

Stakeholders' Challenges and Red Flag Warning Signs Related to Prescribing and Dispensing Controlled Substances

American Academy of Family Physicians

American College of Emergency Physicians

American Medical Association

American Osteopathic Association

American Pharmacists Association

American Society of Anesthesiologists

American Society of Health-System Pharmacists

Cardinal Health

CVS Health

Healthcare Distribution Management Association

National Association of Boards of Pharmacy

National Association of Chain Drug Stores

National Community Pharmacists Association

Purdue Pharma L.P.

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Executive Summary:

In recent years, the misuse and abuse of prescription medications has emerged as a growing public health problem. In addition to the tragic toll on families and communities, prescription drug abuse results in increased costs to the health care and the criminal justice systems. When used appropriately and under the direction and care of licensed health care professionals, prescription medications can improve and save lives. However, prescription medications – most notably controlled substances – can cause negative health consequences if they are abused, diverted, or used inappropriately and not as intended. In an effort to address the nation's prescription drug abuse epidemic and provide guidance to health care practitioners working to minimize diversion, misuse, and abuse of controlled substance medications while ensuring legitimate patient access, stakeholder organizations representing the spectrum of medical and pharmacist care, as well as the supply chain – manufacturers and wholesale distributors, united on October 2, 2013, and numerous times thereafter over the course of 2013 and 2014. The meetings facilitated the communications among stakeholders and resulted in the development of a consensus document detailing the challenges faced by all involved, highlighting red flag warning signs for health care practitioners to detect diversion, misuse, and abuse of controlled substance medications, and identifying aberrant behavior indicators.

The understanding of health care practitioners' roles and the collaboration and communication necessary for a dialogue and resulting consensus document shed light on unappreciated challenges, such as the demands placed on physicians to provide direct patient care and a pharmacist's corresponding responsibility doctrine outlined by Drug Enforcement Administration (DEA) regulations. Determining whether a prescription for an opioid analgesic is issued for a legitimate medical purpose is complicated by the fact that pain is a conscious experience involving interpretation of sensory input that signals a negative event and is influenced by emotion, cognition, memory, interpersonal and social context, and other factors. Appropriate pain management typically is tailored to the individual needs of the patient in collaboration with the prescriber, pharmacist and patient. Red flag warning signs are screening tools for practitioners signaling further review is necessary. Ultimately, red flag warning signs for both physicians and pharmacists were identified and placed into two categories within the consensus document – 1) those factors more indicative of substance abuse or diversion and 2) other aberrant medication-related behaviors and factors potentially indicative of substance abuse or diversion.

In sum, the goal of the stakeholder consensus document is to provide health care practitioners with an understanding of their shared responsibility to ensure that all controlled substances are prescribed and dispensed for a legitimate medical purpose as well as providing guidance on which red flag warning signs warrant further scrutiny. Overall, the challenges faced by health care practitioners can be overcome through collaboration and communication and broader efforts to prevent the diversion of controlled substances while ensuring access to the medications for patients who need them for legitimate reasons. The consensus document however, is not to be construed as establishing any standards of care, but considered as general guidelines and as a reminder that health care practitioners must comply with federal laws and regulations and use their

professional judgment when confronted with red flag warnings and aberrant patient behaviors in regard to controlled substance prescriptions.

Stakeholders' Challenges and Red Flag Warning Signs Related to Prescribing and Dispensing Controlled Substances¹

Section 1 – Introduction

In recent years, the misuse and abuse of prescription medications has emerged as a growing public health problem. In addition to the tragic toll on families and communities, prescription drug abuse results in increased costs to the health care and the criminal justice systems. When used appropriately and under the direction and care of licensed health care professionals, prescription medications can improve and save lives. However, prescription medications – most notably controlled substances – can cause negative health consequences if they are abused, diverted, or used inappropriately and not as intended. The stakeholder organizations noted below represent the spectrum of the medical, pharmacist care, and supply chain – manufacturers, wholesale distributors, physicians, and pharmacists – and are committed to working together to support appropriate prescribing, dispensing, access to, and use of controlled substance prescription medications. The stakeholders recognize that any proposed policy in this area must strike a careful balance to ensure that efforts aimed to minimize the potential for diversion, misuse, and abuse of controlled substance prescription medications do not restrict access for patients with legitimate medical need.

Each of the stakeholder organizations plays an important role in addressing prescription drug abuse, although, at times, conflicting roles and responsibilities may occur among care and supply chain partners. This conflict is oftentimes caused by various reactions to legal requirements enacted to address prescription drug abuse. In fact, the impetus for assembling the stakeholder organizations revolves around the shared responsibility of physicians and other prescribers and pharmacists that ensure all controlled substances are prescribed and dispensed for a legitimate medical purpose.² Fulfilling this responsibility requires increased engagement and communication

¹ This document was compiled by the National Association of Boards of Pharmacy (NABP) addresses challenges and interactions of stakeholders with respect to their roles as it relates to curbing prescription drug abuse. NABP seeks to facilitate discussion and collaboration among the stakeholders; and as such, this document should not be construed as modifying current industry standards.

