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February 11, 2014

Via Electronic Submission

Division of Dockets Management
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

Dear Sir/Madam:

The undersigned, on behalf of Purdue Pharma L.P. ("Purdue"), submit this Citizen Petition pursuant to 21 C.F.R. §§ 10.30, 201.56, 201.57, and Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355. Purdue is the holder of New Drug Application ("NDA") # 022272 for OxyContin® (oxycodone hydrochloride controlled-release) Tablets, a twice-a-day oral formulation of oxycodone; NDA # 021306 for Butrans® (Buprenorphine) Transdermal System, a once weekly transdermal formulation of buprenorphine; NDA # 019516 for MS Contin® (morphine sulfate controlled-release) Tablets, a two to three times a day oral formulation of morphine; NDA # 019892 for Dilaudid® (hydromorphone HCl) tablets and oral solution, immediate-release oral formulations of hydromorphone; and NDA # 019034 for Dilaudid® (hydromorphone HCl), an injectable formulation of hydromorphone.

On September 10, 2013 FDA announced that it was invoking its authority under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to request, and intended ultimately to require, class-wide safety labeling changes for all extended-release and long-acting ("ER/LA") opioid medications intended to treat pain. These requirements are based on cited risks of misuse, abuse, hyperalgesia, addiction, overdose, death, and neonatal opioid withdrawal syndrome. The Agency also announced that it was requiring

companies that manufacture ER/LA opioid analgesics to conduct postmarketing studies and clinical trials in order to further assess the known serious risks associated with opioid use and misuse. Purdue's OxyContin, Butrans, and MS Contin products are subject to these requirements, but the Dilaudid products are not.

FDA stated its intention to apply these requirements to ER/LA opioid analgesics and not to immediate-release ("IR") opioid analgesics because of what it asserts are disproportionate safety concerns associated with ER/LA opioid analgesics compared to IR opioid analgesics, specifically including the risks of misuse and abuse. FDA added that higher doses of many ER/LA opioids compared to IR opioids may make ER/LA products more desirable for abuse and increases the risk of a fatal outcome in the event of an overdose. The Agency further stated that additional changes to the labeling for the other opioids will be made as needed.

Any assessment of the relative risks between ER/LA and IR products must take into account that IR opioid analgesics contain the same active ingredients as ER/LA opioid analgesics. These active ingredients cause the effects that can lead to the various adverse consequences identified by the Agency. Data presented below indicate that IR opioid analgesics are associated with the same potential adverse consequences as ER/LA opioid analgesics, including the cited risks of abuse, misuse, and overdose, with comparable if not higher incidence. The risks and corresponding public health ramifications associated with IR opioid analgesics therefore should be addressed in a similar fashion, with similar label changes mandated.

Action Requested

Purdue requests that the Food and Drug Administration:

1. Promptly exercise its authority under Section 505(o) of the Federal Food, Drug and Cosmetic Act to seek and, if necessary, impose safety labeling changes on immediate-release opioid analgesics that parallel the final safety labeling changes resulting from completion of the 505(o) procedures initiated on September 10, 2013 for extended-release and long-acting opioid analgesics.

2. Assure that the indications for use and other safety labeling information for immediate-release and extended-release and long-acting opioid analgesics convey the same warnings and precautions regarding the risks of opioid use and misuse.

Statement of Grounds

I. Factual and Procedural Background

A. FDA Action Impacting Extended-Release And Long-Acting Opioid Analgesic Drug Products

Invoking its authority under Section 505(o) of the Federal Food, Drug and Cosmetic Act, the FDA recently announced proposed class-wide safety labeling changes and new postmarket study requirements for all ER/LA opioid medications intended to treat pain. The impetus for the action is the "crisis of misuse, abuse, addiction, overdose, and death from these potent drugs."[1]

The labeling changes are intended to communicate more clearly to prescribers the risks associated with ER/LA opioid analgesics, encouraging a thoughtful, careful approach to patient selection, and more appropriate prescribing, monitoring, and patient counseling practices involving these drugs.[2]

The postmarket study requirements are intended to generate data to assess further the known and potential serious risks of opioid misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death.[3]

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[1] Press Release, *FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics*, *New boxed warning to include neonatal opioid withdrawal syndrome* (Sept. 10, 2013), available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm (hereinafter "FDA Press Release"); Letter to ER/LA opioid sponsors (Sept. 10, 2013), available at: http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf (hereinafter "Sponsor Letter").

[2] FDA Response to Citizen Petition Docketed as FDA-2012-P-0818 (Sept. 10, 2013) at pp. 6, 9, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0818-0793; FDA Press Release, FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics, *New boxed warning to include neonatal opioid withdrawal syndrome* (Sept. 10, 2013), available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm (hereinafter "FDA Press Release").

[3] FDA Press Release.

B. FDA Rationale For Omitting Immediate-Release Opioid Analgesics From The Class Labeling Changes Initiated on September 10, 2013

FDA stated that the label changes and postmarket study requirements announced on September 10, 2013 were not being extended to IR opioid analgesics because ER/LA opioid analgesics have a "disproportionate" risk of abuse and overdose.[4] In its formal letter to sponsors invoking Section 505(o) of the act, FDA stated:

> ER/LA opioids are the focus of the safety labeling changes because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids. For example, data show that the risk for misuse and abuse is greater for ER/LA opioids. *See* Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm220950.pdf). Further, because they are intended to release the drug over a longer period of time, many ER/LA opioids contain higher doses of opioids compared to IR opioids or opioid non-opioid combinations. This may make certain ER/LA opioids more desirable in the eyes of opioid abusers and addicts, and increases the risk of a fatal outcome in the event of an overdose."[5]

In response to questions about the impact on immediate-release opioids, the Agency indicated that while the announced actions impacted only ER/LA opioids, changes to other product labels, including those of immediate-release opioids, would be implemented as needed.[6]

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[4] FDA Stakeholders Teleconference Briefing, Opioid Labeling and PMR, September 10, 2013, 3 p.m. EST. *See also* Health & Human Services Media Conference Call, September 10, 2013, 12:45 p.m. EST.

[5] Sponsor Letter at p. 2, n.6.

[6] FDA Stakeholders Teleconference Briefing, Opioid Labeling and PMR, September 10, 2013, 3 p.m. EST. *See also* Health & Human Services Media Conference Call, September 10, 2013, 12:45 p.m. EST.

II. Argument

Contrary to the Agency's statements, providing different warnings and related safety label information based on perceived disproportionate safety concerns impacting ER/LA and IR opioid analgesics is both contrary to the public health and inconsistent with available data evaluating the respective risks of these medications. As described below, data from four different reliable sources (a commercial insurance claims database, poison centers, substance-use-disorder treatment centers, and a national prescription database) indicate that IR opioid analgesics are associated with the same potential adverse consequences as ER/LA opioid analgesics generally, including the cited risks of abuse, misuse, and overdose, with comparable incidences and public health ramifications. In addition, the analysis cited by FDA as support for its contrary conclusion provides a factually inaccurate representation of the DAWN data which, when accurately presented, are consistent with the insurance claims, poison center, substance-use-disorder treatment center, and national prescription data described below. Accordingly, FDA should extend the safety labeling initiative on ER/LA opioid analgesics announced September 10, 2013 to include IR opioid analgesics.

