-related ED visits outnumbered synthetic cannabinoid-related visits (455,668 and 28,531 visits, respectively). The average patient age for marijuana-related visits was 30 years of age, and the average patient age for synthetic cannabinoid-related visits was 23 years of age (data not shown). The age distribution also differed between the two drugs (Figure 5). More than half of synthetic cannabinoid-related visits (55 percent) were made by patients aged 12 to 20, with 27 percent aged 12 to 17. In comparison, 26 percent of marijuana-related visits involved patients aged 12 to 20, with 13 percent aged 12 to 17.

Figure 5. Age distribution of synthetic cannabinoid and marijuana-related emergency department (ED) visits: 2011



* Low precision; no estimate reported.

Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

DISPOSITION OF ED VISITS

Among the 28,531 ED visits involving synthetic cannabinoids in 2011, about 3,510 (12 percent) resulted in admission to the hospital or transfer to another health care facility (Table 2).

Table 2. Disposition of emergency department (ED) visits involving synthetic cannabinoids, by age group: 2011

Drug combination	Treated and released		Admitted or transferred	
	Number of ED visits	Percent of ED visits	Number of ED visits	Percent of ED visits
Total ED visits	22,938	100	3,510	100
Aged 12 to 17	6,824	30	745	21
Aged 18 to 20	6,547	29	822*	23*
Aged 21 to 29	4,948	22	702	20
Aged 30 to 44	3,792	17	777	22
Aged 45 or older	**	**	**	**

*Estimate may be unreliable due to low precision.

**Low precision; no estimate reported.

Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Among patients who were admitted or transferred, 21 percent were aged 12 to 17, and 23 percent were aged 18 to 20. Patients aged 21 to 29 and those aged 30 to 44 each made up about one-fifth of visits resulting in admission or transfer (20 and 22 percent, respectively). Of patients that received follow-up care (e.g., patients who were referred to detoxification/treatment, admitted to the hospital (any unit), or transferred), approximately one-half involved synthetic cannabinoids only and no other substance (54 percent; data not shown).

DISCUSSION

As synthetic cannabinoids have become more available, the estimated number of ED visits involving synthetic cannabinoids has increased threefold from 2010 to 2011.¹⁹ Most of the estimated 28,531 ED visits in 2011 involving synthetic cannabinoids were made by males (79 percent). This is consistent with information published in a summarized review of adverse events, medical treatments and outcomes.²⁰ Additionally, 2011 DAWN data indicate a threefold increase in ED visits made by females compared to 2010.

For those aged 12 to 17, the rates of ED visits involving synthetic cannabinoids more than doubled from 14.9 per 100,000 in 2010 to 30.2 per 100,000 in 2011. For patients aged 18 to 20, the rates of ED visits involving synthetic cannabinoids increased more than fourfold from 13.8 per 100,000 in 2010 to 60.8 per 100,000 in 2011. These significant increases in rates of ED visits involving synthetic cannabinoids, especially among adolescents, are of great concern to health care professionals, public health officials, and law enforcement.^{4,5} To date, only acute adverse effects of synthetic cannabinoid use have been reported. There is little information about the health effects and toxicity following chronic use of synthetic cannabinoids, but several cases of new-onset psychosis after multiple uses of synthetic cannabinoids have recently been reported.^{5,21}

Concern is not limited to synthetic cannabinoid use by adolescents and young adults. The substantial number of ED visits involving synthetic cannabinoids in 2011 allowed for statistical analysis and reporting of patients in more age ranges, including patients in the 45 to 54 age range. Reports in scientific literature indicate a wider appeal of synthetic cannabinoids among those not only seeking what is advertised as a legal high, but also by those in parole and probation situations and by those in workplaces that require drug testing.^{4,5,15} This may be because of ease of access to products containing synthetic cannabinoids and the inability to easily test for synthetic cannabinoids using current clinical tests, parole and probation drug tests, and routinely used military and civilian workplace drug tests.^{4,5,15,16} There are several published reports describing the presentation, treatment, and outcome of ED patients who have ingested synthetic cannabinoids. The patients described in these reports range in age from 13 to 59.^{8,22,23,24} For all of the aforementioned reasons, it has been suggested that clinicians, especially in the ED, be constantly on the alert for synthetic cannabinoid toxicity symptoms, even if drug screen results are negative.⁵

Education about the dangers of synthetic cannabinoids needs to be provided to the general public, the medical community, and retailers.¹⁹ Educators can help prevent use of synthetic cannabinoids by addressing use of these substances in programs designed to prevent illicit drug use, such as the White House Office of National Drug Control Policy's Drug-Free Communities Program.¹⁹ Parents can also discuss the dangers of these drugs with their children and use parental controls for online purchases. Recent survey results show that such interventions may have already resulted in teens being less likely to use "synthetic marijuana" because past year use among 12th graders dropped from 11.3 percent in 2012 to 7.9 percent in 2013.²⁵ However, it is important to note that this same survey indicates that 8th, 10th and 12th graders report a low level of perceived risk of using synthetic cannabinoids once or twice.²⁵ Because most synthetic cannabinoid-related ED visits result in discharge, a patient's time in the ED is a valuable opportunity for intervention and education.

Most importantly, medical professionals need to understand the effects of synthetic cannabinoids, so that supportive care and treatment can be provided to patients who experience their adverse effects. Suggested treatment recommendations include intravenous fluids, administration of benzodiazepine medications, and possibly antipsychotic medication if symptoms are severe.²⁶ With new drugs of abuse, it is difficult to disseminate information about their effects when they have only recently been identified and their effects have not yet been studied in a comprehensive way. Furthermore, the changing composition of products containing synthetic cannabinoids, and the inability of routinely used clinical laboratory tests to detect these substances, makes it difficult for treating physicians to make a clear diagnosis and establish a treatment plan for the intoxicated patient. Health professionals in the ED can seek information from other sources, such as medical toxicologists or poison control center staff, who may be better informed about new designer drugs.²⁷

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SUGGESTED CITATION

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (October 16, 2014). Update: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids. Rockville, MD.

SUMMARY

Synthetic cannabinoids are dangerous products which are sold as a legal high and marketed towards youth with names such as “Spice,” and “K2.” Although regulatory agencies have attempted to stop the distribution of these products manufacturers continually change their chemical structures to evade current laws and regulations. In 2012 and 2013, CDC investigated outbreaks that involved synthetic cannabinoids in multiple states. Based on our analysis using data from the Drug Abuse Warning Network (DAWN), the number of visits made to emergency departments (EDs) that involved synthetic cannabinoids more than doubled between 2010 and 2011 (11,406 visits in 2010 to 28,531 visits in 2011). When stratified by age, the rate of ED visits increased more than fourfold for those aged 18 to 20 (from 13.8 visits per 100,000 population in 2010 to 60.8 visits per 100,000 population in 2011) and doubled for those aged 12 to 17 (from 14.9 visits per 100,000 population in 2010 to 30.2 visits per 100,000 population in 2011). In 2011, synthetic cannabinoids were the only substance involved in 65 percent of ED visits by those aged 20 or younger. These results demonstrate the harmful effects of synthetic cannabinoids, especially on youth, and how education continues to be needed for parents, the medical community and to retailers who sell such products.

AUTHOR INFORMATION

KEYWORDS

Short Report, Emergency Department Data, Adolescents as Audience, College Students as Audience, Law Enforcement, Men as Audience, Parents and Caregivers, Prevention Professionals, Women as Audience, Marijuana, Synthetic Marijuana

The Substance Abuse and Mental Health Services Administration (SAMHSA) is the agency within the U.S. Department of Health and Human Services that leads public health efforts to advance the behavioral health of the nation. SAMHSA's mission is to reduce the impact of substance abuse and mental illness on America's communities.

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related morbidity and mortality. DAWN uses a probability sample of hospitals to produce estimates of drug-related emergency department (ED) visits for the United States and selected metropolitan areas annually. DAWN also produces annual profiles of drug-related deaths reviewed by medical examiners or coroners in selected metropolitan areas and States.

Any ED visit related to recent drug use is included in DAWN. All types of drugs – licit and illicit – are covered. Alcohol involvement is documented for patients of all ages if it occurs with another drug. Alcohol is considered an illicit drug for minors and is documented even if no other drug is involved. The classification of drugs used in DAWN is derived from the Multum Lexicon, copyright 2012 Lexi-Comp, Inc., and/or Cerner Multum, Inc. The Multum Licensing Agreement governing use of the Lexicon can be found at <http://www.samhsa.gov/data/emergency-department-data-dawn>.

DAWN is one of three major surveys conducted by SAMHSA's Center for Behavioral Health Statistics and Quality (CBHSQ). For more information on other CBHSQ surveys, go to <http://www.samhsa.gov/data/>. SAMHSA has contracts with Westat (Rockville, MD) and RTI International (Research Triangle Park, NC) to operate the DAWN system and produce publications.

For publications and additional information about DAWN, go to <http://www.samhsa.gov/data/emergency-department-data-dawn>.



U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Substance Abuse & Mental Health Services Administration
Center for Behavioral Health Statistics and Quality
www.samhsa.gov/data



Drug Fact Sheet

K2 or Spice

Overview

K2 or "Spice" is a mixture of herbs and spices that is typically sprayed with a synthetic compound chemically similar to THC, the psychoactive ingredients in marijuana. The chemical compounds typically include HU-210, HU-211, JWH-018, and JWH-073. K2 is commonly purchased in head shops, tobacco shops, various retail outlets, and over the Internet. It is often marketed as incense or "fake weed." Purchasing over the Internet can be dangerous because it is not usually known where the products come from or what amount of chemical is on the organic material.

Street names

Bilss, Black Mamba, Bombay Blue, Fake Weed, Genie, Spice, Zohai

Looks like

K2 is typically sold in small, silvery plastic bags of dried leaves and marketed as incense that can be smoked. It is said to resemble potpourri.



Methods of abuse

K2 products are usually smoked in joints or pipes, but some users make it into a tea.

Affect on mind

Psychological effects are similar to those of marijuana and include paranoia, panic attacks, and giddiness.

Affect on body

Physiological effects of K2 include increased heart rate and increase of blood pressure. It appears to be stored in the body for long periods of time, and therefore the long-term effects on humans are not fully known.

Drugs causing similar effects

Marijuana

Overdose effects

There have been no reported deaths by overdose.

Legal status in the United States

On Tuesday, March 1, 2011, DEA published a final order in the Federal Register temporarily placing five synthetic cannabinoids into Schedule I of the CSA. The order became effective on March 1, 2011. The substances placed into



Drug Fact Sheet

K2 or Spice – cont'd.

Schedule I are 1-pentyl-3-(1-naphthoyl) indole (JWH-018), 1-butyl-3-(1-naphthoyl) indole (JWH-073), 1-[2-(4-morpholinyl) ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue). This action is based on a finding by the Administrator that the placement of these synthetic cannabinoids into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions, and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cannabinoids.

Common places of origin

Manufacturers of this product are not regulated and are often unknown since these products are purchased via the Internet whether wholesale or retail. Several websites that sell the product are based in China. Some products may contain an herb called damiana, which is native to Central America, Mexico, and the Caribbean.



American Association of Poison Control Centers

Synthetic Cannabinoid Data
October 31, 2015

These numbers reflect the closed human exposures to synthetic cannabinoid (THC homologs) reported to poison centers as of October 31, 2015. The numbers may change as cases are closed and additional information is received.

Year	Number of Cases
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015 Through October 31, 2015	6,949

2015 by Month	Number of Cases
January 2015	358
February 2015	273
March 2015	269
April 2015	1,511
May 2015	1,204
June 2015	654
July 2015	740
August 2015	717
September 2015	627
October 2015	596
November 2015	
December 2015	
Total	6,949

Information continues on next page.

2014 by Month	Number of Cases
January 2014	181
February 2014	167
March 2014	205
April 2014	250
May 2014	312
June 2014	337
July 2014	280
August 2014	442
September 2014	395
October 2014	439
November 2014	357
December 2014	315
Total	3,682

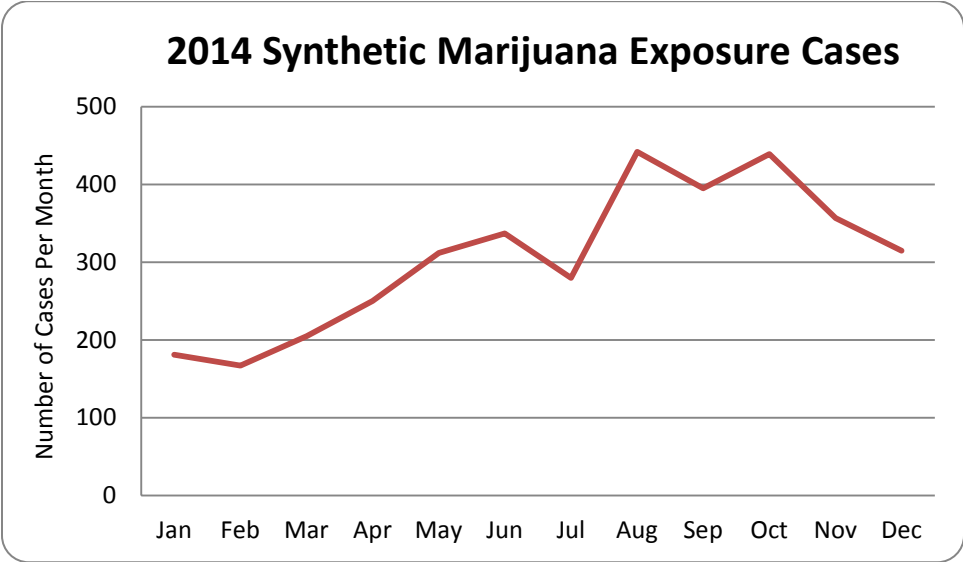
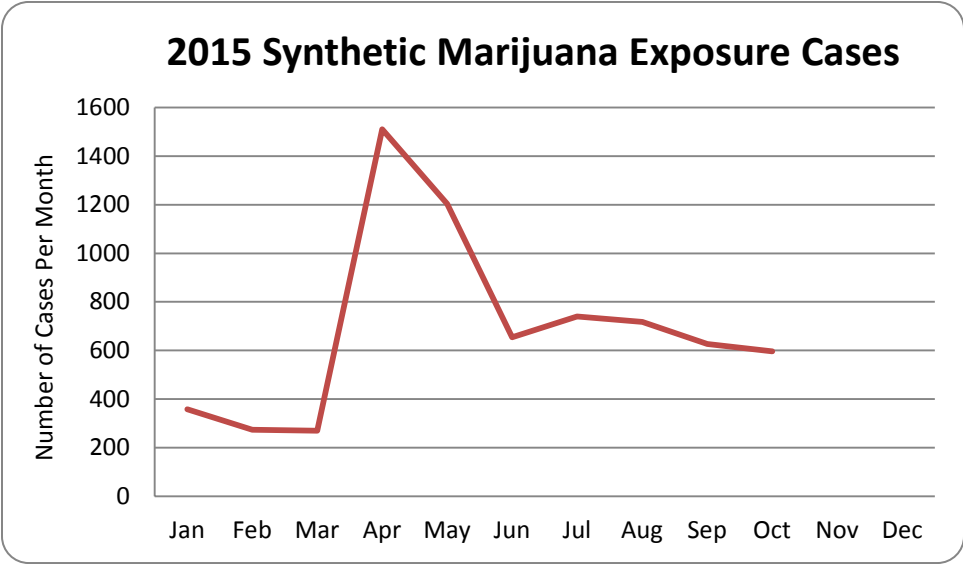
2013 by Month	Number of Cases
January 2013	177
February 2013	252
March 2013	253
April 2013	267
May 2013	277
June 2013	230
July 2013	186
August 2013	204
September 2013	213
October 2013	200
November 2013	209
December 2013	200
Total	2,668

2012 by Month	Number of Cases
January 2012	657
February 2012	634
March 2012	644
April 2012	498
May 2012	507
June 2012	497
July 2012	459
August 2012	346
September 2012	315
October 2012	252
November 2012	202
December 2012	219
Total	5,230

Please note: American Association of Poison Control Center data for this year and last is considered preliminary because it is possible that a poison center may update a case anytime during the year if new information is obtained. In the fall of each year, the data for the previous year is locked, and no additional changes are made.

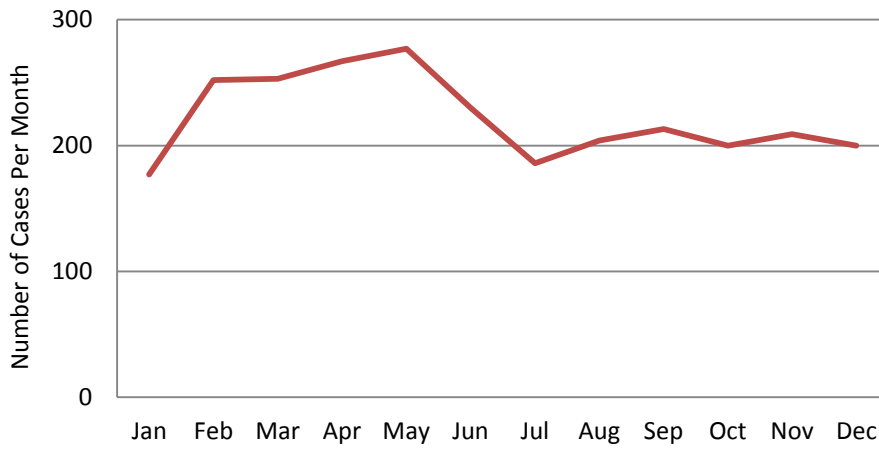
The term “exposure” means someone has had contact with the substance in some way; for example, ingested, inhaled, absorbed by the skin or eyes, etc. Not all exposures are poisonings or overdoses.