² United States Drug Enforcement Administration. 21 CFR §1306.04 Purpose of issue of prescription.

(www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol9/pdf/CFR-2014-title21-vol9-sec1306-04.pdf). Accessed August 1, 2014.

(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person

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between pharmacists and physicians and other prescribers, which has resulted in confusion and the subsequent adopting of policies that can disrupt the collaborative interactions of these health care practitioners and ultimately affect patient care.

This document addresses the challenges each stakeholder faces, as well as the warning signs they must be aware of related to the prescribing and dispensing of controlled substances in regard to this serious public health problem and how to best collaborate to provide patient care.

Section 2 – Challenges

A. Manufacturers

Manufacturers are actively engaged in a broad range of efforts with health care practitioners, law enforcement, patient groups, family advocates, and other stakeholders to support appropriate use of medicines, but also face significant challenges related to abuse of their analgesic drug products.

Those manufacturing extended-release or long-acting opioid analgesics are subject to a stringent Risk Evaluation and Mitigation Strategy (REMS) imposed by Food and Drug Administration (FDA) which, in part, requires funding of third parties to provide continuing medical education (CME) about the safe use of these medications. If the number of prescribers completing this REMS-compliant CME doesn't reach FDA-mandated milestones, there could be substantial restrictions on access to these products. These manufacturers are also required to conduct five complicated and expensive post-marketing studies to determine if and how frequently opioid-induced hyperalgesia occurs, to quantify known risks of opioids, eg, abuse and misuse, and to study doctor-shopping, etc.

Manufacturers, like distributors discussed below, struggle to discern what constitutes a “suspicious order” to comply with Drug Enforcement Administration (DEA)-mandated monitoring of orders for products.

One approach that is unique to manufacturers for reducing abuse is the development of novel, innovative preparations of opioid analgesics that are designed to deter certain methods of abuse, (“abuse-deterrent” formulations or ADF). While FDA has issued a draft Guidance on what types of evidence yield particular label claims, a final Guidance has yet to be issued. Likewise, FDA has not issued a draft Guidance on how generic drug products referencing an innovator product with labeled abuse-deterrent properties should be developed and labeled.

Additionally, FDA has repeatedly stated that it seeks to encourage development of ADF opioid analgesics, but has yet to specify which tier(s) of labeling language outlined in the draft Guidance a specific product has earned, which limits manufacturers’ ability to communicate ADF messages. Although FDA believes that ADF study summaries in the label will be informative to prescribers,

knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

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it is not clear that study descriptions alone will be meaningful to most prescribers, pharmacists, or payers for interpreting the expected impact on abuse or the relative differences between drug products.

It is critical that any policies adopted to address misuse, abuse, and addiction must be balanced with and not impede the ability for patients to access needed medicines prescribed for legitimate medical purposes. Lastly, the societal benefit of these novel ADF opioids could remain unrealized if public and private payer policy disadvantages their use through formulary coverage decisions.

B. Distributors

Distributors of prescription medications – specifically controlled substances – provide a vital service to pharmacies, prescribers, and patients. The logistics of ensuring that the prescription medication supply chain operates effectively and safely are overwhelming. Amidst the processing of orders to ensure daily deliveries of needed medications and supplies is a matrix of legal requirements and business challenges.

Legal Requirements

- Record keeping – Distributors are required to create and maintain a variety of records, such as records of receipt and distribution of controlled substances and inventories.
- Verification of Registration – Distributors are required to know that the entities to which they distribute controlled substances are properly registered with DEA and applicable state agencies or make a good faith inquiry in accordance with 21 CFR §1301.74(a).³
- Reporting – Distributors are required to file a variety of reports with DEA. Most germane to the issue of prescription drug abuse is the requirement that distributors detect and report to DEA suspicious orders for controlled substances in accordance with 21 CFR §1301.74(b).⁴ Suspicious orders are “orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.”

Prescribers and pharmacists are required by DEA regulations to ensure that prescriptions for controlled substances are issued for a legitimate medical purpose by a practitioner acting in the usual course of professional practice.⁵ Distributors, unlike prescribers and pharmacists, do not

^{3,4} United States Drug Enforcement Administration. 21 CFR §1301.74 Other security controls for non-practitioners; narcotic treatment programs and compounders for narcotic treatment programs. (www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol9/pdf/CFR-2014-title21-vol9-sec1301-74.pdf). Accessed August 1, 2014.

(a) Before distributing a controlled substance to any person who the registrant does not know to be registered to possess the controlled substance, the registrant shall make a good faith inquiry either with the Administration or with the appropriate State controlled substances registration agency, if any, to determine that the person is registered to possess the controlled substance.

(b) The registrant shall design and operate a system to disclose to the registrant suspicious orders of controlled substances. The registrant shall inform the Field Division Office of the Administration in his area of suspicious orders when discovered by the registrant. Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.