A. Data Indicate That The Potential Adverse Consquences Associated With ER/LA Opioid Analgesics Are Comparable To Those Associated With IR Opioid Analgesics

Data from four separate databases are useful in evaluating the association between opioid formulation and specific risks discussed by FDA in its September 10, 2013 action. Analyses of data from these sources were performed by Paul M. Coplan, Howard D. Chilcoat, Angela M. DeVeaugh-Geiss, and Hrishikesh Kale of the Department of Risk Management and Epidemiology, Purdue Pharma L.P. Each of these analyses indicates that the risks associated with ER/LA opioids and IR opioids are comparable.

- First, data from a commercial insurance claims database indicate that the risk of opioid overdose is similar among patients prescribed IR opioid analgesics alone as compared to ER opioid analgesics alone, and that patients prescribed both ER and IR opioid analgesics together have a several-fold higher risk of overdose than ER alone or IR alone.
- Second, data from the National Poison Data System indicate that the number of calls to poison centers in situations involving abuse is more than three times greater for IR single-entity oxycodone than for ER oxycodone, the prescription-adjusted rates of abuse are also significantly greater for IR single-entity oxycodone than for ER oxycodone, and abuse rates per milligram of oxycodone dispensed for IR oxycodone products are double the abuse rate of ER oxycodone.

- Third, data from the NAVIPPRO substance-use-disorder treatment network indicate that, when adjusted only for the number of prescriptions, ER oxycodone has a higher rate of abuse than IR single-entity oxycodone products; however, that conclusion does not hold after adjustments for average dosage strength and average days of therapy per prescription, which better account for drug availability.
- Fourth, the proportion of individuals prescribed IR oxycodone single-entity products who appear to be doctor-shopping for these products is three times higher than the proportion doctor-shopping for ER oxycodone or ER oxymorphone.

In addition, in 2010, a group of experts within CDER reviewed data on abuse of various categories of opioid analgesics and determined that available data do not support the conclusion that ER/LA opioid analgesics pose a higher risk than IR opioid analgesics. The more recent data provided here underscore the validity of that conclusion.

1. MarketScan Data Indicate That The Risk Of Opioid Overdose Is Similar Among Patients Prescribed IR Opioid Analgesics And Patients Prescribed ER Opioid Analgesics

Data from a cohort covered by the MarketScan® Commercial Claims and Encounter dataset enable an evaluation of the association between opioid analgesic formulations (IR, ER, or the combination of the two) and overdose.[7] The MarketScan Commercial dataset represents a United States employed population that is under 65 years of age (and their dependents) and contains eligibility, pharmacy claims, and medical claims data reflecting healthcare utilization of individuals covered by a variety of commercial health plans around the country.[8] Medical claims or encounter data are collected from all available health care sites (inpatient, outpatient, long-term care), for

[7] The MarketScan® databases are maintained by Truven Health Analytics, a private company providing data, technology, and analytic expertise to a wide range of clients including hospitals, clinicians, employers, health plans, state and federal government, and life sciences researchers. The MarketScan® Commercial Claims and Encounter dataset is widely used by researchers. *See, e.g.,* Lin, J. *et al., Incremental health care resource utilization and economic burden of venous thromboembolism recurrence from a U.S. payor perspective,* J. Manag. Care Pharm, 2014 Feb;20(2):174-86; Baker, C.L., *et al., Risk assessment of readmissions following an initial COPD-related hospitalization,* Int. J. Chron Pulmon Dis. 2013;8:551-9. A list of recent published studies using various of the MarketScan databases is available in Truven Health Analytics' White Paper, *Health Research Data for the Real World: the MarketScan Databases* (July 2011), at pp. 21-29, available at: http://truvenhealth.com/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL.pdf.

[8] Healthcare for these individuals is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans, including preferred and exclusive provider organizations (PPOs and EPOs), point of service plans, indemnity plans, health maintenance organizations (HMOs), and consumer-directed health plans.

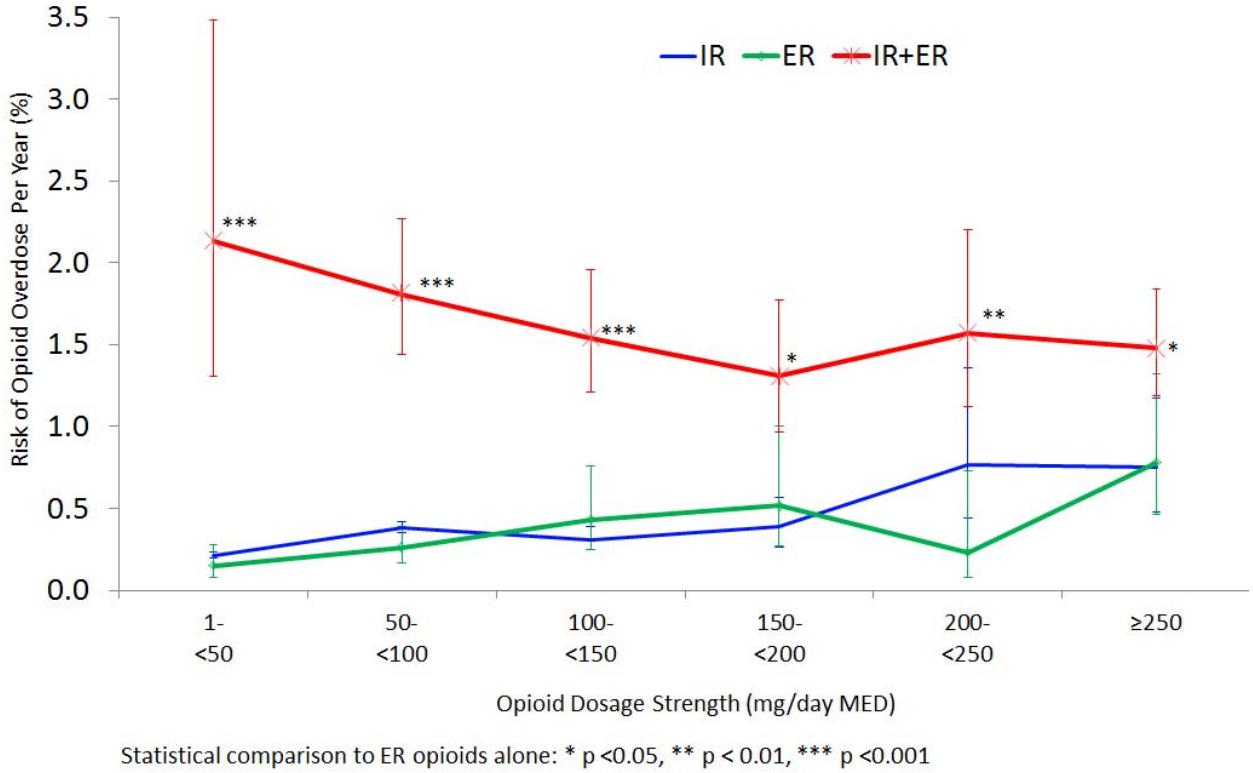
virtually all types of services provided, including specialty, preventive and office-based treatments. Pharmacy data include National Drug Code, date of service, and days' supply, and are linkable to the Red Book, which includes information such as generic drug name and dosage forms. Claims are linkable based on unique patient identification numbers. Individual level, de-identified data were used for all analyses. Of the more than 90 million individuals in this dataset (1Q2008-1Q2012), 9.6 million patients 18-64 years of age had a new opioid analgesic dispensed between July 2008 and March 2012.