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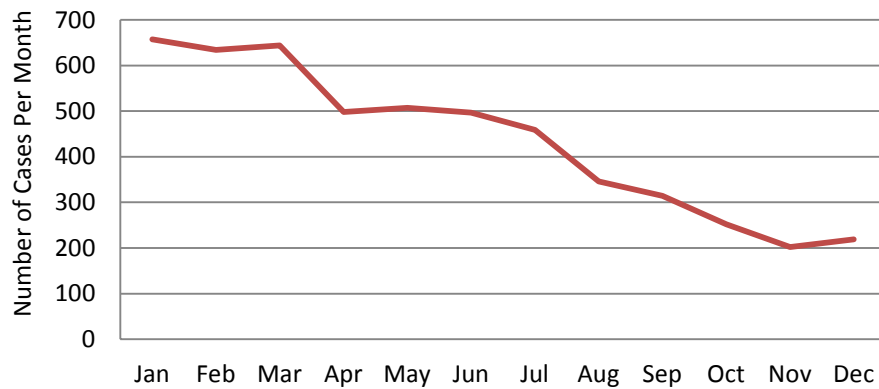


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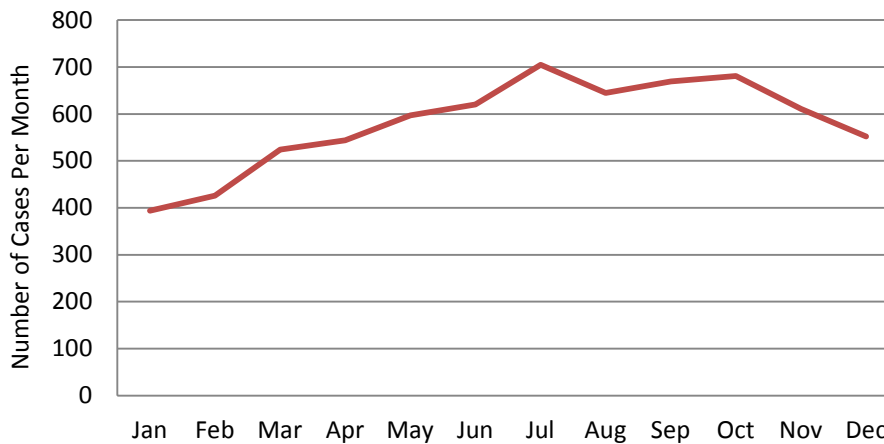
2013 Synthetic Marijuana Exposure Cases



2012 Synthetic Marijuana Exposure Cases



2011 Synthetic Marijuana Exposure Cases





American Association of Poison Control Centers

Synthetic Cannabinoid Data
November 30, 2015

These numbers reflect the closed human exposures to synthetic cannabinoid (THC homologs) reported to poison centers as of November 30, 2015. The numbers may change as cases are closed and additional information is received.

Year	Number of Cases
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015 Through November 30, 2015	7,369

2015 by Month	Number of Cases
January 2015	358
February 2015	273
March 2015	269
April 2015	1,511
May 2015	1,204
June 2015	654
July 2015	740
August 2015	717
September 2015	627
October 2015	596
November 2015	420
December 2015	
Total	7,369

Information continues on next page.

2014 by Month	Number of Cases
January 2014	181
February 2014	167
March 2014	205
April 2014	250
May 2014	312
June 2014	337
July 2014	280
August 2014	442
September 2014	395
October 2014	439
November 2014	357
December 2014	315
Total	3,682

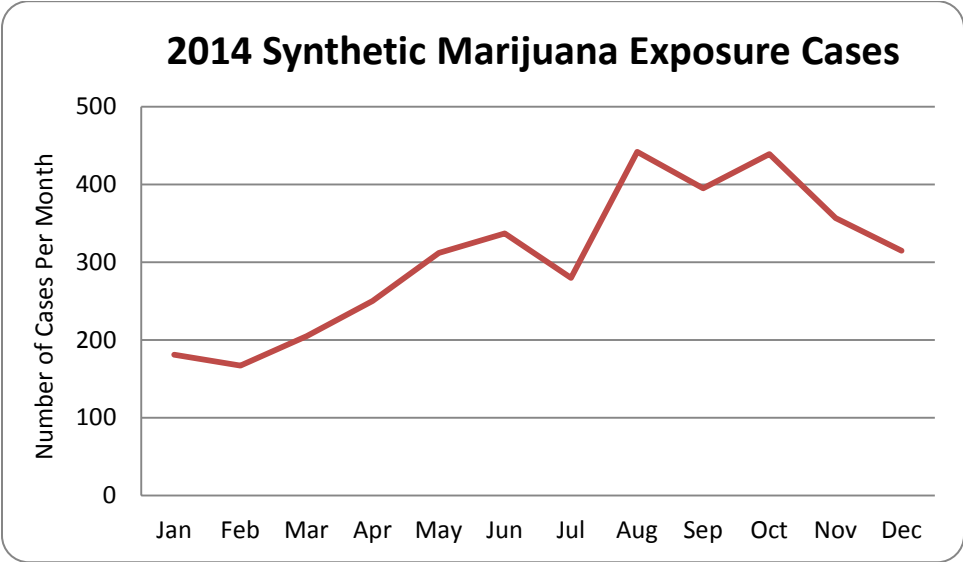
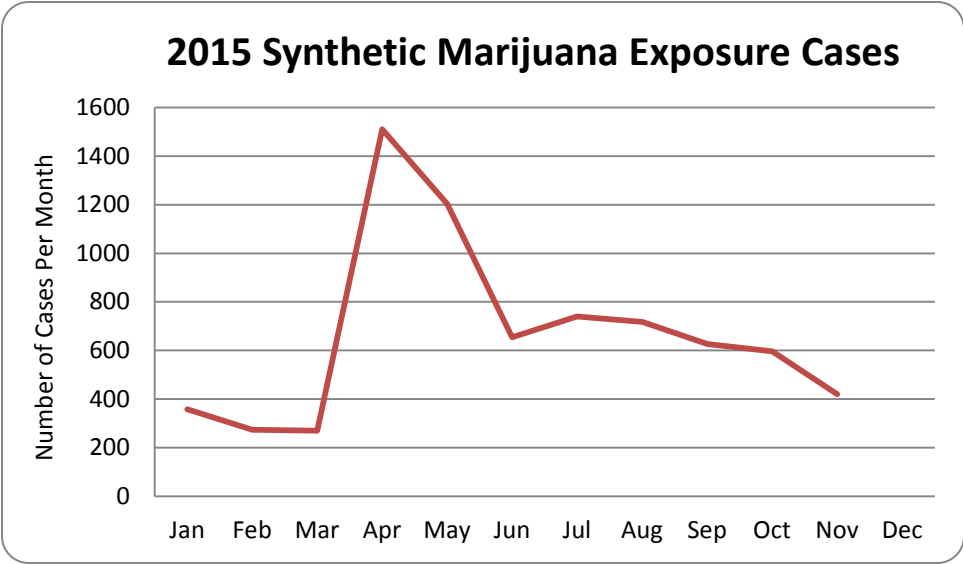
2013 by Month	Number of Cases
January 2013	177
February 2013	252
March 2013	253
April 2013	267
May 2013	277
June 2013	230
July 2013	186
August 2013	204
September 2013	213
October 2013	200
November 2013	209
December 2013	200
Total	2,668

2012 by Month	Number of Cases
January 2012	657
February 2012	634
March 2012	644
April 2012	498
May 2012	507
June 2012	497
July 2012	459
August 2012	346
September 2012	315
October 2012	252
November 2012	202
December 2012	219
Total	5,230

Please note: American Association of Poison Control Center data for this year and last is considered preliminary because it is possible that a poison center may update a case anytime during the year if new information is obtained. In the fall of each year, the data for the previous year is locked, and no additional changes are made.

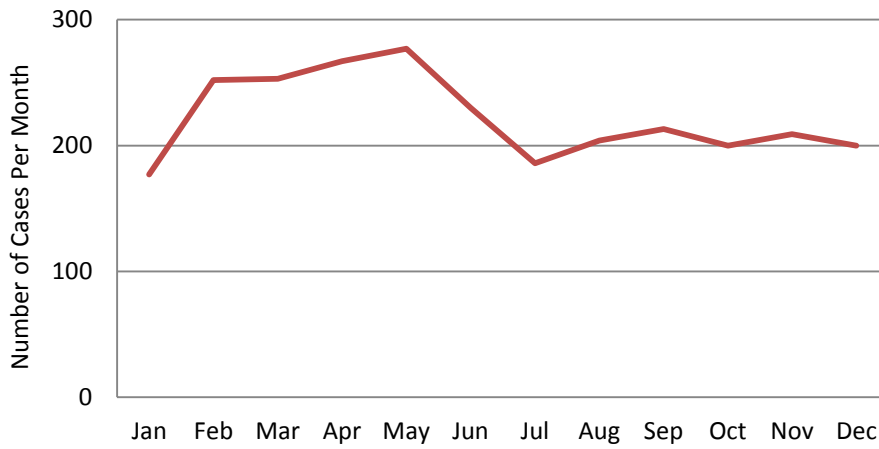
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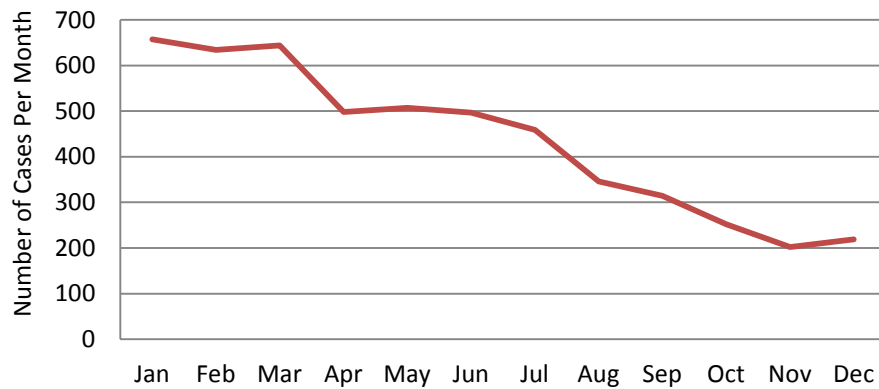


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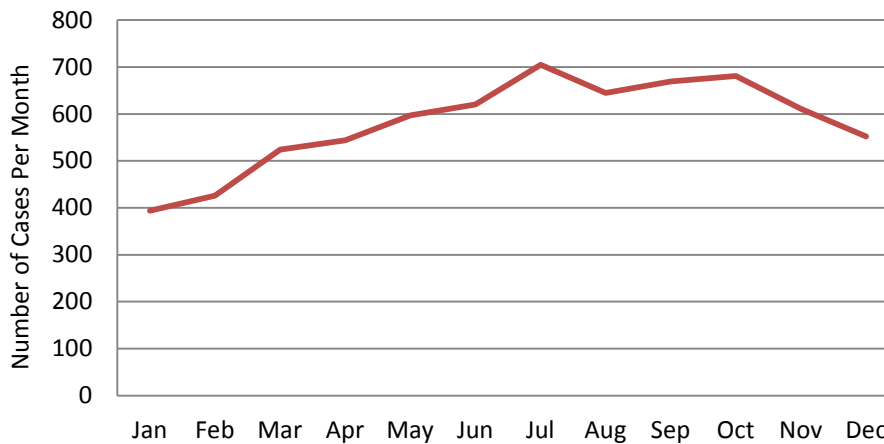
2013 Synthetic Marijuana Exposure Cases



2012 Synthetic Marijuana Exposure Cases



2011 Synthetic Marijuana Exposure Cases



Rise in Synthetic Marijuana Use by Teens an Issue Locally and Nationally

A form of synthetic marijuana, commonly referred to as “Spice” or “K2”, began appearing across the U.S. in 2008, and its popularity grew over the past few years mainly because it could be sold legally and not be detected in urinalysis drug tests. However, its legality has been temporarily suspended after the DEA took emergency action in late 2011 by giving five synthetic cannabinoids Schedule 1 status under the Controlled Substances Act (through August 2012), making it illegal to sell, buy, or possess it. While a urinalysis test was recently developed to detect Spice, the test remains cost prohibitive for many jurisdictions to include in their regular drug testing panel. Unfortunately, Spice remains available, particularly through black market Internet sites, indicating a need for continued education and prevention¹. As awareness about synthetic marijuana broadened across the U.S., the Monitoring the Future survey added questions in 2011 that asked high school seniors about their experience using these drugs, with nearly 1 in 9 (11%) reporting they had used them in the past year (not shown)².

Locally, SANDAG added new questions about Spice to their 2011 Substance Abuse Monitoring (SAM) interview conducted in Juvenile Hall with recently arrested youth. As Table 1 shows, these interviews revealed that one in every two juvenile arrestees had ever tried Spice, with 41 percent having done so in the past year and 18 percent having used it as recently as three days prior to their arrest. The youth who had ever tried Spice did so for the first time on average at age 15.17 ($SD=1.30$, range 11 to 18 years) (not shown).

Table 1

MORE THAN HALF OF LOCAL JUVENILE ARRESTEES EVER TRIED SPICE	
Ever tried Spice	52%
Used Spice in last year	41%
Used Spice in last 3 days	18%

NOTE: Cases with missing information not included

SOURCE: Substance Abuse Monitoring Survey, 2011

Through the SAM project, SANDAG will continue to monitor trends in arrestees’ use of Spice to determine if recent federal controls on its availability and developing drug screens have an effect on its use among this population. In June 2012, SANDAG will release its SAM bulletin summarizing 2011 data from interviews with juvenile arrestees. To access the SAM bulletin and other SANDAG publications, go to www.sandag.org/cj. For more information about Spice, visit the National Institute of Drug Abuse Web site at www.drugabuse.gov.

¹ National Institute on Drug Abuse. (2011). InfoFacts: Spice. Available [on-line] at www.drugabuse.gov.

² Johnston, L.D., O’Malley, P., Bachman, J.G., and Schulenberg, J.E. (2011). *Monitoring the Future national results on adolescent drug use: Overview of key findings, 2011*. Ann Arbor: Institute for Social Research, The University of Michigan.

Parents Warn Against Synthetic Marijuana After 19-Year-Old Son Dies

POSTED 11:25 PM, AUGUST 7, 2014, BY KTLA 5 WEB STAFF AND LU PARKER,
UPDATED AT 06:29AM, AUGUST 8, 2014



A California teen recently died after smoking one hit of synthetic marijuana, and now his parents are on a mission to prevent similar deaths from happening. "In a moment of peer pressure, he gave into that, thinking that was OK, it was somehow safe, and one hit later he goes to sleep and never wakes up," Connor Reid Eckhardt's father said. Effects of smoking the often-legal product can include altered mental state, irregular heartbeat and seizures. Watch KTLA's video here: <http://ktlanc.ws/1mt0eLL>

Parents of a 19-year-old California teen who recently died after smoking synthetic marijuana spoke to KTLA about trying to prevent similar deaths from happening in the future.

On July 11, Connor Eckhardt inhaled one hit of dried herbs that had been sprayed with chemicals to cause a pot-like high, his parents said.

“In a moment of peer pressure, he gave into that, thinking that was OK, it was somehow safe, and one hit later, he goes to sleep and never wakes up,” Connor’s father, Devin Eckhardt, said.

Connor Eckhardt quickly slipped into a coma and experienced brain swelling, his parents said.

Effects of smoking the often-legal product include altered mental state, irregular heartbeat and seizures, the [Los Angeles Times](#) reported.

“These substances are not benign,” Dr Andrew Monte, the lead author of an editorial in the New England Journal of Medicine, said. “You can buy designer drugs of abuse at convenience stores and on the Internet. People may not realize how dangerous these drugs can be – up to 1,000 times stronger binding to cannabis receptors when compared to traditional marijuana.”

Since Connor Eckhardt’s death, his parents fulfilled his wish to have his organs donated and [created a Facebook page](#) meant to carry on his memory and tell others about his untimely death.