⁵ United States Drug Enforcement Administration; *Practitioner's Manual*; 2006:30

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interact with patients and do not have access to the information necessary to determine whether a prescription that is being dispensed by a pharmacy is legitimate. However, in addition to determining and reporting suspicious orders under 21 CFR § 1301.74(b), distributors are also expected to block, ie, prevent the distribution of suspicious orders, per DEA guidance letters.⁶

A significant challenge for distributors is applying in practice what defines a suspicious order. For distributors, the appropriate metrics to identify a suspicious order are, for the most part, the responsibility of the distributor and not delineated specifically in federal or state laws and requirements. Because of this, the metrics that are actually used vary considerably among distributors. Questions persist as to which factors should be used or how much weight certain factors should be given for determining what constitutes a suspicious order. Such factors include: the overall size of the pharmacy; how many prescriptions are filled per day; both non-controlled and controlled substances in relation to controlled substances purchased; any specialty practice within a pharmacy; affiliation(s) with health care institutions such as hospitals or clinics; the type(s) of patient population a pharmacy serves; variations in geographical or regional prescribing patterns that may affect which products are dispensed and purchased; and other factors that influence the quantity of controlled substances ordered and the ordering pattern of a pharmacy. Although an indicator of certain activities, some factors, such as national averages, may not necessarily identify abuse or diversion, nor determine whether an order or group of orders is suspicious. Absent more specific requirements, distributors must make decisions about whether to distribute an order for controlled substances based upon factors that may cause an order to be suspicious. This has led several distributors to place limits on the quantity of controlled substances they will distribute to customers and, depending on the distributor that the customer chooses, the limits may vary based upon what criteria that distributor uses and how much weight the distributor gives factors within that criteria. As a result, distributors have faced lawsuits and threats of lawsuits from DEA-registered pharmacies for either ceasing distribution of controlled substances to the pharmacies or limiting the quantity of controlled substances they will sell, which ultimately have, in some cases, negatively impacted patient access to care.

C. Prescribers/Physicians

According to the Controlled Substances Act, physicians and other prescribers have a responsibility to ensure that a prescription for a controlled substance is “issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice.” The responsibility for the proper prescribing and dispensing of controlled substances is upon the

“Federal courts have long recognized that it is not possible to expand on the phrase ‘legitimate medical purpose in the usual course of professional practice’ in a way that will provide definitive guidelines to address all the varied situations physicians may encounter.”

⁶ These guidance letters are from DEA's Deputy Assistant Administrator, Office of Diversion Control, sent to registered manufacturers and distributors on September 27, 2006, February 7, 2007 and December 27, 2007.

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prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription (see below).

Determining whether a prescription for an opioid analgesic is issued for a legitimate medical purpose is complicated by the fact that pain is a conscious experience involving interpretation of sensory input that signals a noxious event and is influenced by emotion, cognition, memory, interpersonal and social context, and other factors. Patient-reported intensity of pain may not correlate with the magnitude or identifiable source of injury. Because objective tests for pain intensity (or even the presence or absence of pain) are still at a rudimentary stage of development, the best clinical approach in most circumstances is to assume that the patient is reporting a true experience. Accepting a patient's complaint of pain as valid does not require clinical identification of a physical cause, or demand the initiation of a specific treatment. It does, however, provide a foundation for assessment and the basis for developing an effective patient-physician dialogue.

During the past two decades, growing numbers of patients with persistent non-cancer pain have been offered long-term opioid therapy. This change in prescribing behavior has been influenced by several competing interests. Undertreatment of cancer pain was described, and the aggressive use of opioid analgesics was endorsed as the most effective approach to address patient suffering. With the advent of a new array of products, this approach was extended to patients with chronic non-cancer pain, even in the absence of evidence obtained from long term, randomized controlled trials, which are not feasible. In both hospital and outpatient settings, the recognition of pain as the fifth vital sign, and the evolution of patient satisfaction surveys that include a focus on the extent to which a patient's pain is relieved, created a practice environment that, although intended to promote pain assessment and effective treatment, in general ultimately led to an increase in opioid prescriptions. Despite the substantial burden of persistent pain in the United States, access to multidisciplinary care and reimbursement for non-pharmacologic approaches is woefully inadequate. All of these factors may have contributed to the routine use of opioid analgesics.

In parallel with this increase in medical use has been a deeply concerning rise in various measures of prescription drug misuse and abuse, including nonmedical use, as well as unintentional overdoses and deaths. Non-adherence during treatment, drug abuse, addiction, unintentional overdose and diversion into the illicit marketplace are known risks of opioids and other controlled drugs. Whenever opioid analgesic drugs are considered for use, pain assessment and patient selection, risk assessment and risk stratification, drug choice, and structuring of therapy (including monitoring, maintenance, and exit strategies) are key elements comprising appropriate care.^{7,8} Currently available instruments for implementing these approaches are imperfect and difficult to integrate into primary care practice, placing additional emphasis and responsibility on a

⁷ Katz NP, Adams EH, Benneyan JC, et al. Foundations of opioid risk management. *Clin J Pain*. 2007;23(2):103-118.