Opioid overdose events were identified using the 965.00, 965.02, 965.09 ICD-9 opioid poisoning or overdose codes.[9] In this cohort, over half of the overdose cases had been prescribed an IR opioid analgesic in the 30-day period before the overdose event: 43.8% had been prescribed *only* an IR opioid analgesic, while 9.7% had been prescribed both IR and ER opioid analgesics. Only 2.2% of the overdose cases had been prescribed an ER opioid analgesic, but no IR opioid analgesic. A large proportion of overdose cases (44.3%) had no prescription for any opioid analgesic during the 30-day period preceding the overdose event. (Appendix 1). Even based on these unadjusted data, it is incontrovertible that IR opioids represent a significant overdose risk with important public health ramifications. Accordingly, these data alone indicate that IR opioid analgesic labels warrant modified indication statements, warnings, and precautions at least commensurate with those proposed by FDA for ER/LA opioid analgesic formulations.

To assess the risk of overdose in this cohort by formulation, risk of opioid overdose per year was calculated for patients prescribed IR opioid analgesics alone, ER opioid analgesics alone, or IR and ER opioid analgesics concomitantly. This analysis was stratified by dosage strength of opioid used, with daily morphine equivalent dose used to standardize dosage strength among different types of opioids. The results indicate that the risk of opioid overdose was similar for IR opioids alone and ER opioids alone (relative risk adjusted for dosage strength, age, sedative-hypnotic use, and psychiatric/substance abuse diagnoses = 0.90 (95% CI: 0.70-1.15)), but the concomitant use of IR and ER opioids was associated with a significantly higher overdose risk (adjusted relative risk = 3.60 (95% CI: 3.05-4.26)). As reflected in the graph below, the combination of prescriptions for IR opioid analgesics with prescriptions for ER opioid analgesics significantly increased unadjusted overdose risk at every daily-dose increment compared to ER opioid analgesics alone.

[9] A study to assess the use of ICD-9 codes, compared to medical chart review, to detect opioid overdoses, sponsored by Purdue at Kaiser Permanente, found that 965.xx ICD-9 codes had high positive predictive value in detecting opioid overdoses and none of the other ICD-9 codes yielded more than 1 or 2 opioid overdoses out of 1000 charts reviewed.

Incidence of Opioid Overdose by Prescribed Dose Stratified by Formulation (IR opioids alone, ER opioids alone, and IR and ER opioids together) in MarketScan Commercial Insurance Database (1Q2008 through 1Q2012)



Statistical comparison to ER opioids alone: * p <0.05, ** p < 0.01, *** p <0.001

Data from this cohort can also be used to assess the risk separately for each type of opioid analgesic drug formulation, as well as by opioid analgesic drug substance. The risk of overdose among patients prescribed IR oxycodone alone was 0.36, for ER oxycodone alone was 0.39 and for ER oxycodone used with any IR opioid concomitantly was 1.13 per 100 person years of opioid use. The incidence rate ratio comparing the risk of overdose for ER oxycodone plus IR opioids versus ER oxycodone alone was therefore 2.89 (95% CI = 1.81-4.60). In addition, the incidence rate ratio comparing the risk of overdose for ER morphine plus IR opioids versus ER morphine alone was 6.32 (95% CI 3.16-12.65). Across seven opioid drug substances, there was no statistically significant difference in the incidence rate of opioid overdose for IR opioids alone and ER opioids alone (0.26 versus 0.31 overdoses per 100 person years, IRR=1.19, 95% CI 0.94, 1.52). However, patients concomitantly prescribed ER opioids plus an IR opioid had a 5-fold higher risk than patients prescribed ER or IR opioids alone (unadjusted incidence rates are shown in Appendix 2, adjusted incidence rate ratios in Appendix 3).

These data indicate that the risk of opioid overdose diagnosed using ICD-9 965.00, 965.02, 965.09 (opioid poisoning or overdose) is similar among patients prescribed IR opioids alone as compared to ER opioids alone, but patients prescribed both ER and IR

opioid analgesics together have a several-fold higher risk of overdose than those prescribed either ER alone or IR alone.

2. Data from the National Poison Data System Indicate That Abuse Rates for IR Oxycodone Products Are Higher Than The Rate for ER Oxycodone

Regional Poison Centers are staffed twenty-four hours a day, seven days a week with trained healthcare professionals who field calls from consumers and healthcare practitioners. These Poison Centers gather data collected during the course of providing callers with specific exposure management recommendations.[10] These data also aid in evaluating the association between opioid formulation and adverse events associated with medical or nonmedical use of opioids.

Each poison center utilizes a nationally standardized data collection tool through which the reason for each exposure is coded. Exposures coded as intentional are further classified as suspected suicide, misuse, abuse, or unknown. Exposures coded as unintentional are further classified as unintentional-therapeutic error, unintentional-misuse, unintentional-general, or unintentional-unknown.[11] Calls to Poison Centers reporting that an individual was exposed to a product and seeking emergency advice or help, and documented in this way, are a proxy measure for adverse events associated with medical or nonmedical use of a product or drug class. The American Association of Poison Control Centers compiles data from all Poison Centers in the United States into a database known as the National Poison Data System ("NPDS").[12]

(a) The Numbers And Prescription-Adjusted Rates of Abuse And Other Exposures Reported To Poison Centers Are Greater For IR Oxycodone Than For ER Oxycodone

Using 2012 NPDS data, exposures for a category of products including oxycodone alone or in combination, but excluding combinations with acetaminophen or aspirin, were analyzed. This category included IR single-entity oxycodone, ER oxycodone, a relatively small number of IR oxycodone-ibuprofen combination products, as well as unknown

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[10] Background information on the methodology used to collect data on exposures reported to poison centers is available in Bronstein, Alvin C. *et al., 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report,* Clin. Tox. (2012), 50, 911-1164, at pp. 917-920, 1139, available at: https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2011_NPDS_Annual_Report.pdf.

[11] The standardized data collection tool includes additional categories, most of which are inapplicable to drug exposures (*e.g.,* "unintentional – bite/sting"). *See id.* at p. 926, Table 6A.