Reports of Synthetic Cannabinoids Overdoses in the United States

Synthetic Marijuana Suspected in 3 Deaths, 75 Hospitalizations in Colorado (Colorado)

September 9th, 2013

<http://www.drugfree.org/join-together/synthetic-marijuana-suspected-in-3-deaths-75-hospitalizations-in-colorado/>

Almost 120 People In Texas Overdose On Synthetic Marijuana In Just 5 Days; All Linked To Same Dallas-Based Supplier (Texas)

May 7, 2014

<http://www.medicaldaily.com/almost-120-people-texas-overdose-synthetic-marijuana-just-5-days-all-linked-same-dallas-based-280814>

Governor Hassan Declares State of Emergency as a Result of Overdoses from Synthetic Cannabinoid (New Hampshire)

August 14, 2014

<http://governor.nh.gov/media/news/2014/pr-2014-08-14-emergency.htm>

Mississippi and Alabama 'Spice' Overdoses Send More Than 300 to ER in 2 Weeks (Mississippi and Alabama)

Apr 16, 2015

<http://abcnews.go.com/Health/mississippi-alabama-spice-overdoses-send-300-er-weeks/story?id=30362036>

Governor Cuomo Issues Health Alert: Illegal Synthetic Marijuana Sends More Than 160 New Yorkers to the Hospital Since April 8 (New York)

APRIL 17, 2015

<http://www.governor.ny.gov/news/governor-cuomo-issues-health-alert-illegal-synthetic-marijuana-sends-more-160-new-yorkers>

Spice Causes More Than 50 Overdoses In 11 Days (Maryland and Virginia)

April 21, 2015

<http://www.your4state.com/news/news/spice-causes-more-than-50-overdoses-in-11-days>

Spice overdoses now an 'epidemic' for Tucson

July 23, 2015

<http://www.tucsonnewsnow.com/story/29620570/spice-overdose-calls-stressing-city-resources>

Attachment 3

Study of Expanded Use of an Automated Delivery Device

UPDATE 12-14-15

Jan D. Hirsch, BPharm, PhD

UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences



Update

- ScriptCenter Kiosk Installation
 - Location
 - Progress and timeline
- Update on Study
 - Reminder of Research Questions
 - Updated Timeline

ScriptCenter Kiosk Location Sharp Memorial Hospital

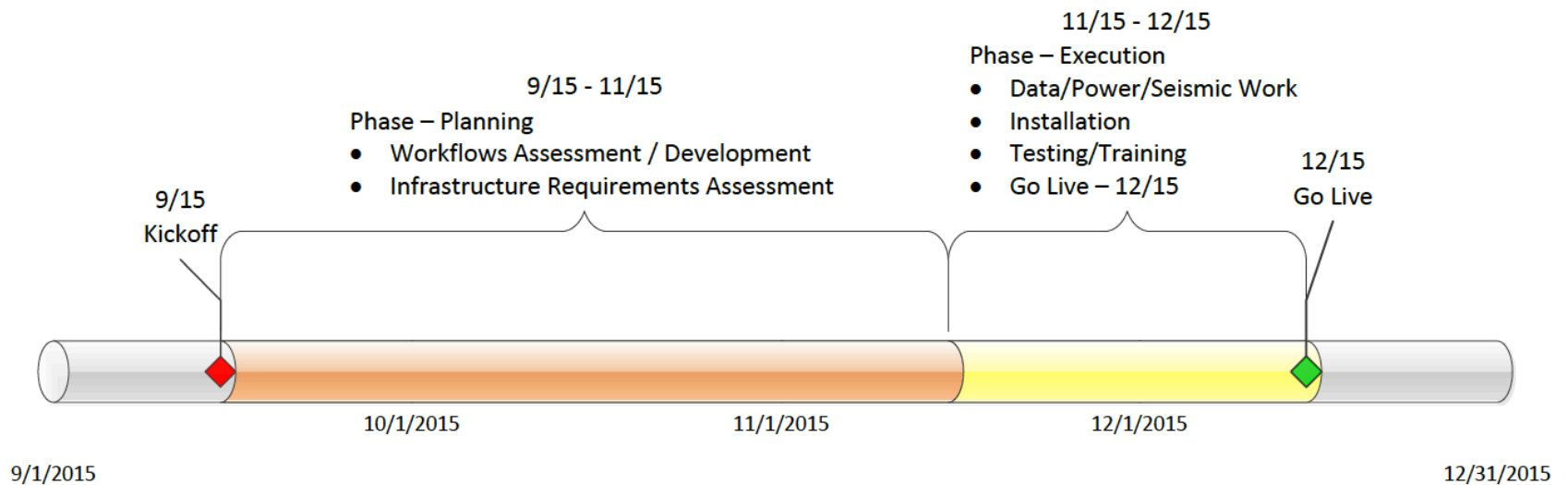


Sharp Memorial Hospital employee entrance located on ground floor. Secure access only.

ScriptCenter Kiosk Installation



Asteres ScriptCenter Implementation, Sharp Memorial Hospital



After 12/15/15 “go-live” date

- Employees will be able to enroll to use the kiosk
- Employees will be encouraged to use the ScriptCenter to feel how it works – before they have enrolled to really use for their prescriptions.
 - There will also be a spokesperson at machine during set times.
- Employees will be able to receive forms from the ScriptCenter to allow them to “transfer” their prescriptions to the SRS Pharmacy for future delivery to the Script Center
- Email will be sent to employees with current prescriptions – for them to be able to transfer their Rx's to the Script Center
- Marketing at the regular pharmacy counter also will be telling people about possibility of transfer – plus other opportunities as the as the marketing plan progresses

Study Research Questions

Primary: Is patient *primary adherence* (prescription retrieval rate; all prescriptions) greater for kiosk vs.

- Historical and concurrent regular counter rate?
- Rx retrieval rate based on Return to Stock (RTS) rate per month

RTS rate = # Rxs RTS after 14 days/# Rxs filled

Secondary: Kiosk vs. Regular Counter Patients

- Is number or nature of questions for pharmacists during consultation for new prescriptions different? (*consultation log*)
- What is mean time from fill (RPh verified) to pick up?

Kiosk patients:

- Satisfaction with access to pharmacist for questions & convenience

Sharp Memorial Hospital employees:

- Would kiosk be beneficial and increase primary adherence?

Study Design

Quasi-experimental with
non-randomized control group

- Pre-Kiosk Implementation Survey (Sharp Employees)

Kiosk Start

6 months pre-kiosk

Month 1

Month 6

Regular Counter

- RTS rate*

Kiosk

- RTS rate
- Consultation Log
- Time to Pick-up
- Kiosk Patient Satisfaction

Regular Counter

- RTS rate*
- Consultation Log (1 week sample pts w/ new Rx)
- Time to Pick-up*

RTS = Return to Stock

* For employees and dependents

Projected Study Timetable

- Q4 2015 Pre-kiosk 6-month data collection phase begins

- Q1 2016 Implement Kiosk device (12/15/15)
Refine data collection tools & process
Deployment of program/enroll patients

- Q2 & Q3 2016 Post-kiosk implementation
Data collection and analysis

- Q4 2016 Report Results to Board



Questions?

UC San Diego
SKAGGS SCHOOL OF PHARMACY
AND PHARMACEUTICAL SCIENCES

Attachment 4

Preventing Diversion in the ED

Philippe Mentler, PharmD, BCPS

Although drug addiction in the general population is well studied and documented, limited epidemiologic surveillance data exist on addiction and drug diversion patterns among health care workers (HCWs). In fact, the dearth of evidence might suggest that drug diversion among HCWs is uncommon or poses no harm, but, unfortunately, the opposite is true. The rates of opiate and benzodiazepine abuse, for example, are higher among HCWs than among the population at large.¹ One possible reason for this is their almost ubiquitous access to, and extensive knowledge of, controlled substances. It is not unusual for HCWs to conflate their understanding of therapeutic and toxic doses, pharmacokinetics, and addictive potential with a false sense of control over these agents.

Drug diversion by HCWs poses significant risks to the diverter, the hospital, and to patients. For example, patients may receive incorrect medications or lower doses than prescribed, resulting in inadequate pain control or sedation. Drug diversion also can confer a significant risk of infection. In one case, 45 patients contracted hepatitis C from a radiology technician who was injecting himself with fentanyl and reusing the syringes during patient procedures.² As a result of this one HCW's diversion, almost 5,000 patients were potentially exposed to, and required testing for, hepatitis C.³

Because of the potential risks, it is important to be able to identify drug diversion and prevent it whenever possible. Although diversion of controlled substances receives the most attention, diversion of non-controlled agents, for example, by the nauseated employee who pockets an ondansetron, or the worker who snatches sildenafil for street sale, is no less important and should be addressed in hospital drug diversion policies.

Detecting Diversion

Identifying drug diversion is challenging, as anyone, regardless of their academic degrees and accomplishments, work ethic, or personality, can become addicted to controlled substances. An impaired HCW often appears normal and may maintain a high level of productivity, particularly in the early stages of addiction. To identify a potential diverter, management must keep an open mind, remove any prejudices, and pay close attention to subtle changes in behavior, such as:

- Taking long breaks or disappearing from the floor for prolonged periods
- Exhibiting mood swings throughout the workday
- Being exceptionally helpful (eg, frequently offering to administer medications, particularly controlled substances, for other nurses)
- Staying beyond a scheduled shift or coming to the workplace on days off
- Being prone to mistakes, such as automated dispensing cabinet (ADC) miscounts, or frequently dropping pills or breaking vials
- Wearing long sleeves to conceal injection drug use

HCWs can divert controlled substances in countless ways. Common methods include retaining wasted product for future use or removing multiple tablets or capsules when only one is ordered for the patient. Despite the risk of needle exposure, diverters also have stolen sharps containers to retrieve discarded drugs (see **TABLE 1**).

Preventing Diversion

A multifaceted approach, including use of technology, policy adherence, staff education, and robust oversight, is necessary to prevent diversion. Most of the technology aimed at drug diversion-prevention pertains to ADCs. For example, individually locking bins have been available since ADCs were introduced into hospitals. More recently, diversion-detection software has become available, which allows a hospital to record typical usage and waste patterns for specific areas or ADCs in the hospital. These data then can be used as benchmarks for individual staff and groups of employees, to highlight and flag aberrance in practice patterns.

For example, imagine two ED ADCs have a combined typical usage of 100 units per day of hydromorphone 1 mg. Sixty percent typically comes from ADC 1, and 40% from ADC 2. The average nurse pulls 10 units per day, with a standard deviation (SD) of 2. Nurse Bob's average pull is 12 units per day. Over a short period, the ADC software report shows an increase in Bob's withdrawals per day to 18 units (SD >3). In addition, he has changed where he pulls hydromorphone; although he formerly used ADC 1 exclusively, he now alternates between the two machines. As a result, the report is flagged, and a review is initiated.

It should be noted that while available software helps in preventing diversion, facilities should maintain a human component when monitoring ADCs and avoid relying solely on software reports. Hospitals also should limit access to ADCs; HCWs should use only the ADC at their primary workstation. In addition, facilities should update access to ADCs regularly as personnel move to different primary work areas. Passwords should be changed at least every 6 months, and personnel must be trained to never share their passwords. Wasting must be witnessed, and should occur at the time the drug is removed from the ADC.

Diversion awareness is important for all hospital employees. Education should be included in all employee orientations and continued, at a minimum, as part of the institution's annual competencies. The curriculum should include the risks of addiction, common diversion behaviors, the process for reporting suspicious behaviors, and a review of the hospital's controlled substances policy.

Implementing a Diversion Response Team

Developing a formalized drug diversion response team is recommended for the prevention and detection of drug diversion and the enforcement of drug diversion policies. A diversion response team should be multidisciplinary in nature, including representation from pharmacy, nursing, medical staff, security, and human resources. A response team with dedicated FTEs is necessary to interpret data, review suspected cases, conduct interviews, and document outcomes. A dedicated team also allows team members to develop greater expertise in diversion methods, which leads to more professional, confidential, and expedited diversion investigations and a more robust enforcement program. A valuable resource for institutions considering the implementation of a drug diversion response team is available from the Minnesota State Department (<http://www.health.state.mn.us/patientsafety/drugdiversion/divroadmap041812.pdf>).

Helping the Addicted HCW

Some health care systems are reluctant to report diversion or offer drug addiction support for fear of negative publicity, added scrutiny by regulatory agencies, or employee retaliation. However, HCW drug addiction is a treatable disorder with a high treatment success rate. Studies show that the abstinence rates of various groups of chemically dependent HCWs who receive treatment for addiction exceed 80%, which is significantly greater than that of the general population.⁴

Common Methods Used to Divert Controlled Substances	Methods to Prevent Diversion*
Saving excess product that should have been wasted	<ul style="list-style-type: none"> Implement a policy that another staff member must witness waste at the time of ADC withdrawal
Preceding to drop product on the floor or breaking a vial and wasting it in the ADC	<ul style="list-style-type: none"> Require physical return to pharmacy with a report of all products that are considered contaminated
Removing product after a patient has left the hospital	<ul style="list-style-type: none"> Ensure rapid discharge and inscription of patient from the ADC upon discharge Use ADC diversion-prevention software
Spicing off a portion of the contents of a product and replacing with saline	<ul style="list-style-type: none"> Take patient complaints of limited pain relief seriously Product should never be left unattended The HCW responsible for the patient should both remove and administer product
Using a co-worker's ADC password to obtain product or act as second waste witness	<ul style="list-style-type: none"> Implement a policy of not sharing passwords Require password changes at least every 6 months Use ADC diversion-prevention software
Switching a similar looking product for a controlled substance prior to administration	<ul style="list-style-type: none"> Review look-alike products in ADCs Run regular reports and investigate discrepancies of non-controlled substances Use ADC diversion-prevention software
Removing remnants of disposed product from sharps bins	<ul style="list-style-type: none"> Use specialized waste bins that contain controlled substances or render them otherwise unusable
Removing more product than was ordered	<ul style="list-style-type: none"> Have a policy whereby only the amount of product needed at the lowest dosage strength is removed for each valid order Use ADC diversion-prevention software
"Forgetting" product in a shirt pocket and requesting waste on the following day	<ul style="list-style-type: none"> Require product be sent to pharmacy for testing and a report be completed for the event Consider drug testing HCWs in this scenario
Removing product for a crashed good patient from a separate unit	<ul style="list-style-type: none"> Limit ADC access only to those working on a given unit Maintain and regularly update user access of ADCs Use ADC diversion-prevention software
Removing product by override and asking for a physician order afterward	<ul style="list-style-type: none"> Prohibit the practice or create specific circumstances for which a controlled substance override is allowed (i.e. high level trauma, rapid sequence intubation, seizure) Use ADC diversion-prevention software

*Implementation of a diversion-prevention team is recommended, along with these methods for diversion prevention.

Conclusion

Although the dearth of evidence might suggest the opposite, controlled substance addiction and drug diversion actually are quite common among HCWs. As any employee can divert drugs, it is the responsibility of all hospital employees to be aware of drug diversion practices and immediately report suspicious behavior. A number of tools are available to aid in the detection of drug diversion, but tools are successful only when humans remain engaged in the process and use them correctly. Once diversion with the intent to use is proven, it is imperative that the institution offers the diverter entry into a treatment program for the benefit of the diverter and for the safety of the public at large.

References

1. Baldisseri MR. Impaired healthcare professional. *Crit Care Med*. 2007;35(suppl 2):S106-S116.
2. Centers for Disease Control and Prevention. Risks of Healthcare-associated Infections from Drug Diversion. <http://www.cdc.gov/injectionsafety/drugdiversion/index.html>. Accessed April 1, 2015.
3. New Hampshire Department of Health and Human Services Division of Public Health Services. State of New Hampshire Hepatitis C Outbreak Investigation Exeter Hospital Public Report. June 2013. <http://www.dhhs.nh.gov/dphs/cdcs/hepatitisc/documents/hepc-outbreak-rpt.pdf>. Accessed July 7, 2015.
4. Cross W, Bologeorges S, Angres D. Issues and Data Associated with Addictive Disease in Pharmacists. *US Pharm*. November, 2013. http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/109516/. Accessed July 7, 2015.



Philippe Mentler, PharmD, BCPS, is a senior medication management consultant with VHA, Inc. He joined VHA after more than 10 years as an emergency department pharmacist.

Philippe received his doctorate of pharmacy from Ernest Mario School of Pharmacy, and completed a PGY1 general practice residency at the University of Illinois at Chicago and a PGY2 residency in emergency medicine at Robert Wood Johnson University Hospital in conjunction with the Ernest Mario School of Pharmacy.

CASE STUDY 1

The Moody Veteran Nurse

A skilled and trusted ED nurse with more than 20 years of experience was caught diverting injectable opiates. He admitted to diversion and to his addiction only after another nurse witnessed multiple wasted medications in his pocket. His addiction to pain medications began after a simple surgical procedure the prior year. When his physician limited his pain medications, he began diverting from the hospital. The nurse had been taking on extra assignments and completing other nurses' tasks in order to increase access to opiates, and he wore long sleeves to hide track marks from multiple daily injections. In retrospect, staff members noted that he tended to have mood swings during the workday.

CASE STUDY 2

Medication Substitution

A nurse asked the emergency pharmacist to speak with an irate patient, a regular at the hospital and a known drug seeker. The patient complained that the generic 512s (a street name for oxycodone/acetaminophen, derived from the fact that the number 512 is imprinted on the branded 5 mg Percocet tablet) prescribed do not work. This was the third time in a week that the patient was in the ED complaining of not receiving pain relief from the hospital's 512s. The following day, a pharmacy technician reported to the ED pharmacist that he had to replace a large number of missing prednisone 50 mg tablets for the second time within a week. Upon initiating an investigation, the ADC report on prednisone showed that one nurse performed a cancelled transaction every time a discrepancy was noted (several more prednisone discrepancies were identified during the investigation). When the nurse was confronted, she admitted filling the oxycodone/acetaminophen orders with prednisone tablets prior to patient administration. She removed the tablet from its unit-dose container and placed it in a unit-dose cup prior to entering the patient's room. Prednisone 50 mg is almost identical in size and appearance to 5 mg oxycodone/acetaminophen.



Prednisone 50 mg

Oxycodone/
acetaminophen 5/325 mg

CASE STUDY 3

Mishandling Confirmed Diversion

A pharmacist with a history of brief employment in numerous pharmacy settings was hired to staff the evening shift of the central pharmacy. Within 3 months, discrepancies in the controlled substances cabinet were noted. One evening, a pharmacy technician witnessed the pharmacist pocket several oxycodone tablets. The technician reported the incident directly to pharmacy administration. The pharmacist was immediately offered the choice to resign, which she eagerly accepted. She then went on to work in a retail pharmacy where she was caught on video stealing a handful of hydrocodone/acetaminophen from a 1000-count bottle. She was again offered the option to resign from that position, and accepted. The actions of both of these facilities—which are intended to serve and care for the public—place the general population at continued risk and leaves adrift a person with a treatable disease. Instead, the addict should have been offered access to an addiction treatment program, and the offenses should have been reported to the appropriate authorities.

