Available online at www.sciencedirect.com
ScienceDirect
Research in Social and Administrative Pharmacy ■ (2015) ■–■
RESEARCH IN SOCIAL & ADMINISTRATIVE PHARMACY

Commentary

Recent developments toward the safer use of opioids in the USA, with a focus on hydrocodone

Jordan R. Covvey, Pharm.D., Ph.D., B.C.P.S.*

Division of Clinical, Social and Administrative Sciences, Duquesne University Mylan School of Pharmacy, 600 Forbes Ave., Pittsburgh, PA 15282, USA

Summary

Opioids have become a mainstay of treatment for pain in the United States, with over 250 million prescription issued in 2012 alone. The increased prescribing of these medications has also contributed to the unintended consequence of a widening prevalence of abuse and misuse, and therefore safety has become a top agenda item for both government and health care providers alike. The move toward new abuse-deterrent formulation technologies, enhanced regulatory requirements from the Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA), and developments in national/state policies have worked together to target a goal of promoting safer clinician prescribing, pharmacy dispensing and patient use of opioids. Hydrocodone in particular, as the most widely prescribed opioid product, has recently been subject to a myriad of changes, both through the federal rescheduling of hydrocodone-combination products (HCPs) to Schedule II, as well as the introduction of two new extended-release formulations to the USA market. These efforts represent a first step toward tackling the opioid harms epidemic, although continuing follow-up through research and policy implementation is needed to see any measureable impact on safety in the future.

Keywords: Drug Enforcement Administration; Food and Drug Administration; Controlled substance scheduling

Introduction

Chronic pain has been estimated to affect approximately 100 million Americans with an annual national economic cost of $560–635 billion, equating to nearly $2000 for each person living in the United States (USA).[1] As anticipated, pain is one of the most common issues encountered in clinical care, reported by 20–50% of primary care encounters.[2,3] The use of opioid analgesics, a mainstay of pain treatment, has increased dramatically in recent years. In the USA, the rates of opioid prescribing nearly doubled among pain visits during 2000–2010 from 11.3% to 19.6% in one national analysis, without accompanying increases in non-opioid analgesics or the proportion of patients receiving pharmacologic treatment.[4] Deaths associated with prescription analgesic overdoses have also increased over three-fold from 1998 to 2008, and

Conflicts of interest: None.
Funding: None.
* Corresponding author. Tel.: +1 412 396 2636.
E-mail address: covveyj@duq.edu.

1551-7411/$ - see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.sapharm.2015.02.001

nearly 500,000 emergency visits to hospitals in 2009 alone were associated with abuse/misuse of prescription analgesics.[5]

Hydrocodone in particular has been touted as a primary driver behind opioid-related abuse and misuse due to its widespread availability and use. Since the approval of the first product in 1943, hydrocodone has gained increasing popularity as a 'middle-level' opioid. In 2012, over 135 million prescriptions were issued for hydrocodone/acetaminophen products (e.g. Vicodin®, Lortab®), making it the most widely dispensed prescription medication in the USA market, at nearly 25% and 50% higher volume than next top-ranked medications levothyroxine and lisinopril, respectively.[6] An observational study of opioid prescriptions issued at clinic visits to older adults from 1999 to 2010 found that the percentage of visits where an opioid was used increased from 4.1% to 9.0% over the study period; hydrocodone was the largest contributor, increasing from 1.1% to 3.5% alone.[7] This increased use has been accompanied by concerning safety issues; in 2011, approximately 97,000 drug-related emergency room visits for abuse/misuse involved hydrocodone products, a 96% relative increase from 2004.[8]

In response to these trends, there have been several recent regulatory developments affecting opioids, and more specifically, hydrocodone. Most recently on August 22 2014, the Drug Enforcement Administration (DEA) published a final rule announcing the federal rescheduling of hydrocodone-combination products (HCPs) from Schedule III to Schedule II, which went into effect on October 6 2014.[9] Additionally, two new single-agent extended-release (ER) hydrocodone products were recently approved by the Food and Drug Administration (FDA): Zohydro™ ER and Hysingla™ ER, in October 2013 and November 2014, respectively. These developments have been preceded by several years of debate, public and professional consultation, and split opinions due to the increasing number of safety issues associated with opioids balanced with the need for access to effective pain management. An understanding of this history is key to promoting future improvements in the safe use of opioids. Therefore, the objective of this commentary is to examine recent regulatory/policy developments regarding opioid safety in the USA, with a special focus on hydrocodone and opportunities for improving the future safe use of these medications.