[12] *Id.* a p. 917.

formulations of oxycodone. ER oxycodone cases were extracted from this larger category to create an "OxyContin" category for purposes of analysis.[13] OxyContin exposures were compared with exposures to the remaining products, termed IR single-entity oxycodone, due to the small number of combination products included in this category, and the likelihood that the unknown category is mostly comprised of IR single-entity oxycodone, given the manner in which other oxycodone formulations are coded.

As reflected in the table below, the analysis of NPDS data for 2012 comparing exposure cases for OxyContin and IR single-entity oxycodone revealed that the exposure cases were significantly lower for OxyContin than for IR single-entity oxycodone for all exposure categories. The sheer number of adverse events associated with medical or nonmedical use of IR single-entity oxycodone documented in the NPDS database reflects the significant public health ramifications associated with these products. These unadjusted data alone indicate that IR opioid analgesic labels warrant modified indication statements, warnings, and precautions at least commensurate with those proposed by FDA for ER/LA opioid formulations.

The table below also presents exposure rates for OxyContin and IR single-entity oxycodone. Exposure rates per 100,000 population were significantly lower for ER oxycodone (OxyContin) than for IR single-entity oxycodone for all exposure categories. Prescription-adjusted rates (exposures per 10,000 prescriptions) were also significantly lower for ER oxycodone than for IR single-entity oxycodone, with the exception of unintentional-general errors and unintentional-therapeutic errors. For unintentional-general errors, the prescription-adjusted rate was lower for ER oxycodone (0.279 vs. 0.455) although the difference did not reach the threshold of significance ($p = 0.3696$). For unintentional-therapeutic errors (*i.e.,* mistakes in administration),[14] the prescription-adjusted rate was higher for ER than IR single-entity oxycodone (0.760 vs. 0.671, $p = 0.0247$).

[13] Generic versions of ER oxycodone were rare in this 2012 dataset because sale of generic ER oxycodone had largely stopped by January 2011.

[14] This category includes exposures resulting from an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance.

Comparison of Poison Center Rates for ER Oxycodone and IR Single-Entity Oxycodone in the National Poison Data System in 2012

Category/ Metric	OxyContin*	IR Single-entity Oxycodone*	Difference	P value**
Number of exposure cases				
Intentional abuse	273	997	-724	<.0001
Intentional misuse	132	434	-302	<.0001
Intentional suicide	485	2203	-1718	<.0001
Unintentional general	173	736	-563	0.0003
Unintentional misuse	10	36	-26	<.0001
Unintentional therapeutic errors	471	1087	-616	<.0001
Adverse reactions	73	347	-274	0.0186
Others	151	669	-518	<.0001
Total	***1768***	***6509***	***-4741***	***<.0001***
Exposures per 100,000 population				
Intentional abuse	0.087	0.319	-0.232	<.0001
Intentional misuse	0.042	0.139	-0.097	<.0001
Intentional suicide	0.155	0.705	-0.55	<.0001
Unintentional general	0.055	0.235	-0.18	0.0003
Unintentional misuse	0.003	0.012	-0.009	<.0001
Unintentional therapeutic errors	0.151	0.348	-0.197	<.0001
Adverse reactions	0.023	0.111	-0.088	0.0186
Others	0.048	0.214	-0.166	<.0001
Total	*0.566*	*2.082*	*-1.516*	*<.0001*
Exposures per 10,000 prescriptions* **				
Intentional abuse	0.440	0.616	-0.176	<.0001
Intentional misuse	0.213	0.268	-0.055	0.0207
Intentional suicide	0.783	1.361	-0.578	<.0001
Unintentional general	0.279	0.455	-0.176	0.3696
Unintentional misuse	0.016	0.022	-0.006	<.0001
Unintentional therapeutic errors	0.760	0.671	0.089	0.0247
Adverse reactions	0.118	0.214	-0.096	<.0001
Others	0.244	0.413	-0.169	<.0001
Total	***2.853***	***4.020***	***-1.167***	***<.0001***

*IR Single-Entity Oxycodone and OxyContin exposures were calculated as described in the text above.

** P value calculated using a Poisson regression model to measure difference between OxyContin and IR SE oxycodone rates

*** Prescriptions for IR single-entity oxycodone were used to calculate these rates for the "IR Single-entity Oxycodone" category, though, as described in the text, the category includes other types of oxycodone products.

(b) Abuse Rates For IR Single-Entity And Combination Oxycodone Products Are Higher Than The Rate For ER Oxycodone Using Exposures Reported To Poison Centers Adjusted By Milligrams Of Oxycodone Dispensed

Studies looking at prescription-adjusted abuse rates have focused on the number of prescriptions as a proxy for availability of a given prescription opioid analgesic in the community. While this approach is informative, it has certain limitations that must be considered in interpreting the findings. Among the limitations of this method is the fact that it treats each prescription as contributing equally to the amount of drug substance available for abuse. It does not, in other words, take into account that prescriptions are written and dispensed for different drug products of varying dosage strengths, for different daily dosages, and for varying numbers of intended days of therapy. As discussed further in section B.3. below, this observation is consistent with FDA's recent analysis of hydrocodone abuse, where the Office of Surveillance and Epidemiology and the Controlled Substances Staff concluded that a comparison of abuse potential should take into account any differences in (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage units per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications. These offices further determined that retail prescriptions do not adequately reflect drug availability because that measure does not account for differences in the number of dosage units per prescription or the average number of days of therapy. These offices determined that "total number of extended units dispensed," a measure which takes into account variability in days of therapy and dosage units per prescription, is a more refined estimate of drug availability for purposes of comparing abuse of hydrocodone products and the comparator oxycodone products, adjustment by which yielded a more accurate patient exposure based risk profile.[15]