⁸ Gourlay DL, Heit H, Almahrezi A. Universal precautions in pain medicine: A rational approach to the treatment of chronic pain. *Pain Med*. 2005;6:107-112.

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physician's judgment and clinical experience, which cannot be replicated outside of the patient-physician relationship.

Just as pharmacists are operating in a multitasking environment that places high demands on time management, the ability of physicians and other prescribers to be responsive to requests for additional information is constrained by an array of existing demands that already erode their ability to provide direct patient care. These include a high frequency of requests related to refills and prescription re-authorization, prior authorization, and errors related to electronic prescribing interfaces; adapting to meaningful use, physician quality reporting systems, value-based modifiers; and, HIPAA concerns. Accordingly, responding to calls from pharmacists to clarify the legitimacy of an opioid prescription may be viewed as intrusive, depending on the nature of that call, especially if the prescriber is unaware of the pharmacist's corresponding responsibility.

D. Pharmacists

Pharmacists' associated professional services and activities vary from practice to practice and site to site. The variance is in response to the diversity of patient care needs and patients' medication use through self-care, acute care, and long-term or chronic care. These varying needs manifest in virtually all practice settings and add complexity to the patient care provided by pharmacists. Regardless of practice setting, the basis and essence of pharmacist care is communication, education, and information exchange with patients and their caregivers, prescribers, and other health care professionals. The central point of this care is the pharmacist management of medication use that strives to provide patient-centered medication therapy with the goal of positive patient outcomes.⁹ In the effort to provide this patient-centered medication therapy management, collaboration between patients, prescribers, and pharmacists is imperative.

Pharmacists serve a critical role in the continuum of patient care and often serve as one of the most accessible members of the health care team. The pharmacist, through standards of care and federal and state legal requirements, assumes diverse and sometimes conflicting roles. When a patient or caregiver presents a prescription to the pharmacist, what transpires next is a complex coordination of care and oversight. The presenting of a prescription is one of a myriad of items the pharmacist is reviewing and trying to resolve in a multitasking environment involving the receipt and evaluation of prescriptions for multiple patients at once, interactions or pending interactions with prescribers, and resolution of insurance coverage and formulary issues. All of these activities occur within a limited time frame being conducive to patient convenience, while not compromising patient safety, and taking into consideration a prescription's legitimacy.

If the prescription is issued for a controlled substance, there is also the specific legal, "corresponding responsibility" requirement with which pharmacists must comply.¹⁰

⁹ J Am Pharm Assoc (2003) 2010;50:e35-e69. DoI:10.1331/JAPHA.2010.10510.

¹⁰ 21 CFR §1306.04

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Unfortunately, the fact that pharmacists have a corresponding responsibility to ensure the legitimacy of a controlled substance prescription appears to be relatively unknown to many prescribers and has contributed to the potential for confusion and conflict between prescribers and pharmacists. This corresponding responsibility requirement overlies the existing responsibility of the pharmacist to evaluate a prescription in the context of the patient's broader medication need and history. In this regard, it is appropriate and at times necessary for pharmacists to contact prescribers to obtain additional information or clarification regarding a prescription issued for a controlled substance. In doing so, pharmacists do not intend to engage in activities outside of their scope of authority, nor intrude into the scope of practice of other professions; however, pharmacists must comply with corresponding responsibility requirements or risk being subject to the penalties for violations of controlled substance law.

Summarily, in the compressed amount of time during which a prescription is presented to the pharmacist and the patient receives his/her medication, the pharmacist's responsibilities to review, evaluate, and dispense the prescription include:

- Completing a drug utilization review that includes, but is not limited to, the evaluation of the prescription and patient record for known allergies; rational therapy contraindications; reasonable dose, duration of use, and route of administration; considering age, gender, and other patient factors; reasonable directions for use; potential or actual adverse drug reactions; drug-drug interactions; drug-food interactions; drug-disease contraindications; therapeutic duplication; proper utilization (including over- or under-utilization) and optimum therapeutic outcomes; and abuse/misuse;
- Interacting with patients or caregivers who may be unaware of what the prescription was issued for, or who are unable to provide additional information beyond the symptoms that are being experienced and discussed with the prescriber; and
- Having to decipher illegible prescriptions and/or contact prescribers due to the limited use of electronic prescribing.

The presentation of a controlled substance prescription adds the following complicating factors:

- Recognizing “red flag” warnings^{11, 12} that call the prescription into question. Such warnings require the pharmacist to ensure that the prescription is being issued for a legitimate medical purpose by the prescriber acting in the usual course of his/her professional practice. This may include communicating with the prescriber to clarify the prescription and/or evaluate the legitimacy of a prescription, which may at times be difficult depending on the prescriber's availability, especially when prescriptions are presented outside normal business hours or on weekends.

¹¹ Holiday CVS, L.L.C., d/b/a CVS/Pharmacy Nos. 219 and 5195; Decision and Order; 77 FR 108, 62,315 (Dept of Justice Oct. 12, 2012). www.deadiversion.usdoj.gov/fed_regs/actions/2012/fr1012.htm.