Discussion

Recent regulation/guidance aimed at opioid safety

Class-wide, opioids have been the subject of several key policy developments which have occurred in response to the increasing prevalence of opioid-related adverse events (for the purposes of this text, including misuse, abuse, addiction, overdose and death). Recent actions by the FDA have focused on two areas: ER/long-acting (LA) products and abuse-deterrent formulations.

ER/LA opioids

Starting in 2009 in response to public inquiries, the FDA consulted with several key stakeholders (patient advocacy groups, prescribers, pharmacists and insurance companies) regarding the need for an enhanced safety program for ER/LA opioids. As these products generally contain larger doses in a single tablet released over an eight to 24 h period, they have an increased attractiveness and higher potential for adverse events. Accordingly, in July 2012, the FDA introduced a risk evaluation and mitigation strategy (REMS) for ER/LA opioid products.[10] Under the new program, sponsors of included products were required to make available (through independent providers, but funded by industry) educational programs for over 320,000 DEA-registered prescribers focusing on patient assessment, initiation, modification, monitoring or discontinuation of therapy, appropriate patient counseling and how to recognize potential abuse, misuse or addiction.[10] Patients are required to be provided with an updated medication guide with each prescription as a part of the program.[10] The overall focus of this enhanced regulation was to improve education, in concert with the first objective in the White House's policy action plan, entitled "*Epidemic: Responding to America's prescription drug abuse crisis*", released in 2011.[11] It is important to highlight that while updated medication guides are mandated to be given to patients with each prescription, the new educational training is completely voluntary, although prescribers are "strongly encouraged to successfully complete a REMS-compliant program [and] … if this national problem [abuse and misuse of prescription drugs] is not addressed, additional steps may need to be taken to restrict the use of these drugs."[12]

In September 2013, the FDA further introduced a set of regulatory measures for ER/LA opioids instituting labeling changes and mandating new post-marketing study requirements.[13] Aimed at the

further decreasing the incidence of adverse events associated with these products, the labeling changes developed new and standardized language class-wide. Most importantly, the indication section was updated to reflect that ER/LA opioids should only be used when alternative treatments have not been successful, and not for as-needed pain relief.[13] Additionally, boxed warnings regarding the risk of neonatal opioid withdrawal syndrome (NOWS) after chronic maternal use and the generalized but serious risks of opioid-related adverse events have also been added.[13] For post-marketing requirements, the FDA has requested the manufacturers of targeted products to perform several analyses (with mandated reporting timelines ranging from 2015 to 2018), including (1) studies quantifying and describing the incidence of opioid-related adverse events, (2) development and validation of measures to inform these studies, (3) validation of coded medical terminologies used to identify these events, (4) studies to define and validate "doctor/pharmacy shopping" as outcomes indicative of these events, and (5) studies to estimate the long-term risk of hyperalgesia with the use of ER/LA opioids.[13] These post-marketing studies are aimed toward a long-term goal of enhancing opioid safety through improved data transparency surrounding risks, but may be considered by some to be merely peripheral moves in fighting the opioid epidemic.