Attachment 5

SETTLEMENT AGREEMENT

This Settlement Agreement (“Agreement”) is made and entered into by and between the United States of America, acting through the United States Department of Justice and its Drug Enforcement Administration (“DEA”) (collectively, the “United States”), and The General Hospital Corporation, d/b/a Massachusetts General Hospital, and its sole member, The Massachusetts General Hospital (collectively, “MGH”) (together, the “Parties”).

Recitals

- A. MGH is the largest hospital in Massachusetts, the largest teaching hospital of Harvard Medical School, and a biomedical research facility. It currently holds twelve active DEA registrations as set forth in Attachment 1 hereto.
- B. Each DEA registrant is required to conduct its operations in accordance with the Controlled Substances Act, 21 U.S.C. § 801, *et seq.* (the “Act”), and the regulations promulgated thereunder.
- C. The DEA is the Department of Justice component agency primarily responsible for enforcing the Act and is vested with the responsibility of investigating violations of the Act.
- D. The United States Attorney General, through the United States Attorney’s Office, has primary authority to bring civil actions to enforce the Act. See 21 U.S.C. § 871 and 28 C.F.R. § 0.55(c).
- E. The United States contends that, during the period from October 4, 2011, through April 1, 2015, MGH negligently failed to make, keep, or furnish certain records required to be kept under the Act, and failed to provide effective controls and procedures to guard against theft and loss of controlled substances. More specifically, the United States contends that it has civil

claims against MGH for engaging in the alleged conduct described in the United States'

Statement of Relevant Conduct set forth in Attachment 2 and as follows:

1. MGH failed to notify the DEA of nurse J.S.'s theft of controlled substances within one business day of discovery, in violation of 21 C.F.R. § 1301.76(b);
2. MGH failed to notify the DEA of nurse J.Z.'s theft of controlled substances within one business day of discovery, in violation of 21 C.F.R. § 1301.76(b);
3. MGH failed to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71;
4. MGH failed to maintain complete and accurate records of all controlled substances that it received, sold, delivered, or otherwise disposed of, in violation of 21 C.F.R. §§ 1304.21 and 1304.22(c);
5. MGH failed to document 358 transfers of Schedule II controlled substances using the required DEA Form 222, in violation of 21 C.F.R. § 1305.03;
6. MGH failed to document 407 transfers of Schedule IV controlled substances with invoices, in violation of 21 C.F.R. § 1304.22(b);
7. The MGH medical practice with DEA registration number xxxxxx349 failed to conduct an initial inventory, in violation of 21 C.F.R. § 1304.11(b);
8. The MGH medical practice with DEA registration number xxxxxx349 and the MGH pharmacy with DEA registration number xxxxxx423 failed to conduct biennial inventories, in violation of 21 C.F.R. § 1304.11(c);
9. MGH's inpatient pharmacy conducted a biennial inventory that was incomplete, in violation of 21 C.F.R. § 1304.11(a) and (c); and

10. MGH failed to maintain current and accurate records of controlled substances in its automatic drug-dispensing machines (“ADMs”), in violation of 21 C.F.R. § 1304.22(a).

The conduct referred to in this Recital E and Attachment 2 is referred to below as the Covered Conduct.

In consideration of the mutual promises and obligations of this Agreement, the Parties agree and covenant as follows:

Terms of Agreement

1. No later than 10 days after the date on which this Agreement is signed by all Parties, MGH shall pay the United States Two Million, Three Hundred Thousand Dollars (\$2,300,000.00) (the “Settlement Amount”). The Settlement Amount shall be paid by electronic funds transfer pursuant to written instructions from the United States.

2. No later than 10 days after the date on which this Agreement is signed by all Parties, MGH and DEA will enter into the three-year Corrective Action Plan (“CAP”) that is Attachment 3 hereto.

3. In consideration of the obligations of MGH in this Agreement, conditioned upon MGH’s timely paying the Settlement Amount and entering into the CAP, and subject to the conditions in Paragraph 4, the United States releases MGH and Partners Healthcare System, Inc. (“Partners”), and their assigns, successors, principals, management, officers, directors, agents, and employees, from any civil or administrative claims the United States has, could have, or may assert in the future related to the Covered Conduct under the Act.

4. This Agreement in no way alters or restricts the United States’ right to enforce the Act and regulations promulgated thereunder by commencing a civil or administrative action

against MGH or Partners for any violations of the Act which are not based on the Covered Conduct, nor does it restrict the United States or any other sovereign or governmental entity from bringing any criminal charge against MGH, Partners, or any employee of either MGH or Partners. Also, this Agreement does not prevent any sovereign other than the United States from pursuing civil, criminal, and/or administrative claims against MGH or Partners for the Covered Conduct and/or any other conduct. However, this Agreement in no way waives MGH's or Partners' right to raise any defenses in any such actions.

5. MGH and Partners release the United States and its agencies, officers, agents, employees, and servants, from any claims (including for attorney's fees, costs, and expenses of every kind and however denominated) that MGH and/or Partners has asserted, could have asserted, or may assert in the future against the United States or its agencies, officers, agents, employees, or servants, related to the Covered Conduct and the United States' investigation and prosecution thereof.

6. The obligations imposed upon MGH pursuant to this Agreement and the CAP are in addition to, and not in derogation of, all requirements imposed upon MGH pursuant to all applicable federal, state, and local laws and regulations, including but not limited to the requirements set forth in Title 21 of the United States Code and the regulations promulgated thereunder.

7. Each party and signatory to this Agreement represents that it/he/she freely and voluntarily enters into this Agreement without any degree of duress or compulsion.

8. This Agreement is intended to be for the benefit of the Parties only; it does not create any rights or benefits as to third parties. The Parties do not release any claims against any other person or entity.

9. This Agreement is governed by the laws of the United States. The exclusive jurisdiction and venue for any dispute relating to this Agreement is the United States District Court for the District of Massachusetts. This Agreement shall be deemed to have been drafted by all Parties to this Agreement and shall not, therefore, be construed against any Party for that reason in any subsequent dispute.

10. This Agreement and the CAP constitute the complete agreement between the Parties. This Agreement may be amended only by a writing signed by all Parties.

11. The undersigned counsel represent and warrant that they are fully authorized to execute this Agreement on behalf of the Parties.

12. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same agreement.

13. This Agreement is binding on MGH's successors, transferees, and assigns.

14. Nothing in this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue laws, Title 26 of the United States Code.

15. Each Party shall bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.


16. All parties consent to the United States' disclosure of this Agreement, and information about this Agreement, to the public, except that the names and contact information in paragraph 3 of Attachment 3 may be redacted and kept confidential.

17. The Parties may execute this Agreement via facsimile and/or by portable document format (.pdf), both of which shall be deemed the equivalent of an original signature.

18. This Agreement shall be effective on the date of signature of the last signatory to the Agreement ("Effective Date").


THE UNITED STATES OF AMERICA

DATED: 9/28/15

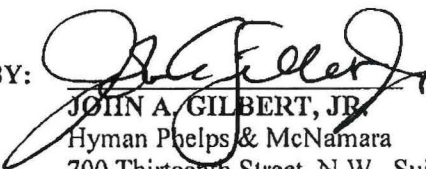
BY: 
JESSICA P. DRISCOLL
Assistant U.S. Attorney
United States Attorney's Office
District of Massachusetts

MASSACHUSETTS GENERAL HOSPITAL

DATED: 9/28/15

BY: 
TOBY R. UNGER
Partners HealthCare System
50 Staniford Street, 10th Floor
Boston, MA 02114

DATED: 9/28/15

BY: 
JOHN A. GILBERT, JR.
Hyman Phelps & McNamara
700 Thirteenth Street, N.W., Suite 1200
Washington, D.C. 20005

Attachment 1: MGH's Active DEA Registrations

DEA #	Address	City	Reg. Type
xxxxxx433	55 Fruit Street	Boston	Hospital/Clinic
xxxxxx926	55 Fruit Street	Boston	Hospital/Clinic
xxxxxx423	55 Fruit Street	Boston	Research
xxxxxx349	165 Cambridge Street	Boston	Hospital/Clinic
xxxxxx242	32 Fruit Street	Boston	Analytical Lab
xxxxxx293	73 High Street	Charlestown	Hospital/Clinic
xxxxxx569	133 ORNAC	Concord	Hospital/Clinic
xxxxxx755	40 Second Avenue	Waltham	Hospital/Clinic
xxxxxx355	300 Ocean Avenue	Revere	Hospital/Clinic
xxxxxx664	151 Everett Avenue	Chelsea	Hospital/Clinic
xxxxxx288	102 Endicott Street	Danvers	Hospital/Clinic
xxxxxx933	52 Second Avenue	Waltham	Hospital/Clinic

Attachment 2: United States' Statement of Relevant Conduct

The United States alleges that the following occurred during the period October 4, 2011, through April 1, 2015.

1. DEA began its investigation after learning that MGH nurse J.S. had stolen 14,492 pills from an automated drug-dispensing machine (“ADM”), and MGH nurse J.Z.1 had stolen 1,429 pills from a different ADM. Most of the pills they stole were oxycodone, a Schedule II drug. MGH did not discover J.S.’s actions until she had been stealing for an entire year – even though she sometimes appeared high to co-workers and other times was seen falling asleep at work. MGH failed to report these diversions to DEA within one business day as required by 21 C.F.R. § 1301.76(b).

2. In November-December 2013, DEA investigators conducted accountability audits of sample controlled substances in MGH’s inpatient pharmacy and its outpatient pharmacy. The government alleges that the audits revealed 16,681 missing or extra pills at the inpatient pharmacy, and 7,177 missing or extra pills at the outpatient pharmacy. Most of the missing or extra pills were oxycodone, a Schedule II controlled substance.

3. The government alleges that MGH failed to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71. Many of these deficiencies concerned ADMs which MGH kept in locked medication rooms, operating rooms (“ORs”), and pharmacies. For example:

- a. During the period October 9, 2013, through December 31, 2013, MGH relied on a pharmacy information system (“PIS”) to generate inventory figures for its ADMs in response to a request by DEA. However, the PIS data did not match the ADM data.
- b. During the period October 4, 2011, through May 2014, patient names remained active in the ADMs up to 72 hours post-discharge. This was one way that J.S. and J.Z.1 were able to divert drugs.
- c. On November 5, 2013, MGH documents listed one doctor, S.J., as having access to ADMs even though S.J. had left MGH four months earlier.
- d. On November 5, 2013, MGH documents listed another doctor, T.A., as having access to the ADMs even though T.A. had surrendered his medical license and his DEA registration in early 2013.
- e. Sometimes ADMs had inaccurate readings of dosage units. For example, during a DEA audit on October 31, 2013, one ADM showed that it contained 22 lorazepam 0.5 mg pills. However, DEA investigators found not only the 22 lorazepam 0.5 mg pills, but also another cartridge in the machine containing an additional 25 lorazepam pills that was not registering on the machine’s computer.

- f. From October 4, 2011, through May 2014, MGH staff could access drugs in some ADMs for up to two minutes before lockout occurred. This extended time period before lockout allowed users to continue to access the machine and make multiple withdrawals.
- g. From October 4, 2011, through February 2014, the inpatient pharmacy staff were not alerted to medication overrides in ADMs. (A medication override occurs when a staff member enters his/her user ID and password into an ADM to get medication for a patient; the ADM displays a list of all patients in the unit and their medication orders; and the staff member selects either a higher dose than what is listed for the patient or a medication not on that patient's list.) Both nurses referenced in paragraph 1 above diverted drugs by using medication overrides.

4. The government alleges that certain members of MGH management demonstrated a supervisory failure to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71. For example:

- a. From October 4, 2011, through March 2014, many nursing supervisors failed to regularly review ADM reports to look for possible diversion, and some, including J.Z.1's supervisor, were not aware how often they were expected to review the reports. Failure to regularly review ADM reports enabled diversion by allowing medication overrides and "wrong bin opened" incidents to go undetected.
- b. When asked why MGH waited so long to implement controlled substance surveillance software, which produces user-friendly reports of ADM data indicating potential drug diversion, one MGH manager told the DEA that MGH is "rooted in tradition" and "change doesn't happen fast around here."
- c. MGH uses an anesthesia electronic health record ("EHR") to document the amounts of controlled substances administered in each OR. On occasions when the anesthesia EHR for a particular surgery did not match the drug kit reconciliation for that surgery, the OR pharmacy asked the medical personnel involved to address the discrepancy.
- d. A certified registered nurse anesthetist, A.S., lost small amounts of controlled substances three different times within eight months. She was not disciplined.
- e. Another certified registered nurse anesthetist, S.W., lost controlled substances four different times within eight months. She was not disciplined. S.W.'s supervisor told the DEA that she chose to have only an "offhand conversation" with S.W. about these incidents because S.W. was up for a promotion and she did not want to hurt S.W.'s chances.

5. The government alleges that MGH also failed to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71, as follows:

- a. From October 4, 2011, until December 2013, every OR at MGH contained an unlocked “Bluebell” cart in which medical staff stored their controlled substances when on break.
- b. During the period October 4, 2011, until November 1, 2012, some anesthesia residents who needed controlled substances for 9:30 am cases signed them out early and took them to off-campus grand rounds at 7:00 am. MGH did not discipline residents for this practice.
- c. On November 14, 2011, three syringes of hydromorphone, remifentanyl, and morphine were found in various ORs. No one knew where they came from or to whom they belonged.
- d. In November 2011, an MGH inpatient pharmacy manager reported 20 syringes of morphine were missing from the pharmacy vault during unit moves and renovations.
- e. An MGH physician, E.P., repeatedly prescribed controlled substances for patients without seeing them and without maintaining medical records, in 2012-2013. His patients included at least one who was simultaneously obtaining prescriptions for controlled substances from other physicians. E.P. voluntarily surrendered his DEA registration in 2014.
- f. From October 4, 2011, through December 2013, medical personnel often took controlled substances with them to lunch at the on-site hospital cafeteria as a matter of convenience.

6. The government alleges that, as a result of MGH’s failure to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71, theft and diversion occurred, and not just by J.S. and J.Z.1. For example:

- a. In May 2014, MGH discovered that nurse M.B. had been diverting controlled substances (oxycodone, Percocet, Dilaudid, Valium, Ativan, morphine, Flexeril, and Vicodin) from the emergency room for four years. MGH was unable to determine the amount she diverted.
- b. In May 2014, MGH discovered that nurse M.M. had diverted Dilaudid for seven years (2007-2010 and 2012-2014).
- c. In June 2014, MGH discovered 34 drug transaction discrepancies that nurse J.L. was unable to explain. The drugs at issue were Ativan, Dilaudid, fentanyl, ketamine, Valium, morphine, and Versed. The nurse denied

diverting the drugs and blamed the discrepancies on lack of documentation and the rushed pace in the emergency room.

- d. In August 2014, MGH discovered that R.C., a pediatric surgery nurse, had had a substance abuse issue off and on for the past twelve years. He was found sleeping at work, unsteady on his feet, and with slurred speech. He admitted diverting Dilaudid, a Schedule II drug, and injecting himself at work.
- e. In August 2014, MGH discovered that nurse J.Z.2 had repeatedly taken home controlled substances, allegedly by mistake, and provided no documentation of waste. (All controlled substances signed out must be used, returned, or wasted. In all cases, the amounts must be documented.)
- f. In December 2014, 42 vials of controlled substances were found in the apartment of a deceased MGH anesthesia resident, who was determined to have died of natural causes. Five of the vials contained MGH labels.
- g. In January 2015, nurse C.F. admitted to diverting various quantities of narcotic waste, including fentanyl, Versed and Demerol, at least 25 times in the past year.

7. The government acknowledges that, since the start of the DEA's diversion investigation in October 2013, MGH has taken significant steps to improve its controls and procedures against theft and diversion of controlled substances, including adoption of the Corrective Action Plan set forth in Attachment 3.

Attachment 3 - Corrective Action Plan

This Corrective Action Plan (“CAP”) between Massachusetts General Hospital (“MGH”) and the U.S. Drug Enforcement Administration (“DEA”) memorializes the policies and procedures that MGH and the DEA (jointly, the “Parties”) have agreed upon to advance MGH’s efforts to ensure compliance with the Controlled Substances Act (the “Act”) and to enhance MGH’s ability to prevent, detect, and address drug diversion.

1. This CAP is incorporated by reference at paragraph 2 of the Settlement Agreement between MGH and the United States dated September 28, 2015 (the “Settlement Agreement”).

2. The period of this CAP shall be three years, starting on the Effective Date of the Settlement Agreement.

3. Whenever this CAP requires notice to the DEA, the persons to be notified will be [REDACTED] and [REDACTED]

[REDACTED]. Whenever this CAP requires notice to MGH, the person to be notified will be [REDACTED]. Either party may change the name and/or contact information of its contact person(s) by so notifying the other party’s contact person(s).