¹² East Main Street Pharmacy; Affirmance of Suspension Order 75 FR 207, 66149 (Dept of Justice Oct. 27, 2010) Available at www.deadiversion.usdoj.gov/fed_regs/actions/2010/fr1027_3.htm.

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- Satisfactorily determining legitimacy of the prescription. Communicating with prescribers can be essential in ascertaining the legitimacy of a controlled substance prescription, although simply phoning a prescriber and inquiring if the prescription is legitimate may not be satisfactory. In the case of prescribers who may be involved in abuse or diversion, it is highly unlikely that the response to an inquiry from the pharmacist concerning the legitimacy of the prescription would be to affirm that the prescription is not legitimate. Thus, the pharmacist may need to initiate additional means to evaluate the prescription. In addition, it can also be difficult to validate a prescriber's authority. For example, a prescriber may issue an otherwise legitimate prescription, but may not be authorized to write for that class of controlled substance.
- Accessing PMP data. This step is valuable and necessary in many situations. Unfortunately, the data from, operation of, and access to individual PMPs lack uniformity, may be incomplete, or are not conducive to real-time patient care demands of the compressed time frame noted above.
- Distribution restrictions implemented by wholesale distributors. Such restrictions implemented in response to enforcement actions or company policies impact the availability of medications to the pharmacist, creating another factor to resolve before dispensing can be completed.

Section 3 – Factors More Indicative of Substance Abuse or Diversion (Red Flags)

A. Patient Population and Behaviors

The patient population with persistent pain is extremely diverse and the strategies used to administer and monitor opioid therapy should be individualized based on the pain assessment, the risk of adverse effects, and the perceived likelihood of problematic drug-related behaviors.^{5,6} A one-size-fits-all approach to guide treatment or to prevent substance abuse ultimately would do a great disservice to patients and the health care professionals who work hard to effectively treat their pain.

While several groups have been working to address issues surrounding the current prescription drug epidemic, the coalition of stakeholders representing the spectrum of medical, pharmacist care, and supply chain — physicians, pharmacists, manufacturers, distributors, pharmacy benefit managers, and federal and state regulatory and law enforcement agencies have come together to collate warning signs that can help assist physicians and other prescribers and pharmacists identify situations that indicate whether a patient may be more likely to be abusing or diverting prescription drugs. These warning signs have been developed to help educate and raise awareness among health care professionals about warning signs, and foster communication and collaboration in order to minimize these activities.

Some of these warning signs are indicators of a substance use disorder, including addiction, or illicit/illegal behavior, or that a patient's health or safety is threatened. They have been identified

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through enforcement actions of the Drug Enforcement Administration and various clinical studies.^{13,14,15,16,17,18,19,20,21,22,23,24} A subset of these actions or behaviors have been termed “red flags,” and are part of a broader array of warning signs reflecting illicit/illegal activities and/or aberrant drug-related behaviors that patients who are receiving opioid analgesics may exhibit in response to therapy. Such behaviors exist along a continuum. As a term of art, red flags typically have been interpreted to be more likely to reflect drug abuse, addiction, or diversion, although a wide range of other aberrant behaviors exist that are indicative of various patterns of non-adherence (see below). When warning signs are present, health care practitioners should immediately assess the situation and/or the patient’s medical and psychological condition, and determine the appropriate action, eg, continuation of treatment, intensify monitoring, refer for substance use/addiction treatment, refuse to issue/dispense a prescription. Activities on the part of the patient that violate state or federal law may require more direct action. While health care practitioners must ethically take steps to help prevent the continued misuse, abuse or diversion of opioids, some patients may need ongoing treatment. In these situations, extra care should be taken, and may include referrals to specialists and other clinically appropriate decisions.²⁵ The following categories of factors more indicative of substance abuse or diversion have been identified.

B. Prescribers

In the vast majority of situations, prescribers play a key role in preventing and identifying prescription drug abuse. Proper education and training, and vigilance with respect to appropriate patient selection and prescribing practices can help minimize diversion and abuse as well as ensure

¹³ Holiday CVS, L.L.C., d/b/a CVS/Pharmacy Nos. 219 and 5195; 77 Fed. Reg. 62,315 (Dep’t of Justice Oct. 12, 2012) (decision and order). Available at: www.deadiversion.usdoj.gov/fed_regs/actions/2012/fr1012.htm.

¹⁴ East Main Street Pharmacy; 75 Fed. Reg. 66,149 (Dep’t of Justice Oct. 27, 2010) (affirmance of suspension order). Available at: www.deadiversion.usdoj.gov/fed_regs/actions/2010/fr1027_3.htm.

¹⁵ Holiday CVS, L.L.C. v. Holder, 839 F.Supp.2d 145 (D.D.C. 2012). Available at: www.gpo.gov/fdsys/pkg/USCOURTS-dcd-1_12-cv-00191/pdf/USCOURTS-dcd-1_12-cv-00191-0.pdf.