Abuse-deterrent formulations

The concept of abuse-deterrent formulations came to light in recent years primarily through the case of Oxycontin®. The product, which was originally approved in 1995 with no abuse-deterrent features, accumulated reports of manipulation of the controlled release technology and resulting abuse. The manufacturer (Purdue Pharma L.P.) re-formulated the product and received new FDA approval in 2010, at which point they voluntarily ceased production of the original product. The new formulation is bioequivalent to the original product but is resistant to crushing, breaking and chewing and forms a viscous hydrogel substance upon dissolution attempts preparatory to injection.[14]

In January 2013, the FDA released a draft document entitled "*Guidance for Industry: abuse-deterrent opioids – evaluation and labeling*" which details the agency's recommendations regarding opioid formulations aimed to reduce the potential for abuse.[15] The document discusses five general categories of abuse-deterrent formulations, including physical/chemical barriers (resistance to extraction of the opioid or alteration of the dosage form), combination of an agonist/antagonist (to interfere with the opioid effects upon product manipulation), aversion techniques (unpleasant effects upon product manipulation), alternative delivery systems with less abuse potential (e.g. depot injectable), and pro-drugs (which lack of opioid activity until gastrointestinal transformation).[15] The bulk of the guidance document relates to the composition of pre- and post-marketing studies that determine whether a formulation in question has established successful abuse deterrence, and how the supporting evidence should translate into claims discussed on the product labeling. Four tiers of labeling are available:[15]

- Tier 1: The product is formulated with physicochemical barriers to abuse
- Tier 2: The product is expected to reduce/block effect of the opioid when manipulated
- Tier 3: The product is expected to result in a meaningful reduction in abuse
- Tier 4: The product has demonstrated reduced abuse potential in the community

These new labeling recommendations have been developed to standardize classifications of abuse-deterrence evidence and to accurately portray the data supporting manufacturer claims. It should be emphasized that 'abuse-deterrent' does not mean 'abuse-proof,' and that FDA guidance and labeling is explicit on this point. At current time, limited data is available for any formulation to substantiate Tier 4 claims, but as abuse-deterrent technology advances, there is potential for this demonstration in the future, and now a mechanism for this achievement to be accurately reflected in product labeling.

It is also important to note that the use of abuse-deterrent formulations are not currently mandated by the FDA and that this recent guidance simply describes "the Agency's current thinking … and should be viewed only as recommendations."[15] Moving forward, newly introduced generic versions of branded abuse-deterrent products will be required to adopt the formulations as a function of equivalency; in the case of Oxycontin®, this prevented introduction of generic versions to the market after the new drug application (NDA) for the original formulation (on which the abbreviated NDAs were based) was pulled in preference of the re-formulated product.[16] The use of abuse-deterrent formulations have been criticized as a barrier to generic

entry to the market. Hence, consensus on how these technologies should be utilized and incorporated into the wider opioid market remains debated; in fact, this recently prompted an FDA public hearing held in October 2014 to examine the issue, of which outcomes are still unclear.[17]

Zohydro™ ER and Hysingla™ ER

In October 2013, the first single-agent ER hydrocodone product was approved by the FDA, named Zohydro™ ER and developed by Zogenix, Inc.[18] The product is taken twice daily and labeled for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate; this labeling is the first new product approved in accordance with the new requirements instituted by the FDA in 2013.[18] The approval of Zohydro™ ER marked an important transition in the hydrocodone market; whereas previously available products were solely available in combination with acetaminophen or ibuprofen and had limited utility in the treatment of chronic pain, a single-agent ER formulation leveled hydrocodone with other available oral ER/LA opioids, such as Oxycontin® (containing oxycodone), Dolophine®/Methadose™ (methadone), MS Contin®, Avinza®, Kadian® (morphine), Opana® ER (oxymorphone), Nucynta® ER (tapentadol), Exalgo® (hydromorphone), Embeda® (morphine/naltrexone) and Targiniq™ ER (oxycodone/naloxone).