4. MGH represents that it began to implement certain diversion controls (“Enhanced Controls”) following the commencement of the DEA’s diversion investigation in October 2013. MGH agrees to promptly complete implementation of the Enhanced Controls at all twelve of its current DEA registrations (as identified on Attachment 1 to the Settlement Agreement), and at every facility that receives a DEA registration during the term of this CAP. The Enhanced Controls include the following:

- a. Employing a full-time Drug Diversion Compliance Officer.
- b. Establishing a drug diversion team consisting of the Drug Diversion Compliance Officer; members of the compliance, pharmacy, and nursing departments; and MGH Police & Security. The drug diversion team is tasked with preventing, monitoring, and responding to incidents of drug diversion.
- c. Conducting mandatory annual training for all staff with authorized access to controlled substances, including training on the signs and symptoms of substance abuse and addiction, drug diversion monitoring and prevention, the duty to report, and the filing of safety reports.
- d. Purchasing controlled substance surveillance software, which produces user-friendly reports of automatic drug-dispensing machine (“ADM”) data indicating potential drug diversion.
- e. Replacing Bluebell carts in all MGH main campus operating rooms with ADMs; having a timed password-reset for all ADMs (every 90 days); and implementing a biometric identification system (fingerprints) on all ADMs .
- f. Permitting only pharmacists and directly supervised nationally certified pharmacy technicians to have access to the pharmacy vault.
- g. Permitting only authorized MGH pharmacy or IT employees to have access to the ADM server.
- h. Requiring the MGH Department of Pharmacy to conduct daily reviews of ADM reports, including but not limited to instances where more than a certain number of pills were dispensed at one time for one patient (“greater than”

reports), destock verifications, null transactions, medication overrides, and discrepancies.

- i. Requiring the MGH Department of Pharmacy to conduct daily operating room post-case reconciliation (“PCR”) of controlled substances dispensed, used, or wasted, and, if any discrepancy is not resolved within 72 hours, to report the discrepancy to the Drug Diversion Compliance Officer.
- j. Requiring at least one nursing leader per clinical area: (i) to conduct weekly reviews of all controlled substance surveillance software anomalous usage reports for the ADMs in that clinical area; and (ii) to conduct daily reviews (Monday through Friday) of controlled substance surveillance software reports of controlled substances dispensed from the ADMs in that clinical area.
- k. Requiring clinical nursing supervisors to review “greater than” ADM reports on Saturdays, Sundays, and holidays.
- l. Requiring Associate Chief Nurses to conduct monthly compliance checks on their nursing leader direct reports.
- m. Requiring trend and pattern reports to be reviewed quarterly by the Drug Diversion Team.

5. MGH will take the following corrective actions in addition to the Enhanced

Controls:

- a. MGH will hire external auditors to conduct unannounced audits at all MGH facilities with active DEA registrations (including all pharmacies and ADMs)

of five Schedule II-V controlled substances randomly chosen by the auditors.

The audits will be conducted at:

- i. 100% of MGH's DEA-registered facilities during the first 12 months following the effective date of this CAP;
- ii. 50% of MGH's DEA-registered facilities between months 13 and 24;
and
- iii. 25% of MGH's DEA-registered facilities between months 25 and 36.

Each audit report will be reviewed and signed by the Pharmacist in Charge or the registrant's DEA-designated person. MGH will have 30 days to cure any deficiencies or resolve any discrepancies, and its efforts to cure will be documented in the audit report. If the auditors find any material discrepancies or other material issues (*e.g.*, diversion, missing records, significant losses), MGH will send the audit report to DEA within five business days after the end of the 30-day cure period. MGH will maintain the audit records, and make them available for review by the DEA upon request, for two years after this CAP expires.

- b. During each year of this CAP, MGH will conduct a self-evaluation of all of its DEA-registered facilities to review compliance with all requirements of the Act, the regulations issued under the Act, and this CAP. At the completion of each evaluation, the Pharmacist in Charge or the DEA-designated person at the registrant will certify that he/she has completed the evaluation and document any corrective action to be taken. MGH will retain the letters of

certification, and make them available to the DEA upon request, for two years following the expiration of this CAP.

- c. MGH will maintain all ADM data for two years after the data is created. MGH will maintain the data in a readily retrievable manner and produce it to the DEA upon request.
- d. MGH will maintain reports of disciplinary action taken against employees found to have lost a significant quantity of controlled substances, or found to have stolen or otherwise diverted controlled substances. To the extent authorized by state or federal privacy laws and regulations, MGH will maintain the reports in an easily accessible manner and produce them to the DEA upon request.
- e. MGH will create and enforce a written policy of progressive discipline applicable to all employees with access to controlled substances.
- f. MGH will promptly investigate all thefts, significant losses, and other potential diversion of controlled substances. MGH will promptly report all such thefts, significant losses, and other diversions to DEA. DEA is aware that MGH has additional reporting duties to licensure boards, and all other relevant agencies (*e.g.*, the Drug Control Program of the Massachusetts Department of Public Health).
- g. If MGH makes a report to an agency that any of its employees has lost or stolen controlled substances, MGH will promptly send a copy of the report to the DEA. If MGH makes a report to an agency that any of its employees has abused or mishandled controlled substances (without a report of loss or theft),

MGH will promptly notify DEA that a report has been made, including the name of the agency and the date of the report.

- h. MGH will promptly notify the DEA when a member of the Drug Diversion team, as identified above in paragraph 4(b), becomes aware that any MGH employee has been arrested or charged by law enforcement on any charges related to theft or diversion of controlled substances.

6. MGH will complete biennial inventories of all of its DEA-registered facilities using physical counts (including counts of all ADMs), witnessed by two individuals.

7. MGH will comply at all times with the Act and the regulations issued thereunder. To the extent that any requirements in the Act or regulations are greater than those imposed by this CAP, the stricter requirements will apply.

8. Each Party and signatory to this CAP represents that it/he/she freely and voluntarily enters into this CAP without any degree of duress or compulsion.

9. This CAP is intended for the benefit of the Parties only; it does not create any rights or benefits for third parties.

10. This CAP is governed by the laws of the United States. The exclusive jurisdiction and venue for any dispute relating to this CAP is the United States District Court for the District of Massachusetts. This CAP shall be deemed to have been drafted by both Parties and shall not, therefore, be construed against either Party in any subsequent dispute.

11. This CAP and the Settlement Agreement constitute the complete agreement between the DEA and MGH relating to the matters addressed herein. This CAP may be amended only by a writing signed by both DEA and MGH.

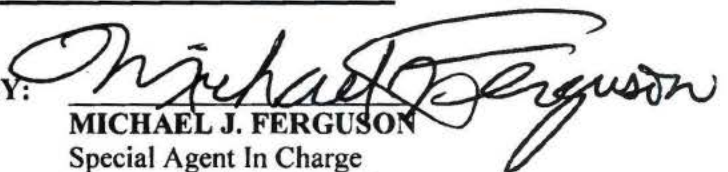
12. The undersigned signatories represent and warrant that they are fully authorized to execute this CAP on behalf of the parties.

13. This CAP may be executed in two counterparts, each of which constitutes an original and both of which constitute one and the same agreement.


14. This CAP is binding on MGH's successors, transferees, and assigns.

THE U.S. DRUG ENFORCEMENT ADMINISTRATION

DATED: 9/28/15

BY: 

MICHAEL J. FERGUSON
Special Agent In Charge
New England Field Division
15 New Sudbury St., Room E-400
Boston, MA 02203


NANCY COFFEY
Program Manager, Diversion
15 New Sudbury St., Room E-400
Boston, MA 02203

MASSACHUSETTS GENERAL HOSPITAL

DATED: _____

BY: _____

TOBY R. UNGER
Partners HealthCare System
50 Staniford Street, 10th Floor
Boston, MA 02114

12. The undersigned signatories represent and warrant that they are fully authorized to execute this CAP on behalf of the parties.

13. This CAP may be executed in two counterparts, each of which constitutes an original and both of which constitute one and the same agreement.

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MASSACHUSETTS GENERAL HOSPITAL

DATED: 9/28/15

BY:



TOBY R. UNGER
Partners HealthCare System
50 Staniford Street, 10th Floor
Boston, MA 02114

Attachment 6

CURES 2.0 Soft Launch and Phased Rollout

Update from July 1, 2015:

The Department of Justice (DOJ) and the Department of Consumer Affairs (DCA) are pleased to announce that the state's new Controlled Substance Utilization Review and Evaluation System – commonly referred to as “**CURES 2.0**” – went live on July 1, 2015. This upgraded prescription drug monitoring program features a variety of performance improvements and added functionality.

In order to ensure a smooth transition from the current system, CURES 2.0 will be rolled out to users in phases over the next several months, beginning with early adoption by a select group of users who currently use CURES and meet the CURES 2.0 security standards, including minimum browser specifications. DOJ is currently identifying prescribers and dispensers who meet these criteria and will contact and coordinate their enrollment into CURES 2.0. For all other current users, access to CURES 1.0 will not change and no action is needed at this time. For users and entities not currently enrolled in CURES, further notification will be provided in August as to the enrollment/registration process.

Practitioners and health systems should begin to prepare for universal adoption of the system by January 2016, at which point all users will be required to meet CURES 2.0's security standards. If you have any questions please contact cures@doj.ca.gov.

Thank you for your continued support of the CURES program.

Note: CURES 2.0 users will be required to use Microsoft Internet Explorer Version 11.0 or greater, Mozilla FireFox, Google Chrome, or Safari when accessing the system.

Attachment 7

1707.2 Duty to Consult.

- (a) A pharmacist shall provide oral consultation to his or her patient or the patient's agent in all care settings:
 - (1) upon request; or
 - (2) whenever the pharmacist deems it warranted in the exercise of his or her professional judgment.
 - (b) (1) In addition to the obligation to consult set forth in subsection (a), a pharmacist shall provide oral consultation to his or her patient or the patient's agent in any care setting in which the patient or agent is present:
 - (A) whenever the prescription drug has not previously been dispensed to a patient; or
 - (B) whenever a prescription drug not previously dispensed to a patient in the same dosage form, strength or with the same written directions, is dispensed by the pharmacy.
 - (2) When the patient or agent is not present (including but not limited to a prescription drug that was shipped by mail) a pharmacy shall ensure that the patient receives written notice: of his or her right to request consultation; and a telephone number from which the patient may obtain oral consultation from a pharmacist who has ready access to the patient's record.
 - (3) A pharmacist is not required by this subsection to provide oral consultation to an inpatient of a health care facility licensed pursuant to section 1250 of the Health and Safety Code, or to an inmate of an adult correctional facility or a juvenile detention facility, except upon the patient's discharge. A pharmacist is not obligated to consult about discharge medications if a health facility licensed pursuant to subdivision (a) or (b) of Health and Safety Code Section 1250 has implemented a written policy about discharge medications which meets the requirements of Business and Professions Code Section 4074.
- (c) When oral consultation is provided, it shall include at least the following:
 - (1) directions for use and storage and the importance of compliance with directions; and
 - (2) precautions and relevant warnings, including common severe side or adverse effects or interactions that may be encountered.
- (d) Whenever a pharmacist deems it warranted in the exercise of his or her professional judgment, oral consultation shall also include:
 - (1) the name and description of the medication;
 - (2) the route of administration, dosage form, dosage, and duration of drug therapy
 - (3) any special directions for use and storage;
 - (4) precautions for preparation and administration by the patient, including techniques for self-monitoring drug therapy;
 - (5) prescription refill information;
 - (6) therapeutic contraindications, avoidance of common severe side or adverse effects or known interactions, including serious potential interactions with known nonprescription medications and therapeutic contraindications and the action required if such side or adverse effects or interactions or therapeutic contraindications are present or occur;
 - (7) action to be taken in the event of a missed dose.
- (e) Notwithstanding the requirements set forth in subsection (a) and (b), a pharmacist is not required to provide oral consultation when a patient or the patient's agent refuses such consultation.

Attachment 8

Board's Current Policy Effective October 2009

In the event that the board is not able to convene a public meeting on regular notice or pursuant to the emergency meeting provisions of the Open Meetings Act, any three members of the board may convene a meeting by teleconference, by electronic communication (e.g., e-mail), or by other means of communication to exercise the powers delegated to full board pursuant to Business and Professions Code section 4062.

Excerpt from October 2009 Board Meeting

Proposed Delegation to the Board President to Act Pursuant to California Business and Professions Code Section 4062 to Waive Statutory Requirements to Benefit Public Safety in Response to a Declared Emergency or Disaster

Mr. Weisser provided that during the October 2006 Board Meeting, the board voted to adopt a policy statement for pharmacies when providing emergency response. He indicated that a copy of this policy statement was published in the January 2007 issue of *The Script*.

Mr. Weisser provided that Business and Professions Code section 4062 provides the board with broad waiver authority and was recently amended in SB 819 (Chapter 308, Statutes of 2009) to allow for the use of a mobile pharmacy in the event of a declared emergency as specified. He stated that the board intends to use this authority when warranted.

Board Discussion

Ms. Schieldge reviewed the board's options with respect to delegating authority collectively to the board or to an individual board member to waive statutory requirements to benefit public safety in response to a declared emergency or disaster. She recommended that the board limit this authority to situations wherein the board is unable to convene.

The board sought general clarification regarding its options and adherence to the Open Meetings Act. The board reached a consensus to allow any three members of the board to teleconference in the event that the board is unable to convene during a declared emergency. Discussion continued with regards to both the authority of the board and of the Governor during a declared emergency.

Public Comment

President Schell sought clarification regarding what would be achieved during the emergency meeting.

Mr. Room provided that the members attending the emergency meeting would establish and issue guidelines regarding the laws that will be waived during the emergency. There was no additional board discussion or public comment.

4062. Furnishing Dangerous Drugs during Emergency; Mobile Pharmacy

(a) Notwithstanding Section 4059 or any other provision of law, a pharmacist may, in good faith, furnish a dangerous drug or dangerous device in reasonable quantities without a prescription during a federal, state, or local emergency, to further the health and safety of the public. A record containing the date, name, and address of the person to whom the drug or device is furnished, and the name, strength, and quantity of the drug or device furnished shall be maintained. The pharmacist shall communicate this information to the patient's attending physician as soon as possible. Notwithstanding Section 4060 or any other provision of law, a person may possess a dangerous drug or dangerous device furnished without prescription pursuant to this section.

(b) During a declared federal, state, or local emergency, the board may waive application of any provisions of this chapter or the regulations adopted pursuant to it if, in the board's opinion, the waiver will aid in the protection of public health or the provision of patient care.

(c) During a declared federal, state, or local emergency, the board shall allow for the employment of a mobile pharmacy in impacted areas in order to ensure the continuity of patient care, if all of the following conditions are met:

(1) The mobile pharmacy shares common ownership with at least one currently licensed pharmacy in good standing.

(2) The mobile pharmacy retains records of dispensing, as required by subdivision (a).

(3) A licensed pharmacist is on the premises and the mobile pharmacy is under the control and management of a pharmacist while the drugs are being dispensed.

(4) Reasonable security measures are taken to safeguard the drug supply maintained in the mobile pharmacy.

(5) The mobile pharmacy is located within the declared emergency area or affected areas.

(6) The mobile pharmacy ceases the provision of services within 48 hours following the termination of the declared emergency.

Attachment 9

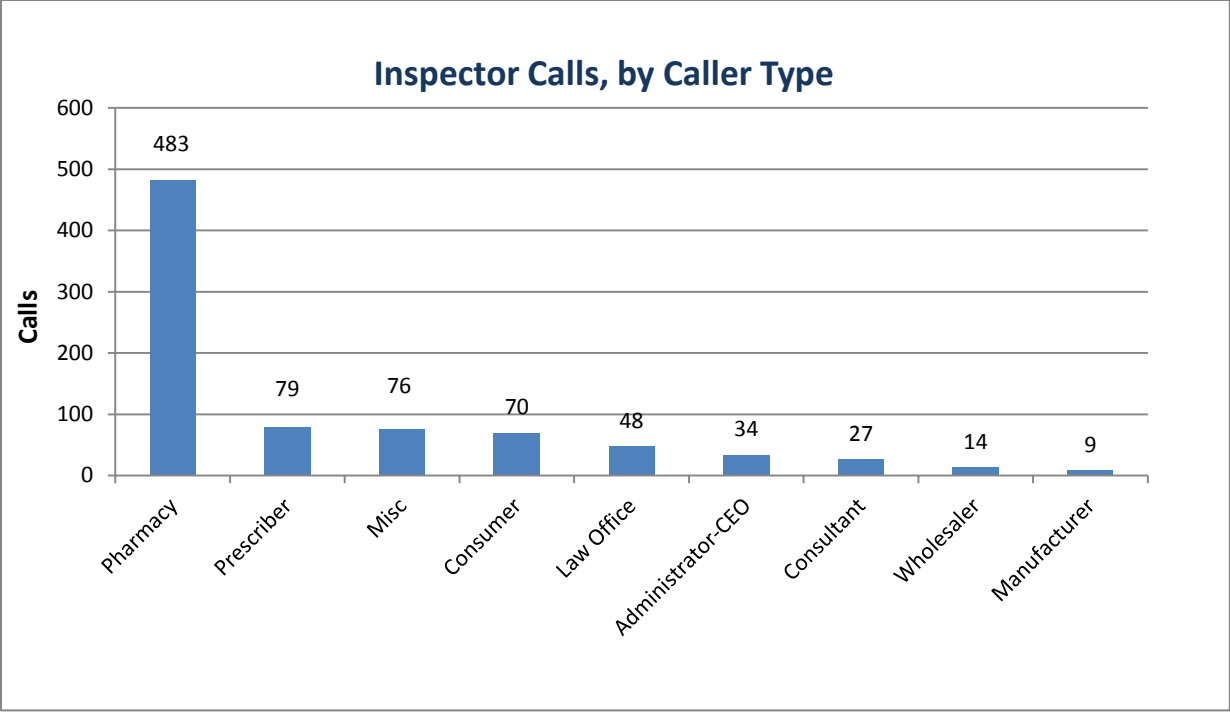
Since July 01, 2015, Pharmacy Board inspectors have responded to 840 calls, an average of 168 calls each month. Our highest month was September, with 252 calls. July was our lowest month, with 100 calls.