¹⁶ Townwood Pharmacy; 63 Fed. Reg. 8,477 (Dep’t of Justice Feb. 19, 1998) (revocation of registration). Available at www.gpo.gov/fdsys/pkg/FR-1998-02-19/pdf/98-4201.pdf.

¹⁷ Grider Drug 1 & Grider Drug 2; 77 Fed. Reg. 44,069 (Dep’t of Justice July 26, 2012) (decision and order). Available at: www.deadiversion.usdoj.gov/fed_regs/actions/2012/fr0726.htm.

¹⁸ The Medicine Dropper; 76 Fed. Reg. 20,039 (Dep’t of Justice April 11, 2011) (revocation of registration). Available at: www.deadiversion.usdoj.gov/fed_regs/actions/2011/fr0411_10.htm.

¹⁹ Medicine Shoppe-Jonesborough; 73 Fed. Reg. 363 (Dep’t of Justice Jan. 2, 2008) (revocation of registration). Available at: www.deadiversion.usdoj.gov/fed_regs/actions/2008/fr0102.htm.

²⁰ Medicine Shoppe-Jonesborough v. DEA, 300 Fed. Appx. 409, 2008 WL 4899525 (C.A.6).

²¹ Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. *Pain Med.* 2009 Nov;10(8):1426-33.

²² Cheatle MD, O’Brien CP, Mathai K, Hansen M, Grasso M, Yi P. Aberrant behaviors in a primary care-based cohort of patients with chronic pain identified as misusing prescription opioids. *J Opioid Manag.* 2013 Sep-Oct;9(5):315-24.

²³ Passik SD, Kirsh KL, Donaghy KB, Portenoy RK. Pain and aberrant drug-related behaviors in medically ill patients with and without histories of substance abuse. *Clin J Pain.* 2006 Feb;22(2):173-81.

²⁴ Passik SD, Kirsh KL. Assessing aberrant drug-taking behaviors in the patient with chronic pain. *Curr Pain Headache Rep.* 2004 Aug;8(4):289-94.

²⁵ Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med.* 2007 Oct-Nov;8(7):573-84.

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patients do not suffer unnecessary delays or denials in care, including access to opioid analgesics when appropriate. Practice guidelines, best practices and model policies have evolved from a variety of sources to promote responsible opioid prescribing and establish standards of care.

Initial Visit/Presentation

- Patients who travel to the prescriber's practice as a group and all request controlled substance prescriptions on the same day.
- Patient declines physical examination, or permission to obtain past records, or to undergo diagnostic tests.
- Patient statements and conduct suggest abuse of controlled substances, eg, appears sedated, confused, intoxicated, or exhibits withdrawal symptoms, or has physical signs of drug abuse.

Medication Taking/Supply

- Patient exhibits multiple unexplained dose escalations or other non-adherence to the treatment plan.
- Patient uses a route of drug administration other than the method prescribed, eg, injecting or inhaling oral formulations; ingesting transdermal formulations.
- Patient repeatedly seeks medications from non-coordinated sites of care; possible examples could include the emergency department, urgent care facilities, or walk-in clinics.
- Patient suffers an unintentional (or intentional) overdose.

Patient Behavior/Communication

- Patient behavior or PDMP report provides evidence that the patient is obtaining controlled substance prescriptions from multiple health care practitioners without the prescribers' knowledge of the other prescriptions.
- Patient was discharged from another physician practice for egregious behavior.
- Patient pressures physician to prescribe by implying or making direct threats to the prescriber or staff.²⁶

Treatment Plan Related

- Patient repeatedly resists changes in the treatment plan, despite clear evidence of adverse physical or psychological effects from the drug.
- Patient refuses to sign, or fails to comply with, an opioid pain care agreement governing their use of opioid analgesics.

Illicit/Illegal

- Prescriber is made aware that patient alters, forges, or rewrites prescriptions.

²⁶ If the prescriber feels physically threatened, issue the prescription to avoid confrontation; then contact authorities.

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- Prescriber receives reliable information that patient is diverting or selling medication, or “borrowing” drugs from others.
- Patient indicates that drugs will be shared with others or sold.
- Patient requests controlled substance prescriptions written in the names of other people for whom the patient is not the designated caregiver.

C. Pharmacists

Patient-centered medication therapy management provided by pharmacists becomes increasingly more complex when a patient is prescribed a controlled substance and the medication therapy involves the management of various types of acute and chronic pain. In these situations, the ethical and legal corresponding responsibilities that help define the dispensing of controlled substances must be considered and followed.

When presented with a prescription for a controlled substance, pharmacists must exercise their professional judgment and must adhere to their corresponding responsibility to determine whether a prescription for a controlled substance has been issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice. That evaluation determines the next steps taken by the pharmacist and includes options such as a discussion with the prescriber in order to ensure the validity of the prescription and address red flag warning signs prior to dispensing.

These red flags may indicate that a controlled substance prescription is not being obtained for a legitimate medical purpose, but for diversion or abuse, thereby possibly necessitating additional steps by the pharmacist. Any time a red flag occurs, it should be evaluated in an attempt to appropriately interpret its nature, and patient management should be pursued based on this interpretation and the seriousness of the warning signs. Of course, the warning signs are not intended to prevent the dispensing of a legitimate controlled substance prescription.