The approval of Zohydro™ ER was met with significant coverage in professional and popular media, viewed by many as contrary to recent efforts with regard to abuse deterrence and promoting safety among ER/LA formulations. Further to this, an internal FDA scientific panel (Anesthetic and Analgesic Drug Products Advisory Committee) had voted 11-2 with 1 abstention against approval of the application, citing a lack of an abuse-deterrent formulation and the need for additional REMS measures (above requirements already in place) to support an appropriate risk–benefit profile.[19] Despite this internal dissent, the application was approved and subsequently met with legislative action, including correspondence from 29 state attorneys general calling for a revocation of the decision or a revised abuse-deterrent formulation,[20] bill introduction in both the Senate (S. 2134) and House (H.R. 4241) asking for market withdrawal,[21] and a legal battle between Massachusetts Gov. Deval Patrick and Zogenix, Inc. after the governor attempted to declare a public health emergency and ban the medication within the state.[22] However, the manufacturer of Zohydro™ ER emphasizes that the product fills a clear need in the market for safe, around-the-clock hydrocodone treatment without the risk for acetaminophen overdose, and that the majority of currently marketed opioid products lack labeling for abuse-deterrent properties, putting Zohydro™ ER on par with other marketed products.[23]

In November 2014, the FDA approved Hysingla™ ER, another ER hydrocodone product, for the same indication as Zohydro™ ER.[24] Unlike its predecessor, the new product by Purdue Pharma L.P. is dosed once daily and employs physical/chemical barriers to reduce abuse potential through RESISTEC™, a proprietary ER solid oral dosage platform held by the company. Limited description on the technology is available but the company notes that the platform is a "unique combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions,"[25] likely in similar fashion to the currently marked formulation of Oxycontin® by the manufacturer.

Both of these new products are subject to the previously discussed regulatory requirements on ER/LA opioids, including REMS. Additionally, Hysingla™ ER is the fourth product released under the new tiered labeling recommendations for abuse-deterrent formulations, after Oxycontin®, Targiniq™ ER and Embeda® At current time, the future of Zohydro™ ER is uncertain as it will encounter direct competition from Hysingla™ ER, which has both enhanced safety features and a preferable dosing schedule. In response to this competition and the significant conversation regarding the product, Zogenix, Inc has contracted with Altus Pharmaceuticals to reformulate Zohydro™ ER with abuse-deterrent features; however, the non-deterrent product remains marketed in the interim.[26]

Rescheduling of hydrocodone-combination products

The Controlled Substances Act (CSA) of 1970 introduced federal policy regarding controlled substances and was the originator of the five-schedule classification used today to classify these substances according to their medical use and potential for abuse/dependence. While hydrocodone as a single entity was listed under Schedule

II, hydrocodone with limited amounts of an isoquinoline alkaloid of opium or one or more therapeutically active nonnarcotic ingredients was listed in Schedule III; this applied specifically to products with not more than 15 mg hydrocodone per dosage unit, which up until recently included all marketed hydrocodone formulations available in the USA.[27] As the first approved single entity hydrocodone products, both Zohydro™ ER and Hysingla™ ER have been approved under Schedule II, having caused a rift in the classification scheme for the first time since its inception. The original motivation for splitting hydrocodone over two schedules was a presumption of reduced abuse potential for lower doses of the medication in combination with nonnarcotic additives such as acetaminophen.

Movement to re-classify HCPs into Schedule II began as far back as the late 1990s with a physician petition. After several iterations of evaluation between the Department of Health and Human Services and the DEA between 2004 and 2009, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed in 2012 by President Obama, which included a directive to obtain public advice and stakeholder input on the topic, which occurred in January 2013 at a meeting held by the FDA Drug Safety and Risk Management Advisory Committee.[27] After two days of presentations and discussion, the committee voted 19-10 in favor of rescheduling HCPs into Schedule II of the CSA.[28] Upon this decision, joint correspondence was sent to the FDA commissioner from 18 patient and health professional groups urging reconsideration, including organizations such as National Community Pharmacists Association (NCPA) and American Academy of Pain Management (AAPM).[29] Significant public opinion was also received, with 577 comments on the public docket regarding the January 2013 FDA committee meeting,[30] and 652 comments on the DEA proposed rule released in February 2014 listed on *Regulations.gov*.[31] An analysis by NCPA in 2013 noted that among 457 public comments available at the time (regarding the FDA meeting docket), over 80% of comments expressed dissent with the proposed rescheduling.[32] However, a later analysis of 573 comments by the DEA regarding the DEA proposed rule docket found support (or support with qualification) at 52%, opposition at 41% and no definitive position at 7% of comments.[9] Support levels ranged 74% among the general public, 56% among physicians, 40% among pharmacists/pharmacy students and 9% among ultimate users.[9] With the publishing of the final rule in August 2014, the DEA estimated that approximately 376,189 entities would be affected by the rescheduling, including 50 manufacturers, 4 exporters, 683 distributors, 50,774 pharmacies, and 314,840 practitioners/mid-level practitioners/hospitals/clinics.[9] Among these, it was estimated that only 55 small entities (0.015%) would experience 'significant economic impact' that would incur costs of greater than 1% of annual revenue as a result of the rescheduling.[9]