Our typical caller is a pharmacist. About half of our callers are pharmacists, and the rest is everyone else. Of the 840 calls inspectors took during this period, 483 callers were pharmacy personnel (406 callers are active pharmacists, or 48 percent of all callers). Some of the other caller groups are: prescribers, consumers, and administrators. However, no single one of these other caller groups stands out. These ratios are stable from each month; pharmacists are consistently the largest single group contacting Board inspectors.

Table: All Inspector Calls

Caller Type	July	August	September	October	November	Total Calls	% of Calls
Administrator-CEO	5	3	17	4	5	34	4%
Consultant	2	6	5	11	3	27	3%
Consumer	9	11	23	12	15	70	8%
Law Office	3	11	14	14	6	48	6%
Manufacturer	1	2	2	2	2	9	1%
Misc.	8	10	22	30	6	76	9%
Pharmacy	56	58	147	125	97	483	58%
Prescriber	14	12	21	16	16	79	9%
Wholesaler	2	7	1	1	3	14	2%
Total	100	120	252	215	153	840	100%
% Growth	na	20%	110%	-15%	-29%		

Chart: All Inspector Calls, by Type of Caller

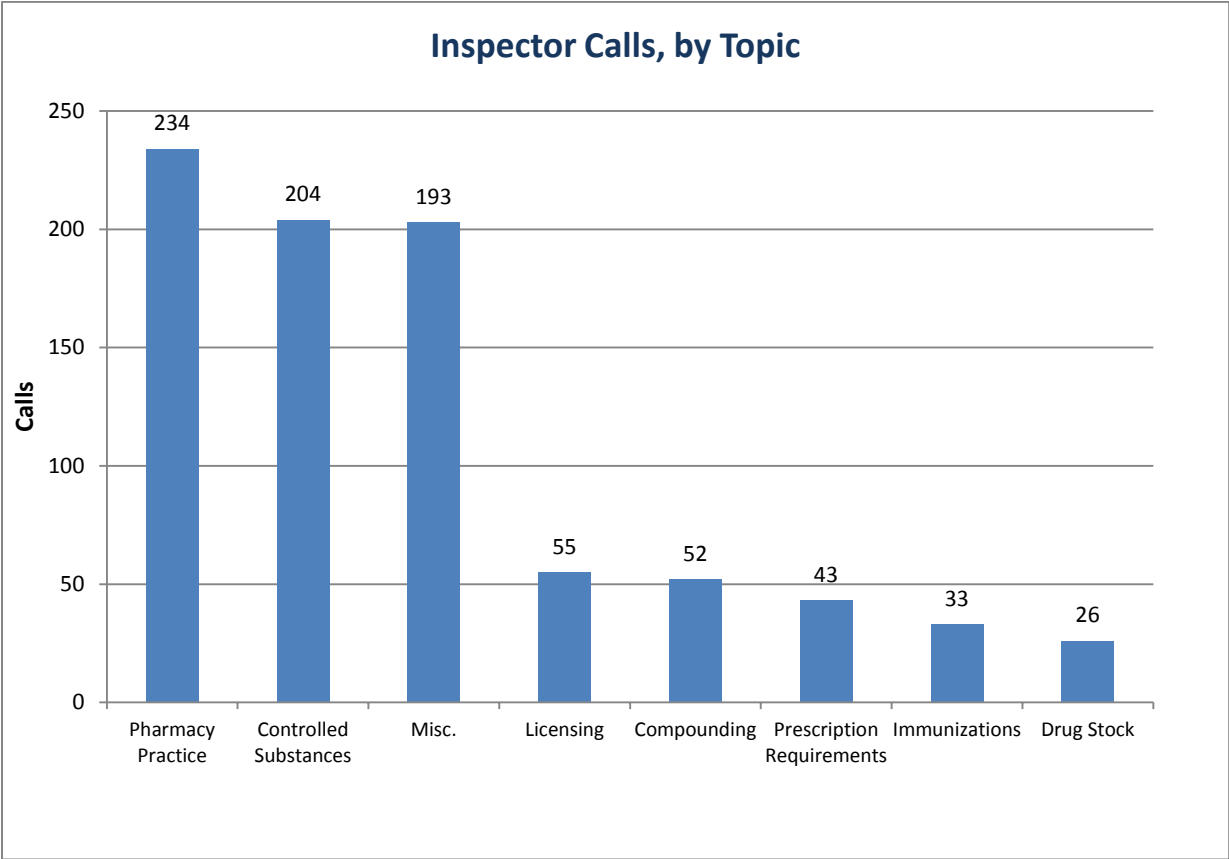


What questions are the inspectors answering? The majority of calls and emails to inspectors are questions regarding general questions about pharmacy practices and regulations regarding controlled substances. However, inspectors answer a wide diversity of questions. About 48 percent of all calls were not directly related to pharmacy practices or controlled substances.


Table: Number of Inspector Calls, by Topic Discussed

Call Topic	No. of Calls	% of Calls
Pharmacy Practice	234	28%
Controlled Substances	204	24%
Misc.	193	23%
Licensing	55	6%
Compounding	52	6%
Prescription Requirements	43	5%
Immunizations	33	4%
Drug Stock	26	3%
Total	840	100%


Chart: All Inspector Calls, by Topic Discussed



Attachment 10


 **FDA Regulatory Actions Involving Drug Compounding**

1

 **Potential Actions**


- Recommend Voluntary Recalls
- Warning Letters
- State Referral Letters
- Injunctions

2

 **Some Factors to Consider**

- Risk to public health
 - Lack of sterility assurance
 - Actual contamination
- Prior violations and likelihood of firm compliance
- How easily can the violations be corrected
- Firm's willingness to take voluntary action


3

 **Voluntary Actions**

- Four outsourcing facilities have recalled compounded products
- Recall events by outsourcing facilities are included on FDA's list of outsourcing facilities


<http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm>

7

 **Warning Letters**

- Advisory actions – provide notice
- Communicate the Agency's position
- Issued to achieve voluntary and prompt corrective action
- Generally used when there is no history of repeat violations

8

 **Warning Letters**

- FDA has issued over 60 warning letters since October 2012
- Many of the warning letters describe violations associated with insanitary conditions

9

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Warning Letters

Warning letters to facilities not registered as outsourcing facilities under section 503B may also include other violations of the Federal Food, Drug, and Cosmetic Act, and if the firm does not compound in accordance with the conditions of section 503A, these may include violations of requirements for new drug approval, labeling with adequate directions for use, and current good manufacturing practice

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Warning Letters

- Warning letters to facilities registered as outsourcing facilities under section 503B may also include:
 - Violations of current good manufacturing practice (CGMP) requirements (independent of 503B compliance)
 - Failure to meet the conditions of section 503B, such as
 - Failure to include appropriate labeling
 - Failure to submit required product reports

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Warning Letters

- Outsourcing facilities received about 20 of the 60 warning letters issued since October 2012
- Several of the outsourcing facilities that received warning letters subsequently deregistered with FDA
- Unapproved new drug and misbranding charges are included in warning letters to outsourcing facilities that fail to meet the conditions of section 503B

12

FDA

Warning Letters: Examples

- Some examples of deviations from adequate sterile practices and conditions cited in recent warning letters include:
 - Mold in unopened vials of purportedly sterile products
 - Production of sterile drugs with exposed skin
 - Failure to use a sporicidal agent to disinfect the ISO 5 area
 - No environmental monitoring during periods of sterile drug production
 - Use of non-sterile cleaning and disinfecting agents in aseptic processing areas

13

FDA

State Referral Letters

- State Referral Letters:
 - Sent to State Board of Pharmacy in the state in which the FDA-inspected compounding pharmacy is located when a
 - Pharmacy apparently compounds drugs in accordance with the provisions of section 503A (e.g., obtains prescriptions for identified individual patients); and
 - Pharmacy has promised to correct deviations, and they are readily correctable
 - FDA has issued approximately 20 state referral letters

14

FDA

Injunctions

- To prevent further production and/or distribution of adulterated, misbranded, and/or unapproved new drug products and to correct the root cause of the violations
- The firm has a history of significant violations and has not made corrections

15

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Injunction Process

- FDA drafts referral letter, complaint, and consent decree and submits to the Department of Justice (DOJ)
- DOJ determines whether to pursue the case
- May issue "sign or sue" letter
- Attempt to negotiate consent decree
- File complaint in court

16

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Compounding Injunction Cases Since 2012

- On June 28, 2013, a federal judge entered a consent decree of permanent injunction against MedPrep Consulting (Tinton Falls, NJ) and the company's president and owner.
- On December 4, 2014, a federal judge entered a consent decree of permanent injunction against Main Street Family Pharmacy (Newborn, TN) and the company's co-owners. In addition, Main Street and one of its co-owners pleaded guilty to a misdemeanor criminal violation of the FD&C Act.
- On March 10, 2015, a federal judge entered a consent decree of permanent injunction against Specialty Compounding (Cedar Park, TX) and the company's co-owners.
- The firms in each case manufactured purportedly sterile injectable drug products that tested positive for bacterial contamination.

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Compounding Criminal Cases Since 2012

- On December 16, 2014, a grand jury returned a 131-count criminal indictment in connection with the New England Compounding Center (NECC) and 2012 nationwide fungal meningitis outbreak. The owner and head pharmacist of NECC and its supervisory pharmacist were charged with 25 acts of second-degree murder, among other criminal acts, and 12 others were charged with additional crimes, including FDCA violations.
- On February 20, 2015, the Government unsealed a 37-count indictment charging Med Prep, its president and owner, and its pharmacist-in-charge, with wire fraud and violations of the FDCA for introducing adulterated and misbranded drugs into interstate commerce with the intent to defraud and mislead the FDA and Med Prep's customers.

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Sterile Drug Production Practices: *USP <797> vs. CGMPs*

1



Summary of Presentation

- Fundamentals
- Facility design and qualification
- Environmental and personnel monitoring
- Equipment, containers and closures
- Components
- Production and process controls
- Laboratory control
- Beyond-use/expiration dating
- Quality assurance



Drug Quality Attributes

- For injectables
 - Sterility
 - Endotoxin
 - Identity
 - Strength (a.k.a. Potency)
 - Purity
 - Other, for example:
 - Content uniformity
 - Anti-microbial effectiveness (if multiple dose container)



Drug Quality Assurance

- Drug quality is built into the drug by paying attention to facility design and production process.
- Drug quality cannot be tested into the product.
 - Vast majority of all drug analytical testing is destructive.
 - Quality of non-tested units is inferred by test results, but not confirmed.
 - The ability of the test to infer quality of the non-tested unit is also dependent upon the quality attribute under assessment.



Sterility Tests

- *USP <71> - Sterility Tests*
 - Most commonly used and best understood
 - Detection method is based upon microbial proliferation

“These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures.” – from *USP <71>*



Sterility Test Hypothetical

- 100 mL stock solution of drug X is prepared to produce a batch of 100, 1-mL vials.
- There is a breach in aseptic processing during production and, unknowingly, 10 colony-forming units (CFUs) are introduced into stock solution before filling into vials.



Hypothetical

- If *USP* <71> sampling requirements are followed, 10 of 100 vials would undergo sterility tests.
- Statistically, even if you assume that the contamination is concentrated in the 10 vials tested at 1 CFU per vial, there's a 15% probability that the vials you pick will not be contaminated



Sterility Test Limitation

- Microbial contamination is highly unlikely to be equally distributed throughout the stock solution and actual distribution is unknown.
- In addition, no guarantees that all 10 CFUs will proliferate during sterility testing.
 - Some may be viable, but not cultivatable (VBNC).
- **Under actual testing conditions, probability of false negative is:**
 - **Higher than simple statistics would estimate and**
 - **Not calculable.**
- Ability of sterility test to detect contamination also decreases if:
 - Less than required (as per *USP <71>*) sample number is used
 - Drug formulation inherently inhibits microbial growth and no modification made in sample preparation to address



Sterility Test – Summary

- If contamination is identified, you have been alerted and can withhold lot. However:
- Ability of sterility tests to detect contamination is dependent upon:
 - Degree of microbial contamination (bioburden), which is unknown
 - Distribution of contamination through batch, which is unknown
 - Percentage of VBNC microbes, which is unknown
 - Number of samples taken from batch



Sterility Assurance

Potential sources of microbial contamination:

- Air
- Water
- Equipment and supplies
- Drug components
 - Drug substances
 - Excipients
 - Container & Closures
- Personnel



Facility Design

- “Normal” air contains numerous suspended particles.
- Suspended particles contain unknown numbers of microbes adhering to particle surfaces.
- Design of firm must include built-in features that remove and control number of air particles in aseptic processing areas.



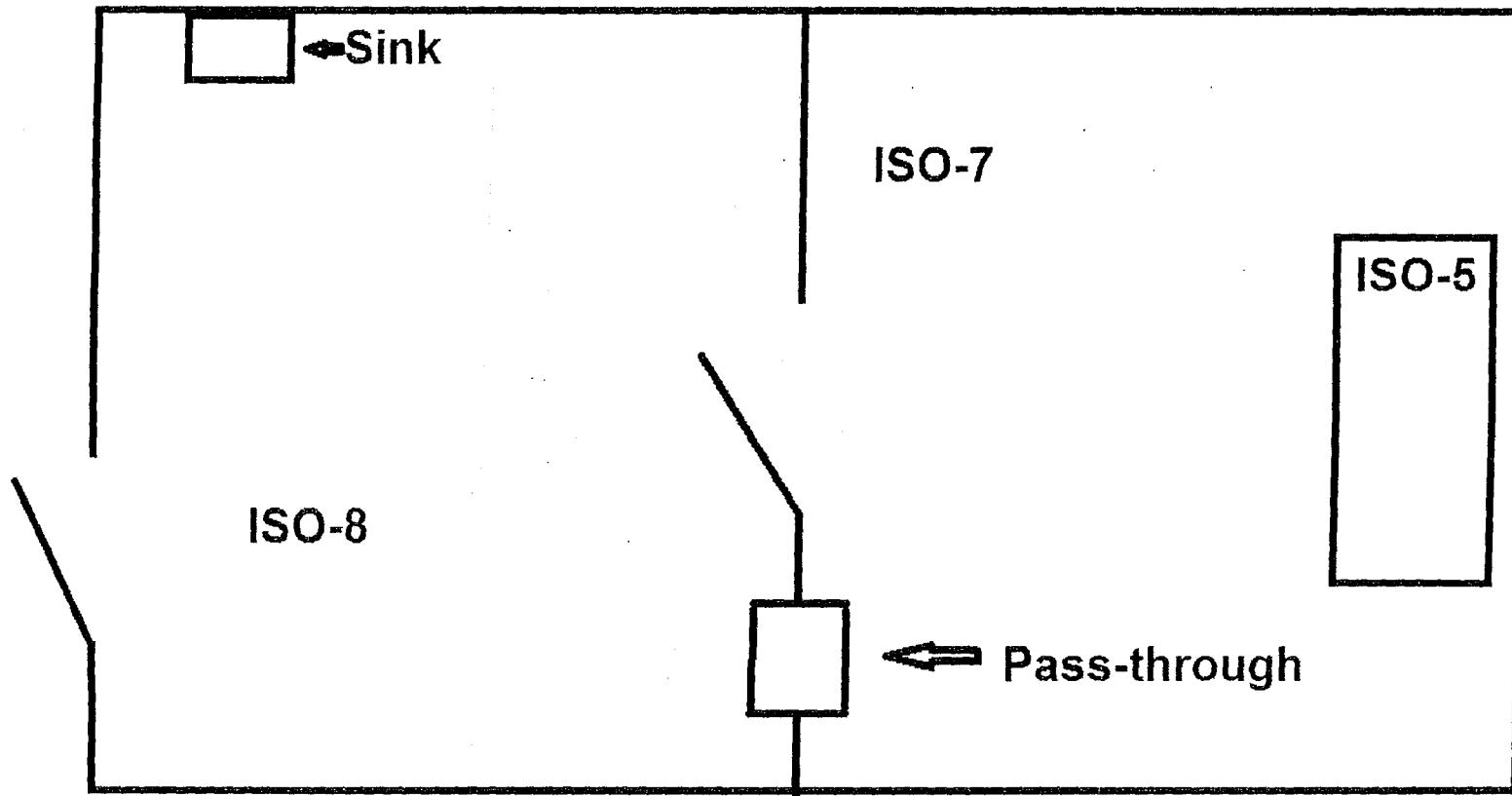
Air Cleanliness

- International Organization for Standardization (ISO) air cleanliness standards:
 - ISO-5: 3,520 particles of $0.5 \mu\text{m}/\text{m}^3$
 - ISO-7: 352,000 particles of $0.5 \mu\text{m}/\text{m}^3$
 - ISO-8: 3,520,000 particles of $0.5 \mu\text{m}/\text{m}^3$
- Air cleanliness within a defined space is brought about by “high-efficiency particulate arrestance” (HEPA) filters incorporated at key location within a firm’s “heating, ventilation, and air-conditioning” (HVAC) system.