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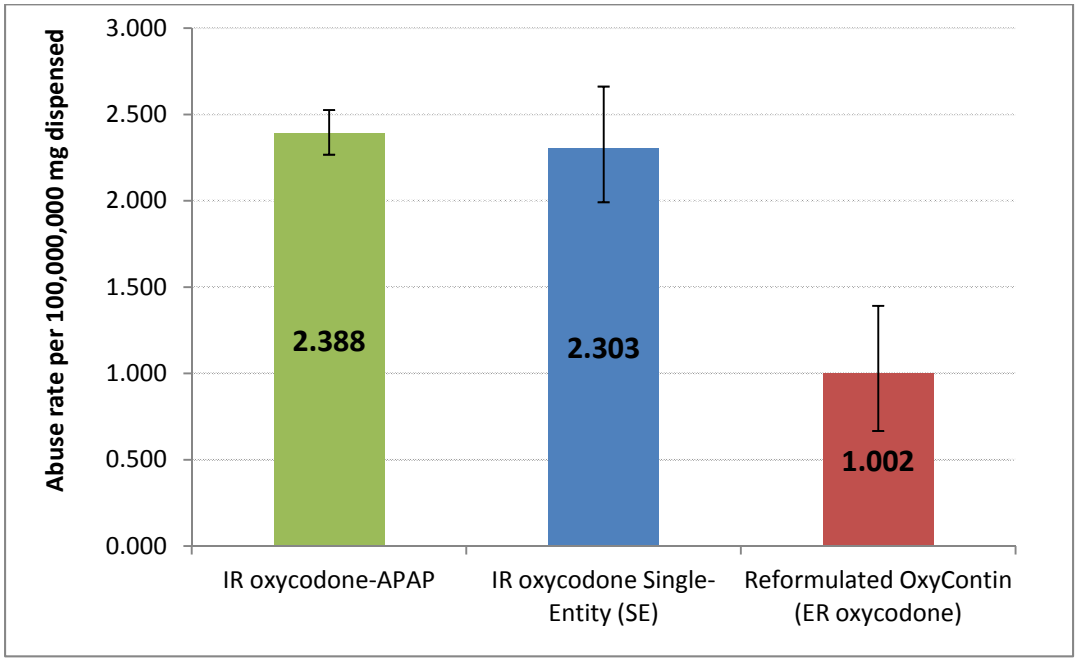
[15] *See* Memorandum to Michael Klein, Ph.D., Director, Controlled Substances Staff from Catherine Dormitzer, Ph.D., MPH, *et. al*, Division of Epidemiology, Office of Surveillance and Epidemiology, *Evaluation of the validity of the epidemiological methods and approaches that were used in the DEA's petition for rescheduling of hydrocodone combination products from Schedule III to II, from* FDA Briefing Document, Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting – January 24-25, 2013, at pp. 43-44, 49-56; *see also* Memorandum to Douglas Throckmorton, M.D., Deputy Director, CDER from Silvia Calderon, Ph.D., Team Leader, Pharmacology, Controlled Substances Staff, *Summary Review of the Controlled Substances Staff (CSS) Assessment of the Abuse of Hydrocodone Combination Products, From* FDA Briefing Document, Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting – January 24-25, 2013, at pp. 22-25, both available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM334276.pdf (Dr. Dormitzer's memorandum begins on page 41 of the linked pdf and Dr. Calderon's on page 6).

There are large differences in the average number of days and average daily dosage strength for different opioid analgesic medications. As reflected in Appendix 4, these differ substantially between different categories of oxycodone formulations.

The street price of drugs for abuse are generally priced in cost per milligram as a metric of relevance to abusers; therefore it is informative to assess abuse rates per milligrams of opioid dispensed when comparing the risk of abuse of IR and ER opioid analgesics. Using NPDS data from the third quarter of 2012 through the second quarter of 2013, exposures coded as intentional abuse of IR oxycodone combination products (over 99% acetaminophen-containing, but also including products containing aspirin), IR single-entity oxycodone products, and ER oxycodone products were analyzed.[16] Abuse rates per milligram of oxycodone dispensed were calculated and are shown in the figure below. These data indicate that the abuse rates for IR SE oxycodone and IR oxycodone combination products are at least twice as high as that for ER oxycodone (OxyContin). As reflected in the figure, the 95% confidence intervals do not overlap, indicating these differences are statistically significant.

Abuse rates per milligram of oxycodone dispensed (in millions) in the National Poison Data System, by categories of oxycodone formulations



[16] These latter two categories were derived in the same manner as described in Section II.A.2.(a) above, except that the relatively small number of exposure for IR oxycodone-ibuprofen combination products were omitted from the IR single-entity oxycodone category.

According to these results, when a measure of drug availability directly relevant to abusers is used (*i.e.*, adjustments milligram of opioid dispensed), IR oxycodone products, both single-entity and combination, have a rate of abuse twice that of ER oxycodone in the NPDS.

3. IR Oxycodone Combination Products Have A Higher Rate Of Abuse Than ER Oxycodone In The NAVIPPRO System After Adjustment For Average Dosage Strength And Average Days Of Therapy Per Prescription

Data from NAVIPPRO's ASI-MV substance-use-disorder treatment network were examined in order to evaluate the association between opioid formulation and abuse, using various measures of drug availability. Data for past 30-day abuse of five products – OxyContin, IR oxycodone combinations, IR oxycodone single-entity products, IR hydrocodone combinations, and IR oral hydromorphone products – between January 1, 2011 (1Q2011) and September 30, 2012 (3Q2012) were used in these analyses. Underlying data used for these calculations is presented collectively in Appendix 4.

Traditionally calculated abuse rates per 10,000 prescriptions (average quarterly prescriptions dispensed) are presented in Appendix 5. These findings indicate that, when adjusted by numbers of prescriptions, ER oxycodone was more likely to be abused by this treatment-seeking population than the IR formulations examined during the study period.[17]

As discussed in Section II.A.2.(b) above, the number of prescriptions is an imperfect proxy for availability of a given prescription opioid analgesic, particularly when the goal is to compare rates of abuse or misuse across product categories that differ meaningfully in terms of therapeutic use and drug dispensed per prescription. In order to address the limitations with use of prescriptions as a proxy for drug availability, the NAVIPPRO data were also evaluated using two other measures of drug availability: average dosage strength and average days of therapy. While the ASI-MV system collects product-specific data, it does not collect dosage of the abused drugs. To approximate the impact of equivalent analgesic doses, the average dose per prescription during the data-collection period (1Q2011 through 3Q2012) was calculated. The adjusted prescription

[17] During the study period, the category "ER oxycodone" includes products classified as the original formulation of OxyContin® and products classified as reformulated OxyContin®, the latter of which was introduced to the market in August 2010. Due to the data collection tool used to assist patients in identifying particular products, some proportion of immediate-release single-entity oxycodone may have been erroneously classified as the original formulation of OxyContin®. The impact of this type of error would be to elevate the abuse rates calculated for ER oxycodone.

denominators were then standardized to be equivalent to the ER oxycodone dosage. This calculation yielded an estimate of number of prescriptions of the IR products that would be equivalent to an ER oxycodone prescription. Hence, it takes, on average, 5.93 prescriptions of IR oxycodone combination to equal one ER oxycodone prescription. For hydrocodone combinations, the calculation took into account the fact that oxycodone is about 1.5 times stronger than hydrocodone so that 7.68 hydrocodone combination prescriptions equal one ER oxycodone prescription. Similarly, one mg of oxycodone is equal to about 0.38 mg of hydromorphone. These adjustments are shown in Appendix 6 and suggest a different picture of the relationship between the availability of a product in the community by prescription and its abuse as detected in the ASI-MV data system, with several IR opioid product categories presenting greater risk than ER oxycodone.

Finally, the impact of a "dose/day"-adjusted denominator was examined to account for the fact that IR medications tend to be prescribed for shorter durations than extended-release opioids. Hence, adjustments were calculated to estimate the number of prescriptions dispensed for IR formulations equal to the dose/day "equivalent" of one ER oxycodone prescription. Appendix 7 presents the results of this adjustment applied to the prescription denominator. IR hydrocodone combination, IR oxycodone combination, and IR hydromorphone combination products present greater risk than ER oxycodone when this adjustment is taken into account.

The table below provides a summary of abuse rates calculated using the three different denominators.