Presentation of the Prescription

- Patients travel in groups and/or have unexplainable common factors in their relationships with each other, for example, groups of patients present prescriptions for the same controlled substances from the same prescriber, or multiple family members or patients living at the same address present similar controlled substance prescriptions to the pharmacy on the same day.^{8,9}
- Patient presents prescriptions for controlled substances written in the names of other people (does not apply to designated caregivers presenting prescriptions for patient).²⁷
- Patient presents a prescription for controlled substance that the pharmacist knows, or reasonably believes, that another pharmacy refused to fill.

²⁷ Drug Enforcement Administration: *Pharmacist's Manual*; 2010:66-68.

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- Handwritten prescription is presented at the pharmacy looking altered (quantity changed) or flawlessly thorough (contains patient address, quantity spelled out, patient date of birth, multiple provider identifiers, lacks common abbreviations, etc.).²⁶
- Pharmacist becomes aware that prescriber's DEA registration has been previously suspended or revoked, or is pending suspension or revocation.⁸

Patient Behavior

- Patient pressures the pharmacist to dispense controlled substance by making implied or direct threats²⁸.
- Patient shows physical signs associated with controlled substance abuse, such as needle tracks or scars on neck, arms, feet, or ankles.
- Patient's statements and conduct suggest abuse of controlled substances, such as appearing sedated, confused, intoxicated, or exhibiting withdrawal symptoms.
- Patient obtains same or similar controlled substance prescription from multiple health care practitioners without disclosing those existing controlled substance prescriptions.^{12,13,14}
- Patient obtains controlled substance medications from one pharmacy while having received the same or similar controlled substance(s) from other pharmacy(ies) without disclosing those existing controlled substance prescriptions.
- Patient presents prescriptions for highly abused controlled substance medications.²⁹
- Patient presents several prescriptions written for controlled and non-controlled substances, but only wants the controlled substance medication(s) dispensed.
- Patient has a history of untruthfulness when filling controlled substance prescriptions.

Medication Taking/Supply

- Patient presents prescriptions for large quantities or large number of prescriptions for controlled substances.⁹
- Therapeutic duplication of two or more long-acting and/or two or more short-acting opiates.
- Patient presents prescriptions for highly abused "cocktails" (combination of opiate, benzodiazepine, and muscle relaxant) of controlled substance medications.³⁰

Illicit/Illegal

- Patient indicates that drugs will be shared with others or sold.
- Prescriber's DEA registration or state license has expired/suspended/revoked.

²⁸ If the pharmacist feels physically threatened, dispense the prescription to avoid confrontation; then contact authorities.

²⁹ Highly abused controlled substances may vary from region to region. Pharmacists should be aware of abuse trends in their area.

³⁰ This is not in reference to specific medication combinations intended to decrease opioid dose.

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- Patient presents prescription from prescriber who is prescribing outside the scope of his/her practice as defined by state law.
- Patient alters, forges, sells or rewrites prescriptions.²⁶
- Patient is diverting/selling medication, or getting drugs from others.

Section 4 – Other Aberrant Medication-Related Behaviors and Factors Potentially Indicative of Substance Abuse or Diversion

A. Prescribers

The population of prescription opioid users is heterogeneous. Among pain patients there are those who are responsive to the medication and adherent, others use the medication to self-treat or as a coping agent, and some develop problems with substance use disorders. Nonmedical users may employ the drug for recreation or have more serious substance use disorders including addiction. Accordingly, other patient characteristics or actions should evoke further scrutiny and must be dealt with, including evaluation of whether an opioid analgesic is indicated for clinical use. These may manifest during the ***initial visit***, eg, patient travels an unexplained long distance for the office visit, is from out of state or “visiting,” refuses or is reluctant to present identification, or insists on paying with cash even though health insurance coverage exists, or during the ***pain assessment and history taking***, eg, patient appears to be faking or exaggerating pain severity, offers only a vague medical history, provides old clinical report and/or radiographic image in support of their request for pain medication, is unwilling or not able to provide the name of regular physician, or indicates the physician is unavailable. Certain patterns of ***communication or specific requests*** also warrant further scrutiny, eg, patient demonstrates an unusual knowledge about opioid medications or other controlled substances, uses “street names,” requests large quantities, specific drugs, or combinations of controlled substances, or aggressively complains about the need for more drug.

As previously noted, patients who are receiving opioid analgesics may exhibit aberrant drug-related behaviors that exist along a continuum. The factors noted above are more likely to reflect drug abuse, addiction, or diversion. Other aberrant behaviors indicative of non-adherence involve ***medication taking/supply*** such as losing a prescription or claiming that it was stolen, a pattern of early refill requests, using the drug without approval to treat another symptom, or in contrast, exhibiting drug hoarding during periods of reduced symptoms. Aberrant behaviors may emerge related to the ***treatment plan*** including a claim of allergy, intolerance or contraindications to the use of alternative, but appropriate, non-opioid pain medications; refusing to try appropriate non-pharmacologic therapies, eg, cognitive-behavioral, rehabilitative, physical medicine approaches; refusing to taper pain medication when clinically indicated; and, violating an opioid pain care agreement. Patients who are concurrently abusing alcohol or other drugs also are at higher risk of abusing opioid analgesics.