While the rescheduling of HCPs was officially effective on October 6, 2014, the DEA final rule did allow for a phased provision of existing HCP prescriptions, where authorized refills could be dispensed for prescriptions written prior to the effective date, as long as dispensing occurred before April 8, 2015.[9] A response from representative pharmacy organizations noted concern with the logistics of transitioning computerized ordering systems and physical storage requirements, as well as the short time period in which to make said changes (10 months from the proposed rule and 2 months from the final rule).[33] At current time, the transition anecdotally appears to have encountered less logistic difficulty than was originally anticipated, although the effect on patient access remains to be seen.

The future of opioid safety

Recent efforts to improve opioid safety have focused on three main areas: education/information, innovation and regulation. There still remain several unanswered questions, primarily pertaining to the follow-up outcomes resulting from these efforts. A key question stemming from the introduction of Zohydro™ ER and Hysingla™ ER is whether abuse-deterrent formulations should be required for ER/LA opioids, and whether this should extend to both new and previously marketed products. There is limited evidence proving the beneficial effect of these formulations on abuse in practice, making justification (particularly with regards to generic market entry) for expensive formulation technology across all products difficult to recommend at this time; in fact, there is emerging concern that these formulations may inadvertently contribute to a shift in abuse toward illicit substances such as heroin, a point that requires further investigation.[34,35] Additionally, the FDA draft guidance on abuse-deterrent formulations highlights several unanswered research questions; most importantly this includes clarifying the links between pharmacokinetic properties of opioid

formulations and the results of clinical abuse studies, and how these translate to actual rates of abuse in the community.[15] The new REMS program for ER/LA opioids makes training available to prescribers, but as this is voluntary, the actual uptake and impact of this education will need to be examined to identify measurable success for continuing the effort; quantifying uptake has indeed been mandated by the FDA, with a goal of 60% of DEA-registered prescribers in the first 3 years. The host of post-marketing studies that are being planned to assess various safety aspects of ER/LA opioids are ongoing; how these data will feed into future safety remains unknown at current time, but an expected result is more standardized methodology to understand and identify abuse in surveillance. Building upon this work will be key to produce any useful outcome. The last critical area of concern is whether the rescheduling of HCPs will have a discernible effect on abuse, or whether it will limit access for patients seeking treatment for legitimate pain. Concerns noted throughout the discussion of the rescheduling included increases cost/time burden for both patients and physicians to obtain HCP prescriptions and an insufficient number of primary care physicians nationally to meet these needs.[28,33] Economic and resource analyses will be required to monitor the downstream effect upon the health care system, or if and how clinicians alter their prescribing habits in response to regulation.

The key message regarding recent regulation/policy is that there is significant work left to be done in the fight against opioid-related harms. Additional infrastructure needs to combat prescription drug abuse outlined in the White House's action plan include (but are not limited to) expansion of prescription drug monitoring programs (PDMPs), increased use of technology (analytic and clinical decision support tools) within pain treatment, implementation of surveillance to identify high-risk prescribing and improved integration of drug abuse treatment within the primary care system.[11] A key component to success in combating opioid safety through these types of changes lies in the need for a concerted national effort; the diversified and often fragmented nature of the USA healthcare system may be a key reason why opioid use has become an epidemic, particularly when compared to trends in countries such as the United Kingdom.[36] Successfully combating it will require national leadership and implementation across multiple sectors, and a continuing dedication to this longitudinal effort.