Comparison of abuse rates calculated using three denominators: number of prescriptions, number of prescriptions weighted by average dosage strength of prescriptions and number of prescriptions weighted by average dosage strength and average duration of prescriptions

Medication	Abuse per 10,000 Prescriptions Dispensed	Abuse per 10,000 Prescriptions Dispensed Weighted by Average Dosage Strength of Prescriptions	Abuse per 10,000 Prescriptions Dispensed Weighted by Average Dosage Strength and Average Duration of prescriptions
IR hydrocodone combination	3.35	25.70	49.40
IR oxycodone combination	9.62	57.03	111.17
IR oxycodone single-entity	9.47	20.65	26.22
IR hydromorphone (oral)	27.91	98.79	174.00
ER oxycodone	42.05	42.05	42.05

These results indicate that when a more precise measure of drug availability is used (*i.e.*, with adjustments for average dosage strength and duration of prescriptions), IR hydromorphone and IR oxycodone combination products have a higher rate of abuse than ER oxycodone in the NAVIPPRO System. The risk of abuse associated with ER opioids appears greater than that of IR opioids only if abuse rates are calculated using a prescription-adjusted measure that does not account for the average dosage strength and average duration of prescriptions, which, as noted previously, has been criticized by FDA's Office of Epidemiology and Surveillance as an imprecise proxy for drug availability for comparing abuse rates.

4. Rates Of Doctor-Shopping Suggest Higher Rates Of Abuse For IR Opioid Analgesics Than For ER Opioid Analgesics

Relative rates of doctor-shopping can be used as another proxy measure to further explore relative rates of abuse of IR and ER opioid analgesics. This analysis used patient

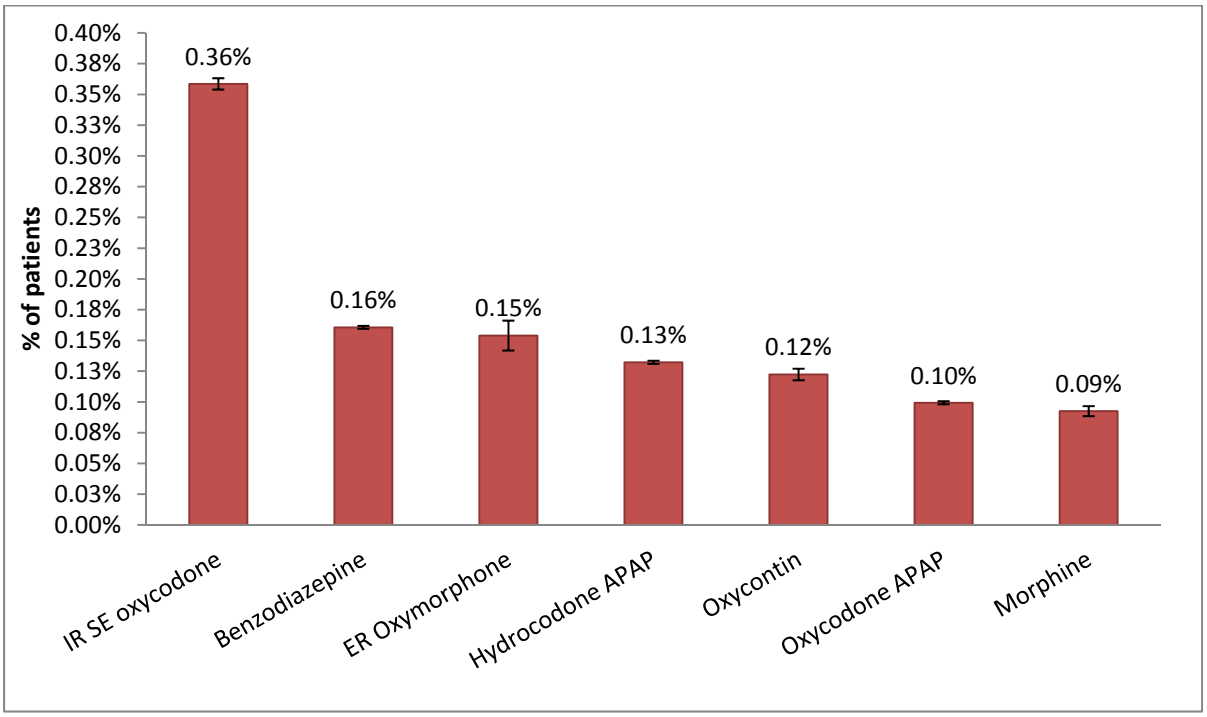
de-identified data from a sample of the IMS LRx database – a database which captures longitudinal patient-level prescription data. This database covers approximately 65% of all retail prescriptions filled in the U.S. The database captures all prescriptions dispensed, regardless of payment type (commercial insurance, Medicare, Medicaid, cash). It includes over 150 million unique de-identified patients, and over 1 million prescribers.

In this analysis, instances of doctor shopping were identified using criteria in the published literature.[18] First, overlapping prescriptions between January 2011 and June 2013 for various categories of opioid analgesics were identified. Prescriptions were considered overlapping when there were multiple prescriptions for the same patient in which the number of days supply of the prescriptions overlap by at least one day. Second, for each such overlap event, the number of unique prescribers and the number of unique pharmacies were counted. If the number of prescribers/pharmacies reached the pre-specified threshold, then the patient was coded as positive for doctor shopping. In this analysis, the threshold for doctor shopping was set using a definition in the published literature; specifically, patients receiving overlapping prescriptions from at least two prescribers and at least three pharmacists in a six-month period.

The doctor shopping rate for each category of opioid analgesic was calculated as the number patients coded as positive for doctor shopping divided by the number of individuals with a prescription for the specified product in a six-month interval. As shown in the figure below, the proportion of individuals prescribed IR oxycodone single-entity products who appear to be doctor-shopping for these products is three times higher than the proportion doctor-shopping for ER oxycodone or ER oxymorphone. Doctor-shopping rates for IR hydrocodone-acetaminophen combination products were similar to the rates for ER oxymorphone and ER oxycodone.

[18] *See* Cepeda, M.S. *et al., Opioid Shopping Behavior: How Often, How Soon, Which Drugs, and What Payment Method,* J. Clin. Pharm. Vol. 53, Issue 1, 112-17 (Jan. 2013); Cepeda, M.S. *et al., Comparison of Opioid Doctor Shopping for Tapentadol and OxyCodone: A Cohort Study,* J. Pain, Vol. 14, Issue 2, 158-64 (Feb. 2013).

National percent of patients who meet a definition of doctor-shopping by categories of oxycodone formulations and other opioid types (January 2011 to June 2013)



5. Experts Within FDA Have Concluded That Data Do Not Support The Conclusion That ER/LA Opioids Pose The Highest Risk Among Opioid Analgesics

In connection with consideration of the opioid analgesic risk evaluation and mitigation strategy ("REMS"), FDA formed several working groups to consider specific aspects of the REMS. One such working group, comprised of experts from the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Surveillance and Epidemiology, and the Controlled Substances Staff, was tasked with considering the products that should be included in the REMS.[19]

[19] *See* Risk Evaluation and Mitigation Strategy for Opioid Analgesics; Final Report of the Scope Working Group (June 2010), *in* Background Package: Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics, for Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (July 22-23, 2010), available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM217510.pdf (the Final Report of the Scope Working Group begins on page 245 of the Background Package) (hereinafter "Scope Working Group Report").