Basic Facility Design – Pharmacy

*most common
design
for
ph*





Qualification of ISO-5

<797>

Proposed <797>

CGMP

Meet ISO-5 particle count

Yes

Yes

Yes

Frequency of monitoring/test

6 months

6 months

Continuously during
production

Conditions of Test

Dynamic

Dynamic

Dynamic



Qualification of ISO-5

<797>	Proposed <797>	CGMP
<u>Demonstration of uni-directional air flow</u>		
Yes	Yes	Yes
<u>Conditions of test</u>		
Dynamic	Dynamic	Dynamic



Qualification of ISO-7 & 8

<797>

Proposed <797>

CGMP

Meet ISO-7/8 particle count

Yes

Yes

Yes

Frequency of monitoring/test

6 months

6 months

Continuously during
operations

Conditions of test

Dynamic

Dynamic

Dynamic

Demonstration of air-flow through and out of rooms

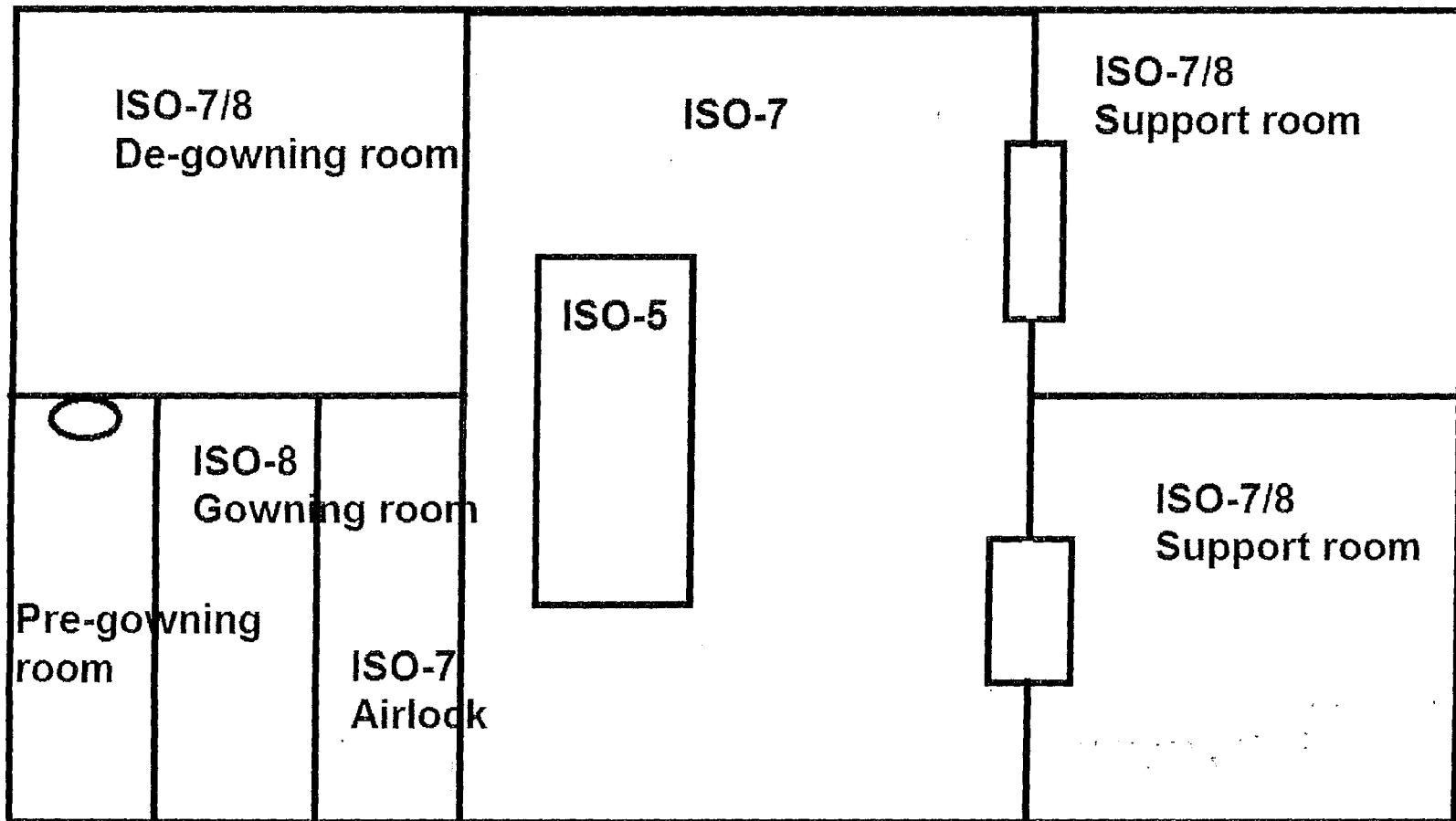
Not addressed

Not addressed

Recommended



Design – Conventional Manufacturer





*Non viablest determine this
is nothing living on
test media*

Environmental Monitoring Frequency

<797>

Proposed <797>

CGMP

Particle count (a.k.a. "non-viable air")

6 months

6 months

Continuously during operation

Viable air particle

6 months

1 month

Continuously during operation

Surfaces

6 months

1 month

Multiple times during operation

Pressure differentials between rooms

Daily before production

Daily before production

Continuously during operation



Personnel Monitoring

<797>

Proposed <797>

CGMP

Frequency

6 months

3 months

Multiple times during operations

Area sampled

Gloved fingertips only

Gloved fingertips only

Gloved fingertips plus other, select areas of gown.



Equipment, Containers and Closures

<797>

Proposed <797>

CGMP

Routine calibration of “measuring” equipment

Implied

Implied

Explicitly required

Ability of container-closures to maintain sterility

Assumed

Assumed

Required to be demonstrated



Components

<797>

Proposed <797>

CGMP

Acceptance of incoming drug components

Review of COA

Review of COA

Review of COA plus
confirmatory testing

Determination of bioburden/endotoxin of incoming non-sterile ingredients

Not required

Not required

Required



Production and Process Controls - Gowning

<797>

Proposed <797>

CGMP

Required sterile gowning items

Gloves, only

Gloves and sleeve covers, only

Gloves and all other gowning items

Exposed skin?

Neck, checks, eyes, and forehead allowed.
Wrist skin not allowed.

Neck, checks, eyes, and forehead allowed. Wrist skin not allowed.

None allowed

Reuse of gowning items?

Gloves and mask, no.
All others, yes, if gloves/mask stored in ISO-8 anteroom.

Gloves, sleeve and mask, no. If other items sterile when first donned, then no. If other items were non-sterile when donned, then yes if stored in ISO-8

No



Production and Process Control – Sterilization and Maintenance of Sterility

<797>

Proposed <797>

CGMP

Filter sterilization

Acceptance of filter based upon certificate of suitability alone

Acceptance of filter based upon certificate of suitability alone

Need to confirm suitability of filter with actual product

Terminal sterilization

Process verified (no qualification of equipment required)

Process verified (no qualification of equipment required)

Process validated and includes qualification of equipment

Aseptic media fill simulation

“most challenging and stressful conditions” – no guidance given

“most difficult and challenging...conditions” – guidance given

Simulate actual process



Production and Process Control – Cleaning and Disinfecting

<797>

Proposed <797>

CGMP

Use of sterile cleaning and disinfecting agents/aids

Isopropanol required to be sterile, silent on all other agents/aids

All agents/aids required to be sterile

All agents/aids required to be sterile

Routine use of sporicidal agents

Recommended if EM data indicates presence of spore-forming microbes

Required (weekly)

Required (weekly recommended)

Disinfecting agent efficacy studies

Not required

Not required

Required



Release/finished Product Testing

<797>

Proposed <797>

CGMP

Sterility Tests

Not required, if default storage times (BUDs) are assigned

Not required, if default storage times (BUDs) are assigned

Required

Endotoxin Test

Required only for CSPs made from non-sterile ingredient(s) and batch sizes of 26+ units

Required only for Category 2 CSPs made from non-sterile ingredient(s).
Elimination of batch size requirement

Required

Strength (potency) and other quality attribute tests

Not required

Not required

Required



Laboratory Controls

<797>

Proposed <797>

CGMP

Sterility and Endotoxin Tests

Compliance with *USP*
<71> and <85> *Bacterial*
Endotoxin Testing
implied

Compliance with *USP*
<71> and <85> *Bacterial*
Endotoxin Testing
explicit

If <71> and <85> are
used, then must comply
with stated requirements.
If alternative methods
are used, methods must
be fully validated.



Beyond-use/expiration Dating

<797>

Proposed <797>

CGMP

Performance of stability tests

Not required, reliance on published literature

Required only for anti-microbial agent, if present. Otherwise, from published literature.

Required

BUD/Expiry limits

Can be based solely upon published literature, no upper limits placed on BUDs

Upper limits placed on BUDs due to lesser sterility assurance compared to CGMP-compliant firms

Expiration date must be supported by comprehensive stability studies



Quality Assurance

<797>

Proposed <797>

CGMP

Sterility and other quality failures – investigations

Recommended, not required. Silent regarding need to consider impact of failure on other products

Required. Investigation must be comprehensive and consider the impact of failure on other products

Required. Investigation must be comprehensive and consider the impact of failure on other products



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Questions?

Attachment 11

Director's Forum

USP <800>: Key Considerations and Changes for Health Systems

Priya Sahadeo, PharmD,* and Robert J. Weber, PharmD, MS, BCPS, FASHP†

On March 28, 2014, The United States Pharmacopeia and The National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3). Pharmacy directors must be proactive in understanding the impact that USP <800> will have on their processes for preparing sterile products. USP General Chapter <797> pertains to the compounding of both hazardous and non-hazardous drugs. USP <800> serves as a new standard to guide the handling of hazardous drugs in order to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, administration, and disposal of both sterile and nonsterile products and preparations. Regardless of all of the requirements listed in USP <800>, there is no substitute for disciplined, consistent work practices regarding proper sterile technique. This point should be emphasized with all compounding personnel. Even if one is compounding in the most compliant USP <800> cleanroom, improper technique can negate all the benefits of the physical structures. Pharmacy leaders at every level will play a key role in assisting an organization to achieve timely compliance with USP <800> standards. Until the standard becomes official, it is important for pharmacists to become familiarized with the latest draft to identify potential barriers to compliance and to strategize a plan to overcome barriers. Although complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way.

INTRODUCTION

The 2012 New England Compounding Center tragedy is well known; 678 confirmed cases of contaminated intravenous preparations resulted in over 60 deaths.¹ As the analysis of the tragedy unfolded, it was obvious that many of the deaths and disabilities could have been prevented if the center had adhered to fundamental guidelines of preparing sterile intravenous preparations. A call to action was generated by many professional organizations and groups to take the recommendations for compounding as set forth by The United States Pharmacopeia (USP) seriously. The authority of the US Food and Drug Administration (FDA) in regulating sterile compounding was reviewed, and accrediting organizations took a firm stand on institutions implementing the standards of USP General Chapter <797>. As a result, a 2014 National Survey of <797> standards

in hospitals showed increases in compliance with both sterile preparation and hazardous drug requirements – but there was room for significant improvement.²

On March 28, 2014, The United States Pharmacopeia and The National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Setting, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3), the free online-only journal in which USP publishes revisions to USP-NF. The first round of public comments ended on July 31, 2014; these comments were incorporated by the USP Compounding Expert Committee into a revised chapter. The second round of public comments on the revised chapter opened on December 1, 2014 and closed on May 31, 2015. The official date of chapter publication has not been determined, but it is highly anticipated by

*PGY2 Pharmacy Administration Resident, †Administrator, Pharmacy Services, The Ohio State University Wexner Medical Center, Columbus, Ohio

stakeholders because this chapter requires key operational changes in the preparation of intravenous medications. Pharmacy directors must be proactive in understanding the impact that USP <800> will have on their processes for preparing sterile products.

The goal of this article is to provide a primer to pharmacy directors and others on new requirements and updates to hazardous drug handling as designated by USP <800>. This article will provide a brief overview of the USP, review the highlights of <800>, describe differences between USP <797> and USP <800>, and describe the impact that <800> will have on sterile compounding programs in health systems. Protecting the public by preventing harm from tainted sterile products is of paramount importance and is a fundamental step in providing patient-centered pharmacy services. Protecting personnel who are involved in the handling of hazardous drugs is just as important and should be given the attention it deserves.

THE UNITED STATES PHARMACOPEIAL CONVENTION

Overview

The United States Pharmacopeial Convention is a not-for-profit scientific organization that develops and publishes general chapters in order to provide the public with quality standards regarding drugs, excipients, and supplements.³ The standards include, but are not limited to, areas such as product identity, strength, quality, and purity. The value of these standards lies in the robust approval process for publication in the USP-NF. Although standards generally originate from sponsors, the supporting data that they provide is first reviewed by USP's scientific staff and volunteer experts; they then undergo rigorous public review and comment, followed by final approval from a USP Expert Committee. Six months after publication in the USP-NF, the standard becomes official and can be enforceable by the FDA and other agencies.

There are 5 USP-NF general chapters on compounding³: USP <795> Pharmaceutical Compounding–Nonsterile Preparations, USP <797> Pharmaceutical Compounding–Sterile Preparations, USP <1160> Pharmaceutical Calculations in Prescription Compounding, USP <1163> Quality Assurance in Pharmaceutical Compounding, and USP <1176> Prescription Balances & Volumetric Apparatus. As a general rule, chapters that are named with numbers under 1000 are enforceable and chapters named with numbers greater than 1000 are informational. Health system pharmacists are most likely familiar with USP <795> Pharmaceutical

Compounding–Nonsterile Preparations and USP <797> Pharmaceutical Compounding–Sterile Preparations. USP <797> is the standard by which to prevent harm and death to patients who are administered compounded sterile preparations (CSPs). USP <797> has undergone one revision that was published in 2008 and is currently undergoing a second revision, which was started in July 2010.⁴

USP <797>and USP <800>

The objective of USP <797> is “to prevent harm, including death to patients that could result from microbial contamination (nonsterility), excessive bacterial endotoxins, variability in the intended strength of correct ingredients, unintended physical or chemical contaminants and ingredients of inappropriate quality in CSPs.”⁴ USP <797> therefore focuses on the minimum practice and quality standards to ensure safe preparation of CSPs for patient use and is divided into sections such as responsibility of compounding personnel, personnel training and evaluation in aseptic manipulation skills, hazardous drugs as CSPs, verification of compounding accuracy and sterility, environmental quality and control, suggested standard operating procedures (SOPs), elements of quality control, finished preparation release checks and tests, storage and beyond use dating, maintaining sterility, purity and stability of dispensed and distributed CSPs, patient monitoring and adverse event reporting, and quality assurance program. These standards are important and, when upheld, can mitigate serious patient harm. The New England Compounding Center fatal meningitis outbreak of October 2012 resulted from noncompliance with compounding standards and highlighted the importance of compliance to scientifically tested practices and techniques as outlined in USP <797>.

USP <797> applies to the compounding of both hazardous and nonhazardous drugs. It defines a hazardous drug as one which studies in animals or humans indicate that exposures have a potential for causing cancer, development of reproductive toxicity, or harm to organs. USP <797> also recommends referring to the most updated National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings to identify whether a drug is classified as hazardous.⁵ A section within USP <797> titled “Hazardous Drugs as CSPs” addresses the risk of adverse effects to health care workers, general storage conditions of hazardous drugs, general

handling of hazardous drugs, allowable preparation hoods, recommended personal protective equipment (PPE), use of closed-system transfer devices (CSTDs), training of personnel handling hazardous drugs, routine environmental sampling, and improvement actions. The recommendations in this section provide a broad scope of guidance and do not offer in-depth recommendations on the areas listed above.

Although USP <797> provides guidelines for preparing sterile compounds, there is a need for defined standards related to the handling of hazardous drugs. Annually, there are over 8 million US health care personnel who are potentially exposed to hazardous medications.⁶ There have been various reports in the literature regarding the harmful effects of hazardous medications to health care workers, such as compromised reproductive health, increased risk for cancers, and a range of adverse effects including rashes, ocular problems, and headaches.⁷ Within the last 25 years, agencies such as Occupational Safety and Health Administration (OSHA) and NIOSH, as well as organizations such as the American Society of Health-System Pharmacists (ASHP), have addressed issues and provided guidance about handling hazardous drugs.

USP <800> Hazardous Drugs—Handling in Healthcare Settings serves as a new standard to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, administration, and disposal of both sterile and nonsterile products and preparations.

Who Can Enforce USP Standards?

USP is not an enforcement agency. State boards of pharmacy usually regulate the compounding practices of the organizations within their jurisdiction. Although boards of pharmacy do not delineate every compounding standard within their laws and rules, most boards have one blanket law that specifically mandates compliance with the USP's compounding general chapters. The FDA also has oversight over compounding and may legally enforce USP's compounding standards,⁸ however the FDA is perhaps most concerned with USP standards from the perspective of ensuring that compounded products are not adulterated from the standards set forth in their monographs. The Joint Commission on Accreditation of Healthcare Organizations has standards that are congruent with USP <797> principles. Even though The Joint Commission does not survey for compliance

with the details of USP <797>, USP standards can assist organizations in complying with relevant and applicable Joint Commission standards.⁹ It can reasonably be anticipated that The Joint Commission may take a similar approach to USP <800>.

HIGHLIGHTS FROM USP <800>

This article is not meant to be a comprehensive review of USP <800>, but rather a review of the most important aspects of these regulations.¹⁰ Pharmacy directors should have a general knowledge of the contents of <800>, along with a general knowledge of the differences between <800> and <797>.

Section 2: List of Hazardous Drugs

Section 2 lists the requirements for entities that should maintain an internal list of hazardous drugs. USP <800> does not provide a comprehensive list of hazardous drugs, but it references the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. Entities can utilize NIOSH's criteria for identification of hazardous drugs when deciding to add drugs to their custom list, along with drugs already on the NIOSH list. Since 2012, NIOSH has updated their list biennially, with the next update anticipated in 2016. USP <800> requires that entities review their own lists at least annually, so this could provide a means by which to ensure that the NIOSH updates are considered each time. The finalized USP <800> may also require an update, as necessary, to the organization's list of hazardous drugs whenever a new agent or dosage form is used by the organization. However, this requirement may undergo wording changes based on the last round of feedback received. The intent of USP <800> seems to be to encourage entities to take a more conservative approach when there is uncertainty about the classification of a drug as hazardous.