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The emergence of a single, or a few, of these aberrant behaviors does not necessarily confirm the presence of a substance use disorder or illicit/illegal behavior. The presence of multiple aberrant behaviors increases that likelihood. Regardless, when a problematic behavior occurs, it should be evaluated by the treating physician. Because not all aberrant behaviors have the same origins or implications, physicians must consider a differential diagnosis and tailor treatment accordingly.^{31,32,33} Management should be pursued based on this interpretation, the seriousness of the behavior(s), and the skills of the clinician, including the need for structured intervention or referral for further treatment.

B. Pharmacists

As previously described, pharmacists must use their professional judgment in order to comply with their corresponding responsibility duty to ensure that controlled substance prescriptions are issued for legitimate medical purposes in the usual course of professional practice. While the above factors or “red flags” are more indicative of substance abuse or diversion, oftentimes more subtle aberrant behaviors exist, that while in and of themselves may not be problematic, may indicate a potential issue that warrants further evaluation prior to dispensing.

Aberrant behaviors that patients may exhibit upon the **presentation of the prescription** include traveling unexplainable and/or unreasonably long distance to a physician office and/or the pharmacy or requesting to pay cash for a controlled substance prescription, when it has been documented that he/she has insurance that would normally cover the prescription.^{8,9} Whereas these types of behaviors may be warning signs, they can also be explained by today’s specialty practice arena as well as third-party payer reimbursement circumstances.

Additionally, certain **patient behaviors**, which may cause concern, such as asking for a certain drug prone to abuse by color, trade name, or markings and/or uses “street names” when discussing opioid analgesics or other controlled substances (eg, xanibars, purple drank, blues, greens), while not typical, may be explained by the patient having a chronic disease state who has become very familiar with the various medications or just by way of today’s drug-savvy culture. Along these lines, other behavior such as a patient claiming to be allergic to other appropriate, non-controlled substance pain medications may very well be a result of a lack of understanding of what constitutes a true allergic reaction versus mere intolerance. Other behaviors that may require additional scrutiny, particularly if they appear to be a pattern include, frequently running out of medication for controlled substances early or claiming to lose prescription(s); controlled substance refill patterns being inconsistent with regular refill patterns for non-controlled chronic prescription

³¹ Argoff CE, Kahan M, Sellers EM. Preventing and managing aberrant drug-related behavior in primary care: Systematic review of outcomes evidence. *J Opioid Manag.* 2014 Mar-Apr;10(2):119-34. doi: 10.5055/jom.2014.0201.

³² Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain.* 2009 Feb;10(2):131-46.

³³ Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician.* 2012 Jul;15(3 Suppl):ES67-92.

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medications; and repeated claims that a pharmacy dispensed a quantity of a controlled substance that is less than what was prescribed.

Section 5 – Disclaimers

A. Prescribers

While it is generally agreed that it is important to monitor outcomes systematically in patients taking opioids, aberrant medication-related behaviors and other factors potentially indicative of substance abuse or diversion are not definitive markers.³⁴ They are patient-specific, occur along a continuum of risk, and require a differential diagnosis. They also should not, in and of themselves, be used to establish general standards of care or to inform statutory or regulatory requirements.

B. Pharmacists

Whereas aberrant behaviors may be indicative of potential drug abuse and/or diversion, they are not in and of themselves, positive identifiers that unequivocally result in a pharmacist taking specific actions or be used to establish general standards of care or to inform statutory or regulatory requirements. These types of behavior should however, result in an increased vigilance with taking all patient circumstances into consideration. Pharmacists, on a case-by-case basis, should always use their professional judgment and, when in doubt, exercise due diligence in determining the legitimacy of a controlled substance prescription.

Section 6 – Conclusion

The challenges faced by manufacturers, distributors, physicians and other prescribers, and pharmacists can be overcome through collaboration and broader efforts to prevent the initial diversion of controlled substances. PMPs have proven effective in identifying abuse, misuse, and diversion. Strengthening these programs will help facilitate appropriate clinical decision-making from both prescribers and pharmacists. Similarly, efforts to eliminate “pill mills”— facilities which inappropriately provide access to controlled substances with no regard for medical necessity and are a significant source of diversion – will help to prevent the initial diversion of controlled substances. Finally, appropriate education and collaboration amongst all key stakeholders is essential to addressing this important public health problem. Strengthening these areas will be critical to ensuring all those involved are provided with the information and tools necessary to support the appropriate use of controlled substance medications.

³⁴ Meltzer EC, Rybin D, Meshesha LZ, et al. Aberrant drug-related behaviors: unsystematic documentation does not identify prescription drug use disorder. *Pain Med.* 2012 Nov;13(11):1436-43.

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