Conclusion

The use and availability of opioids is a delicate balance between the provision of effective pain management and protection against the harms associated with use/misuse. This has been highlighted through a number of recent policies/regulations implemented in effort to enhance the safe use of these medications, particularly with regard to hydrocodone. Whether these measures will ultimately lead to safer use at current time is unknown, but greatly warrants continuing study and a concerted effort among health care professionals, researchers and regulatory agencies to work towards the goal of safe and effective pain treatment.

Acknowledgment

The author thanks Peter P. Cohron, B.S.Pharm., J.D. for his valuable insight on the topic.

References

1. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Available at: http://www.iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx. Accessed 06.02.15.
2. Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet* 1999;354(9186):1248–1252. http://dx.doi.org/10.1016/S0140-6736(99)03057-3.
3. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *J Am Med Assoc* 1998; 280(2):147–151. http://dx.doi.org/10.1001/jama.280.2.147.
4. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of non-malignant pain in the United States, 2000–2010. *Med Care* 2013; 51:870–878. http://dx.doi.org/10.1097/MLR.0b013e3182a95d86.
5. Centers for Disease Control and Prevention (CDC). *Prescription Painkiller Overdoses in the US*. Available from: http://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html. Accessed 06.02.15.
6. IMS Health. *Top 25 Medicines by Dispensed Prescriptions (U.S.)*. Available from: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/2012_U.S/Top_25_Medicines_Dispensed_Prescriptions_U.S..pdf. Accessed 06.02.15.
7. Steinman MA, Komaiko KD, Fung KZ, Ritchie CS. Use of opioids and other analgesics by older adults in the United States, 1999-2010. *Pain Med*; 2014 Oct 28. Epub ahead of print http://dx.doi.org/10.1111/pme.12613.