The 2014 NIOSH update stratified drugs as antineoplastic, non-antineoplastic, and those that pose a reproductive risk. This stratification guides containment requirements as listed in Table 1.

Section 3 and 4: Types of Exposure and Responsibilities of Personnel Handling Hazardous Drugs

Sections 3 and 4 describe various routes of entry of hazardous drugs into the body, including exposure based on the type of activity being performed, such as dispensing, compounding, administration, patient care activities, spills, receipt, and transport. Section 4 has a unique requirement for entities to designate

Table 1. Containment requirements guide

Antineoplastic hazardous drugs		Non-antineoplastic hazardous drugs and drugs that pose a reproductive risk
Require manipulation	Do not require further manipulation other than counting dosage forms	
Must follow containment requirements outlined in USP <800>	Follow containment requirements per manufacturer or conduct an internal assessment of risk to determine if alternative containment strategies are necessary	Perform and document an internal assessment of risk to determine if alternative containment strategies are necessary

a Compounding Supervisor who is qualified and trained to be responsible for all aspects of hazardous drug handling, including, but not limited to, the development and implementation of procedures; compliance with laws, regulations, and standards; personnel competency; and environmental control. USP <800> provides no guidelines as to the credentials of the compounding supervisor nor whether the person has to be a pharmacy employee (pharmacist or pharmacy technician). However, it can be reasonably expected that both organizational leaders and hospital pharmacy leaders would prefer this position to be within the pharmacy department. Pharmacy leaders may choose to create a new position for this compounding supervisor or assign these responsibilities to an existing position within the department.

Section 5: Facilities

Section 5 is separated into 4 sections: receipt, storage, compounding, and containment supplemental engineering controls. *Receipt* refers to the unpacking of the drug from its original shipping containers; this must be done in a neutral/normal pressure or a negative pressure room to prevent the dispersal of any hazardous drug contamination on the packaging. Drugs cannot be unpacked in sterile compounding areas or positive pressure areas. The anteroom to a

negative pressure room is usually always a positive pressure room, so care must be taken to ensure no drugs are unpacked in this area. This requirement can present challenges, as a dedicated space for unpacking that meets these requirements has to be found.

USP <800> section on *storage* presents a change from the guidance of USP <797>. USP <797> states that hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure.⁴ USP <800> recognizes the 2014 NIOSH stratification of hazardous drugs and reflects this in its storage requirements, as depicted in **Table 2**. Of note, USP <800> allows sterile and non-sterile hazardous drugs to be stored together, but only sterile hazardous drugs may be stored in a negative pressure buffer room. If the sterile drug is an antineoplastic that requires manipulation, it must be stored in a negative pressure buffer area anyway.

USP <800> section on *compounding* is subdivided into nonsterile compounding and sterile compounding. It describes the classification of engineering controls as primary (containment primary engineering control or C-PEC or the hood), secondary (containment secondary engineering control or C-SEC or the room in which the C-PEC is contained), and supplemental or adjunct controls that offer additional levels of protection (eg, CSTDs).

Table 2. Storage requirements guide

Hazardous drugs that can be stored with other nonhazardous drug inventory	Hazardous drugs that must be stored separately from other nonhazardous drugs
<ul style="list-style-type: none"> • Non-antineoplastic hazardous drugs • Reproductive risk–only hazardous drugs • Final dosage forms of antineoplastic hazardous drugs 	Antineoplastic drugs or hazardous drugs API requiring manipulation other than counting final dosage forms: store in a negative pressure room with at least 12 air changes per hour (ACPH)
	Refrigerated antineoplastic hazardous drugs: store in a dedicated refrigerator in a negative pressure area with at least 12 ACPH

Note: API = active pharmaceutical ingredient.

For nonsterile hazardous drug compounding, the C-PEC should be externally vented or redundant HEPA filtered in series and must be placed in a C-SEC that has at least 12 ACPH. If a C-PEC is used solely for nonsterile compounding, unidirectional flow is unnecessary. Additionally, a C-PEC that is used for sterile compounding may be used for nonsterile compounding, but it must be properly decontaminated and disinfected before sterile compounding is resumed.

For sterile hazardous drug compounding, the C-PEC must provide a Class 5 or superior air quality and must be externally vented. By these requirements, a laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) should not be used for such compounding. USP <800> requires that the C-PEC be contained within a C-SEC that is an ISO Class 7 buffer room or an unclassified containment segregated compounding area (C-SCA). A C-SCA is a type of C-SEC with nominal requirements for airflow and room pressurization in that it is ISO unclassified but is a segregated room that maintains negative pressure and is externally vented with at least 12 ACPH. The only sterile hazardous drugs that may be prepared in a C-SCA are low-and medium-risk drugs. A C-SCA is a less expensive option to an ISO-classified, negative pressure cleanroom and provides allowance for compounding of hazardous drugs in clinics that do not have negative pressure cleanroom infrastructure, which is often the case for many outpatient settings. However, if a drug is compounded in a C-SCA, the beyond use date (BUD) will be limited to 12 hours to offer protection to the patients from microbial contamination. The requirement described above is a stricter requirement from USP <797>, which allowed a small volume of hazardous drugs to be compounded in a C-PEC located in a non-negative pressure room. Additionally, USP <800> outlines requirements for maintaining an ISO Class 7 buffer room, as well as requirements for a line of demarcation and transport procedures when the entrance to an ISO Class 7 buffer room is a positive pressure nonhazardous drug buffer room.

USP <800>'s requirements with respect to CSTDs are also different from USP <797>. Whereas USP <797> recommended the use of CSTDs, USP <800> mandates that they be used both for compounding and administering once the dosage form allows. Examples of dosage forms that may not allow the use of CSTDs include intrathecal, ophthalmics, and irrigations. This is a very significant change as it may affect entities that currently do not use CSTDs. These devices are more expensive than traditional

needle and syringe compounding equipment. There are currently no universal performance standards for CSTDs. USP <800> enforcement will favor the market for CSTDs, so more stringent device regulation will be necessary to ensure quality control from existing and potential manufacturers. Furthermore, when contracting the purchase of a CSTD product from a vendor, each entity should consider device effectiveness, nursing input, and pharmacy input.

Section 6: Environmental Quality and Control

Section 6 describes surface wipe sampling and states that it should be performed at least every 6 months. There are currently no certifying agencies for the vendors of wipe kits nor set standards for acceptable limits of surface contamination with hazardous drugs. This is an area for future improvement. If contamination is measured, the compounding supervisor must document and contain the contamination, then take specific actions to reassess areas for improvement such as personnel retraining and improvement of engineering controls.

Section 7: Personal Protective Equipment

Section 7 gives specific and thorough guidance on gloves, gowns, head, hair, shoe and sleeve covers, eye and face protection, respiratory protection, and disposal of used PPE. Certain requirements are specifically stated:

- Compounding sterile and nonsterile hazardous drugs: Use gloves, gowns, head, hair and shoe covers.
- Administering antineoplastic hazardous drugs: Use gloves.
- Administering injectable hazardous drugs: Use gloves and gowns.

When handling antineoplastic hazardous drugs, double gloves must be worn; these gloves must have been tested for permeability according to the American Society for Testing and Materials (ASTM) standard D6978. Similarly, a second set of shoe covers must be donned when an individual enters the hazardous drug compounding area or C-SEC, and then removed upon exiting; this can be a tedious task for personnel who move between the negative pressure room to the anteroom. For all other activities, the entity must state their PPE requirements based on exposure risk and type of handling of hazardous drugs, including receipt, storage, transport, compounding, administration, deactivation/decontamination, cleaning, disinfecting, and spill control.

Sections 8, 9, and 10

Sections 8, 9, and 10, Hazard Communication Program, Personnel Training, and Receiving, contain important information. Section 8 refers to the requirement of entities to establish policies and procedures to ensure worker safety during hazardous drug handling. Such policies should include training on labeling, transport, storage, and use of easily accessible Safety Data Sheets (SDS) for every hazardous chemical used. Section 9 lists minimum areas of training for all personnel who handle hazardous drugs and requires that these individuals be fully trained and demonstrate competency before they independently handle hazardous drugs. Reassessment of competency must be performed and documented at least every 12 months, with the introduction of a new hazardous drug or equipment, and when a significant change in process occurs. Section 10 specifies that hazardous drugs must be received from the supplier sealed in impervious plastic and delivered immediately to the hazardous drug storage area. This section also mandates that PPE be worn, including tested, power-free chemotherapy gloves. There are clear instructions on how to handle damaged shipping containers and product, including containment, return, disposal, retrieval of usable items from a container with damaged items, and reporting procedures.

Sections 11 through 14

These sections (Labeling, Packaging, and Transport; Dispensing Final Dosage Forms; Compounding; and Administering) address key considerations in the logistics of hazardous drug safety. When a hazardous drug is in transit, it must be clearly labeled so as to be easily identifiable as such, at all times. Packaging containers should be carefully chosen on the basis of physical integrity, stability, sterility, and protection from damage, leakage, contamination, and degradation. The section on transport encourages compliance with relevant federal, state, and local regulations. It also cautions firmly against the use of a pneumatic tube system to transport any liquid hazardous drug and any antineoplastic hazardous drug due to breakage and contamination risks. Furthermore, clean designated equipment should be used when dispensing final dosage forms that do not require further manipulation. In light of the increasing use of automation by many hospital pharmacies, the following guidance is also very pertinent: Tablet and capsule forms should not be placed in automated

counting or packaging machines, because stress on the dosage forms can introduce powdered contamination into the equipment. Compounding of hazardous drugs must follow the standards within USP <795> and <797>, and compounding equipment must be designated and not intermixed for compounding of nonhazardous drugs. Additionally, section 13 urges the utilization of commercially available products as starting ingredients instead of crushing tablets, opening capsules, and using active pharmaceutical ingredients (APIs). The section on administration guides the use of PPE for administering hazardous drugs and recommends the use of protective techniques and ancillary devices when applicable. This section also lists the Oncology Nursing Society Safe Handling of Hazardous Drugs publication as a valuable resource on hazardous drug administration.

Sections 15 through 18

Sections 15 through 18 (Deactivation/Decontamination, Cleaning and Disinfection; Spill Control; Disposal; Documentation and Standard Operating Procedures) provide very detailed and specific guidance for the use of PPE for such activities, as well as definitions of and agents to be used in each cleaning step, including the use of combination agents (cleaning steps: deactivation, decontamination, cleaning, and disinfection). This guidance directs when cleaning should occur, lists techniques for wiping, and gives guidance on when and how to clean areas under the work tray of a C-PEC. The section on spill control stresses the importance of quick and easy access to a spill kit, signs for restricting access to the area, documentation of the circumstances and management of the spill, and immediate medical evaluation of anyone who has had direct skin or eye contact with hazardous drugs. Only qualified personnel wearing PPE should be involved in spill containment. Section 16 mandates that SOPs be developed for spill prevention and containment, but it does not provide detailed guidance on the content of spill kits nor guidance on appropriate training of personnel for spill management. The disposal section urges compliance with applicable federal, state, and local laws pertaining to hazardous drug waste; it is important for pharmacy leaders to be up to date with such regulations. The documentation and standard operating procedures section provides guidance on which activities must be documented and the content that must be included in the SOPs for the safe handling of hazardous drugs.

Section 19: Medical Surveillance

Section 19 addresses the medical surveillance program, the purpose of which is to minimize adverse health effects in persons potentially exposed to hazardous drugs. The concept of medical surveillance is based on a proactive approach for early detection of health problems that compares trends over time with an employee's baseline health status. This involves tracking of personnel via assessments and documentation of symptom complaints, physical findings, and laboratory values in order to assess deviations from norms and changes over time. It can also provide a means by which to determine population health trends among exposed personnel compared to unexposed personnel; this can be very helpful in determining the significance of findings. Section 19 discusses elements that should be contained in the entity's medical surveillance program, such as creating an organized approach for identifying potentially exposed workers, the importance of confidentiality and maintenance of health records, and follow-up plans for workers who have shown health changes related to toxicity. Although this section provides criteria that can be used to assess exposure history, it does not provide guidance for determining what a high exposure is nor how this information should be interpreted. For example, it suggests using an estimate of the number of hazardous drug preparations/administrations a health care worker performs in a week; however, there is no "acceptable" number for comparison and evaluation. The mandates within this section present significant changes from <797>, especially concerning confidentiality of health records and continuous monitoring. Employees may not feel comfortable with their health information being managed by someone working within their department, so this sensitive information may have to be interpreted by a separate party such as employee health personnel or a separate contracted agency.

IMPACT OF USP <800> ON HEALTH SYSTEM PHARMACY

Executive leadership support from the organizational entity, as well as the pharmacy department, will be instrumental to ensure timely compliance with USP <800>. This standard is broad and all-encompassing and can be legally enforced at both the federal and state levels. Other agencies, such as The Joint Commission and Centers for Medicare and Medicaid Services (CMS), may also request compliance with USP <800> standards. As such,

the impact of these standards on the organization is large and deserves the attention of all necessary stakeholders.

Most pharmacy leaders will agree that they have an unspoken duty to reasonably ensure the safety and protection of their employees. Leaders are looked to for guidance in times of change. As such, they have a responsibility to know the contents of the standard, be able to decipher and analyze it, and lead strategies to uphold it.

Leaders should be proactive in strategizing their organization's compliance with the standards. This will help eliminate unexpected barriers. A team of pharmacy experts in supply chain management, compounding, hazardous drugs (such as oncology pharmacists), and pharmacy administration should perform a gap analysis to identify areas that need special attention. For example, the entity's list of hazardous drugs should be updated, and its facilities should be evaluated for necessary modifications. It is important to make modifications in such a way as to minimize interruptions to ongoing pharmacy operations, as it is important to continue to provide care to patients.

Some other areas that will need to be analyzed include the adequacy of PPE used by individuals who manipulate hazardous drugs, retraining of personnel with documentation of competencies, and the creation or updating of SOPs. Education will be a big project; not only will pharmacy personnel need to be updated, but also nurses, physicians, risk management, legal, and drug delivery personnel from contracted suppliers. The process by which a hazardous drug is delivered to an institution until that drug is safely administered to a patient consists of many steps. It is important that there is tight control at each step in this pathway, along with safeguards to prevent unintended consequences. USP <800> is intended to provide exactly this standardized guidance. If an organization upholds standards throughout the entire process except for one step, then that entity can be considered noncompliant. It is advisable for organizations to provide feedback to USP, even after the standard has been finalized and enforcement has begun. It would also be helpful for separate entities to network and share information on strategies that have worked or not worked and to publish scientific research in this area where possible. There are areas where scientific evidence is lacking and research would greatly assist to streamline recommendations and even redefine standards within USP <800>.

Implementing USP <800> will increase the safety of preparing hazardous drugs, but there will be challenges to compliance. Table 3 lists some challenges along with some recommended strategies.

Regardless of all of the requirements listed in USP <800>, there is no substitute for disciplined, consistent work practices regarding proper sterile technique. This point should be emphasized with all compounding personnel. Even if one is compounding in the most compliant USP <800> cleanroom, improper technique can negate all the benefits of the physical structures.

Additionally, not all changes have to be implemented at once. Having a defined strategy that addresses the parts of USP <800> that are easily implemented is key to achieving success with USP <800> compliance. Many entities are still attempting to achieve compliance with the standards set forth in USP <797>,² so this impending guidance can make it even more difficult for them to keep abreast of changes. However, health systems should view it as an opportunity to target compliance with both standards in one combined effort. For example, if

facilities need to make changes to comply with USP <800>, then it would be wise for them to make any additional necessary updates that would also ensure compliance with USP <797>.

CONCLUSION

USP <800> is a standard that consolidates existing recommendations for handling hazardous drugs into one universally recognized reference. This standard will require many key operational changes for health systems and will have a far-reaching impact for maintaining patient care standards and health care employee safety and protection. Pharmacy leaders at every level will play a key role in helping organizations achieve timely compliance with USP <800> standards. Until the standard becomes official, it is important for pharmacists to become familiar with the latest draft, identify potential barriers to compliance, and strategize a plan to overcome barriers. Although complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way.

Table 3. USP <800> compliance challenges and corresponding readiness strategies

Potential compliance challenges ¹¹	Strategies for USP <800> readiness
Financial and budgetary restrictions	<ul style="list-style-type: none"> • Conduct a gap analysis • Prioritize projects according to feasibility, ease of execution, and resource sharing amongst departments
Physical plant limitations	<ul style="list-style-type: none"> • Involve facilities engineering in plan for redesigning clean rooms
Training and competency	<ul style="list-style-type: none"> • Identify areas where retraining is needed • Rewrite policies and procedures
Resource availability	<ul style="list-style-type: none"> • Form partnerships among departments within the health system • Form partnerships among nearby hospitals • Consider the possibility of outsourcing
Time	<ul style="list-style-type: none"> • Strategize from early on, not when the standard has been published • Focus on areas in which a change in the final guideline will not require a serious overhaul
Resistance to change	<ul style="list-style-type: none"> • Prepare for change management • Maintain staff morale • Manage expectations • Foster teamwork
Lack of support and awareness from executive leadership	<ul style="list-style-type: none"> • Educate on USP <800> especially on risks of noncompliance • Seek buy-in from an early stage • Leverage “culture of safety” principles

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