To develop its recommendation, this Scope Working Group reviewed comments on the opioid REMS and the REMS meeting transcripts, evaluated and analyzed data, reviewed published literature, shared information within CDER, and talked to external experts. In a final report dated June 2010, the working group recommended that the REMS include all opioid drug products, rather than only ER/LA opioid analgesics, as proposed in March 2009.[20]

The working group's recommendation to expand the scope of the REMS to include IR opioid analgesics was based, in part, on its review of several sources of data comparing abuse of various categories of opioid medications. This group of FDA experts concluded: "[There is a] lack of data to support the determination that the LA/ER opioids are the most problematic," "The available data do not necessarily support the conclusion that the LA/ER opioids pose the highest risk when used inappropriately," and "The data . . . do not necessarily support the conclusion that the long-acting and extended-release (ER) (LA/ER) opioids proposed at the March 3, 2009, meeting with industry pose the highest risk."[21]

The conclusions of these experts are consistent with the more recent data presented above indicating that the risks associated with ER/LA opioids and IR opioids are comparable, and are inconsistent with FDA's September 10, 2013 determination to require class-wide safety labeling changes for ER/LA opioid analgesics, but not for IR opioid analgesics.

B. DAWN Data Cited By FDA Do Not Show That The Risk For Misuse And Abuse Is Greater For ER/LA Opioid Analgesics Than For IR Opioid Analgesics

In excluding IR opioids from its recently announced class labeling, FDA asserted that the risk for misuse and abuse is greater for ER/LA opioids. In support, the Agency cited data and analyses presented by the FDA Office of Surveillance and Epidemiology ("OSE") during a joint meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees on July 22-23, 2010 to discuss the Risk Evaluation and Mitigation Strategies for Extended-Release and Long-Acting Opioid Analgesics.[22]

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[20] *See* Scope Working Group Report at p. 2.

[21] *See* Scope Working Group Report at pp. 5, 6, and 3.

[22] FDA Reponse to Citizen Petition Docketed as FDA-2012-P-0818 (Sept. 10, 2013) at p. 7.n.31, available at: http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0818-0793; Letter to Sponsors from B. Rappaport M.D. at p. 2, n.6, available at: http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm367697.pdf.

The July 2010 OSE Slides relied upon by FDA present data from the Drug Abuse Warning Network ("DAWN").[23] DAWN is a public health surveillance system that reports on drug-related visits to hospital emergency departments ("ED"). DAWN provides national estimates of ED encounters by individuals who experience drug-related medical emergencies that are severe enough to require treatment in an ED. DAWN data are used to monitor trends in drug misuse and abuse, identify the emergence of new substances and drug combinations, assess health hazards associated with drug use and abuse, and estimate the impact of drug use, misuse, and abuse on the Nation's health care system.[24]

The data presented in the July 2010 OSE Slides and attributed to the DAWN network erroneously categorize emergency room visits attributable to IR and ER/LA opioids. In addition, the data presented in the July 2010 OSE Slides are inconsistent with slides presented by OSE three months earlier using the same cited DAWN data source, the same metric (rate per 10,000 prescriptions), and the same time period (2004-2008). These earlier slides do not support the conclusion that ER/LA opioids are "associated with a greater risk of overdose and death," and are instead consistent with the data presented in Section A above indicating that the risks are comparable.[25] Finally, the prescription-adjusted data presented in the July 2010 OSE Slides and relied upon for the conclusion that the risk for misuse and abuse is greater for ER/LA opioids is inconsistent with OSE's more recent recognition that retail prescriptions do not adequately reflect drug availability, and that DAWN emergency department data should instead be adjusted by total number of extended units dispensed to yield a more accurate comparison of person-exposure-based risk profiles.

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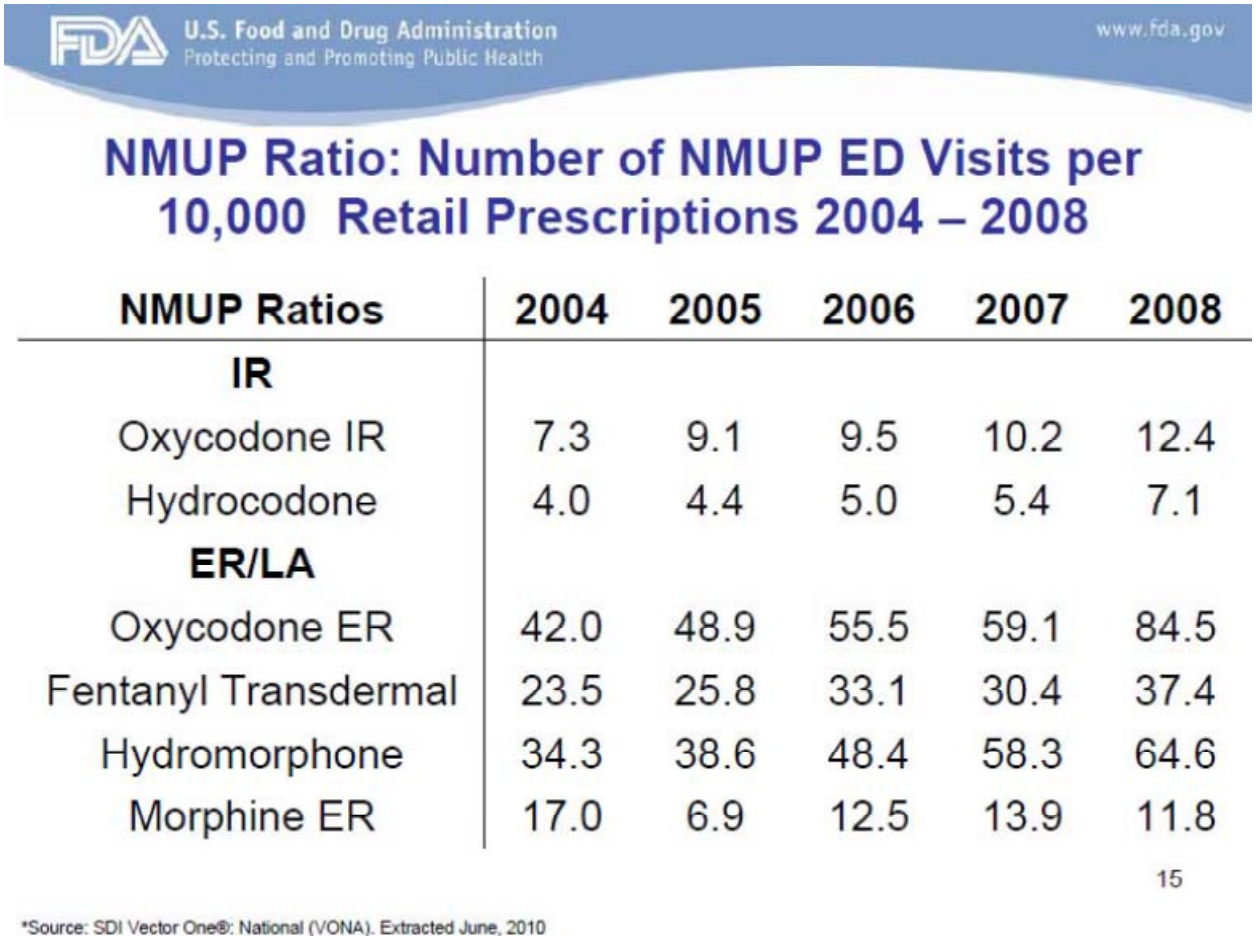
[23] Powerpoint presentation, entitled "Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network," presented at the July 22, 2010 meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf (the relevant presentation begins on page 25 of the linked collection of slide presentations) (hereinafter "July OSE Presentation" or "July 2010 OSE Slides").