8. Substance Abuse and Mental Health Services Administration. *Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-related Emergency Department Visits*. Available at: http://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.pdf. Accessed 06.02.15.
9. Drug Enforcement Administration. Schedules of controlled substances: rescheduling of hydrocodone combination products from schedule III to schedule II. 21 CFR Part 1308 [Docket No. DEA-389] Final rule. *Fed Regist* 2014;79(163):49661–49682.
10. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) for Extended-release and Long-acting opioids. Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. Accessed 06.02.15.
11. Executive Office of the President of the United States. *Epidemic: Responding to America's Prescription Drug Abuse Crisis*. Available at: http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf. Accessed 06.02.15.
12. ER/LA Opioid Analgesics REMS Program Companies. *Frequently Asked Questions*. Available at: http://www.er-la-opioidrems.com/IwgUI/rems/faq.action#prescriber. Accessed 06.02.15.
13. Food and Drug Administration. New Safety Measures Announced for Extended-release and Long-acting Opioids. Available at: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm363722.htm. Accessed 06.02.15.
14. Drug Topics. *FDA Nixes Generic OxyContin, Approves Abuse-deterrent Labeling for Reformulated OxyContin*. Available at: http://drugtopics.modernmedicine.com/drug-topics/news/drug-topics/hse-professionalpractice/fda-nixes-generic-oxycontin-approves-abuse-de?page=full. Accessed 06.02.15.
15. Food and Drug Administration. *Guidance for Industry: Abuse-deterrent Opioids – Evaluation and Labeling*. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed 06.02.15.
16. Food and Drug Administration. Determination that the Oxycontin (oxycodone hydrochloride) products covered by New Drug Application 20-553 were withdrawn from sale for reasons of safety or effectiveness. [Docket Nos. FDA-2001-P-0238, FDA-2010-P-0526, FDA-2010-P-0540, FDA-2011-P-0473]. *Fed Regist* 2013;78(75):23273–23275.
17. Food and Drug Administration. *Development and Regulation of Abuse-deterrent Opioid Medications; Public Meeting*. Available from: http://www.fda.gov/Drugs/NewsEvents/ucm408607.htm. Accessed 06.02.15.
18. Food and Drug Administration. *FDA Approves Extended-release Single-entity Hydrocodone Product*. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm372287.htm. Accessed 06.02.15.
19. Food and Drug Administration. *Summary Minutes of Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee*. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM336475.pdf. Accessed 06.02.15.
20. State Attorneys General. *A Communication from the Chief Legal Officers*. Available at: http://www.oag.state.md.us/Press/Zohydro.pdf. Accessed 06.02.15.
21. McCarthy M. US bill would force FDA to withdraw approval of new pain drug Zohydro. *BMJ* 2014;348:g2195. http://dx.doi.org/10.1136/bmj.g2195.
22. Medscape. *US District Court Overturns Zohydro Ban in Massachusetts*. Available at: http://www.medscape.com/viewarticle/823715. Accessed 06.02.15.
23. Zogenix. *Let's Get the Facts Straight about Zohydro™ ER (Hydrocodone Bitartrate) Extended-release Capsules, CII*. Available at: http://www.zogenix.com/content/viewpoints/zohydro-facts-important-need.php. Accessed 06.02.15.
24. Food and Drug Administration. *FDA Approves Extended-release, Single-entity Hydrocodone Project with Abuse-deterrent Properties*. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm423977.htm. Accessed 06.02.15.
25. Purdue Pharma. *Purdue Pharma L.P. Received FDA Approval for Hysingla™ ER (Hydrocodone Bitartrate) Extended-release Tables CII, a Once-daily Opioid Analgesic Formulated with Abuse-deterrent Properties*. Available at: http://www.purduepharma.com/news-media/2014/11/purdue-pharma-l-p-receives-fdaapproval-for-hysinglatm-er-hydrocodone-bitartrate-extended-release-tablets-cii-a-once-dailyopioid-analgesic-formulated-with-abuse-deterrent-properties/. Accessed 06.02.15.
26. The Pharma Letter. *Altus signs $4 Million Agreement with Zogenix to License Zohydro ER*. Available at: http://www.thepharmaletter.com/article/altus-signs-4-million-agreement-with-zogenix-to-license-zohydro-er. Accessed 06.02.15.
27. 21 US Code § 812.
28. Food and Drug Administration. *Summary Minutes of the Drug Safety and Risk Management Advisory Committee Meeting*. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/Committees%20MeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM344674.pdf. Accessed 06.02.15.
29. *Letter to FDA Commissioner of Food and Drugs. Docket No. FDA-2012-n-0548*. Available at: http://www.nacds.org/pdfs/pr/2013/PCF_FDA_hydro.pdf. Accessed 06.02.15.
30. Regulations.gov. *Drug Safety and Risk Management Advisory Committee Notice of Meeting*. Available at: http://www.regulations.gov/#!documentDetail;D=FDA-2012-N-0548-0086. Accessed 06.02.15.

31. Regulations.gov. *Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II*. Available at: http://www.regulations.gov/#!documentDetail;D=DEA-2014-0005-0004. Accessed 06.02.15.
32. *Letter to the DEA. Docket No. DEA-389; Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II; Notice of Proposed Rulemaking*. Available at: https://www.ascp.com/sites/default/files/NCPA%20Comments%20to%20DEA%20on%20Rescheduling.pdf. Accessed 06.02.15.
33. American Pharmacists Association. *Hydrocodone Moved to Schedule II in DEA Final Rule*. Available at: http://www.pharmacist.com/hydrocodone-moved-schedule-ii-dea-final-rule. Accessed 06.02.15.
34. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. *N Engl J Med* 2012;367(2):187–189. http://dx.doi.org/10.1056/NEJMc1204141.
35. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med* 2015;372(3):241–248. http://dx.doi.org/10.1056/NEJMsa1406143.
36. Weisberg DF, Becker WC, Fiellin DA, Stannard C. Prescription opioid misuse in the United States and the United Kingdom: cautionary lessons. *Int J Drug Policy* 2014;25(6):1124–1130. http://dx.doi.org/10.1016/j.drugpo.2014.07.009.