[24] *See generally* Drug Abuse Warning Network Methodology Report, 2011 Update, U.S. Department of Health & Human Services, Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, Section 2, available at: http://www.samhsa.gov/data/2k13/DAWN2k11ED/rpts/DAWN2k11-Methods-Report.htm#methods-2.1.

[25] The July OSE Presentation also discusses data from the National Survey on Drug Use and Health ("NSDUH"), but NSDUH data does not allow a comparison of ER/LA and IR formulations. The only data in the July 2010 OSE Presentation purporting to assess the risks of ER/LA opioids compared to IR opioids are the DAWN ED data discussed in this Petition.

1. The Presentation On Which FDA Relies Incorrectly Categorizes Hydromorphone As An ER/LA Opioid During The Years 2004 to 2008

Slide 15 from the July 2010 OSE Presentation shows the number of non-medical use of pharmaceuticals ("NMUP") emergency department ("ED") visits per 10,000 prescriptions. NMUP is described on slide 11 of that presentation as comprising those DAWN ED visits coded as overmedication, seeking detox, and "other."[26]



NMUP Ratios	2004	2005	2006	2007	2008
IR					
Oxycodone IR	7.3	9.1	9.5	10.2	12.4
Hydrocodone	4.0	4.4	5.0	5.4	7.1
ER/LA					
Oxycodone ER	42.0	48.9	55.5	59.1	84.5
Fentanyl Transdermal	23.5	25.8	33.1	30.4	37.4
Hydromorphone	34.3	38.6	48.4	58.3	64.6
Morphine ER	17.0	6.9	12.5	13.9	11.8

[26] In contrast to the description of NMUP provided in the July 2010 OSE Slides, DAWN publications state that the DAWN Case Types that contribute to the NMUP Analytic Group are: "Overmedication," "Malicious Poisoning," and some classified in "Other" but not cases coded as "Seeking Detox." *See* Substance Abuse and Mental Health Services Administration, DAWN Glossary, 2011 Update, available at: http://www.samhsa.gov/data/2k13/DAWN2k11ED/rpts/DAWN2k11-Glossary.htm; Substance Abuse and Mental Health Services Administration Office of Applied Studies. *Drug Abuse Warning Network, 2004: National Estimates of Drug-Related Emergency Department Visits.* DAWN Series D-28, DHHS Publication No. (SMA) 06-4143, Rockville, MD, 2006, at p. 39. It is unclear whether or to what extent this error may have systematically affected the estimates for NMUP cases involving either ER/LA opioid analgesics or IR opioid analgesics.

Slide 16 from the July 2010 OSE Presentation shows the number of ED visits per 10,000 prescriptions attributed in DAWN to "all misuse/abuse" (abbreviated as "ALLMA" or "AllMA," depending on the presentation). ALLMA is described on slide 11 of that presentation as comprising all NMUP ED visits plus other ED visits where illegal drugs or alcohol were present.

AllMA Ratio: Number of AllMA ED Visits per 10,000 Retail Prescriptions 2004 – 2008

AllMA Ratios	2004	2005	2006	2007	2008
IR					
Oxycodone IR	8.8	10.4	10.8	12.2	14.3
Hydrocodone	4.7	5.2	5.8	6.4	8.4
ER/LA					
Oxycodone ER	53.2	59.0	68.3	74.2	106.8
Fentanyl Transdermal	24.4	27.1	34.4	31.9	39.7
Hydromorphone	40.5	40.6	53.1	62.3	70.1
Morphine ER	17.1	7.6	13.5	14.0	12.7

16

*Source: SDI Vector One®: National (VONA). Extracted June, 2010

Both slide 15 and 16 of the July 2010 OSE Presentation incorrectly identify hydromorphone as an ER/LA opioid during 2004-2008. Palladone™ (extended-release hydromorphone) was approved on September 24, 2004. However, the product was introduced in January 2005 and was only sold for a few months before being suspended. Exalgo™ (extended-release hydromorphone) was not approved by FDA until March, 2010, well after the timeframe of the data presented in these slides. While it is possible that some DAWN ED hydromorphone mentions during the timeframe of analysis were associated with Palladone, the vast majority of hydromorphone-containing dosage units available during the 2004-2008 timeframe were in immediate-release formulations of Dilaudid and generic versions of Dilaudid. Indeed, the April 2010 slides presented by

OSE consistently categorize the hydromorphone cases captured in DAWN ED data from 2004 to 2008 as immediate-release.[27]

Slides 15 and 16 show hydromorphone products as having the second highest NMUP and ALLMA ratios, surpassed only by ER oxycodone. If these slides are corrected to categorize hydromorphone as an IR opioid, they no longer support the blanket distinction between IR and ER/LA opioid analgesic risks that seems to underlie the Agency's determination to limit the September 10, 2013 safety labeling action to ER/LA opioids. As discussed below, it also appears that Slides 15 and 16 from the July OSE Presentation may include additional errors that further undermine the justification for differing regulatory approaches to IR and ER/LA opioid analgesics.

2. The Presentation On Which FDA Relies Is Inconsistent With Data Presented Three Months Earlier

Three months before the July 2010 OSE Presentation cited by FDA, in April 2010, FDA convened an Advisory Committee hearing to review a formulation of immediate-release single-entity oxycodone intended to be abuse-deterrent. During that April meeting, OSE presented DAWN ED data from 2004 to 2008 stratified by ER single-entity, IR single-entity and IR combination opioid products. Like the data presented by OSE in July 2010, these April data report NMUP ED visits per 10,000 prescriptions and ALLMA ED visits per 10,000 prescriptions. The values presented in the July 2010 OSE slides relied upon by the Agency for its decision to require class labeling changes for ER/LA opioids, but not IR opioids, are not consistent with the rates illustrated in the graphs presented by OSE in April.

Slide 12 of the April 2010 OSE Presentation reports NMUP ED visits per 10,000 prescriptions as follows:

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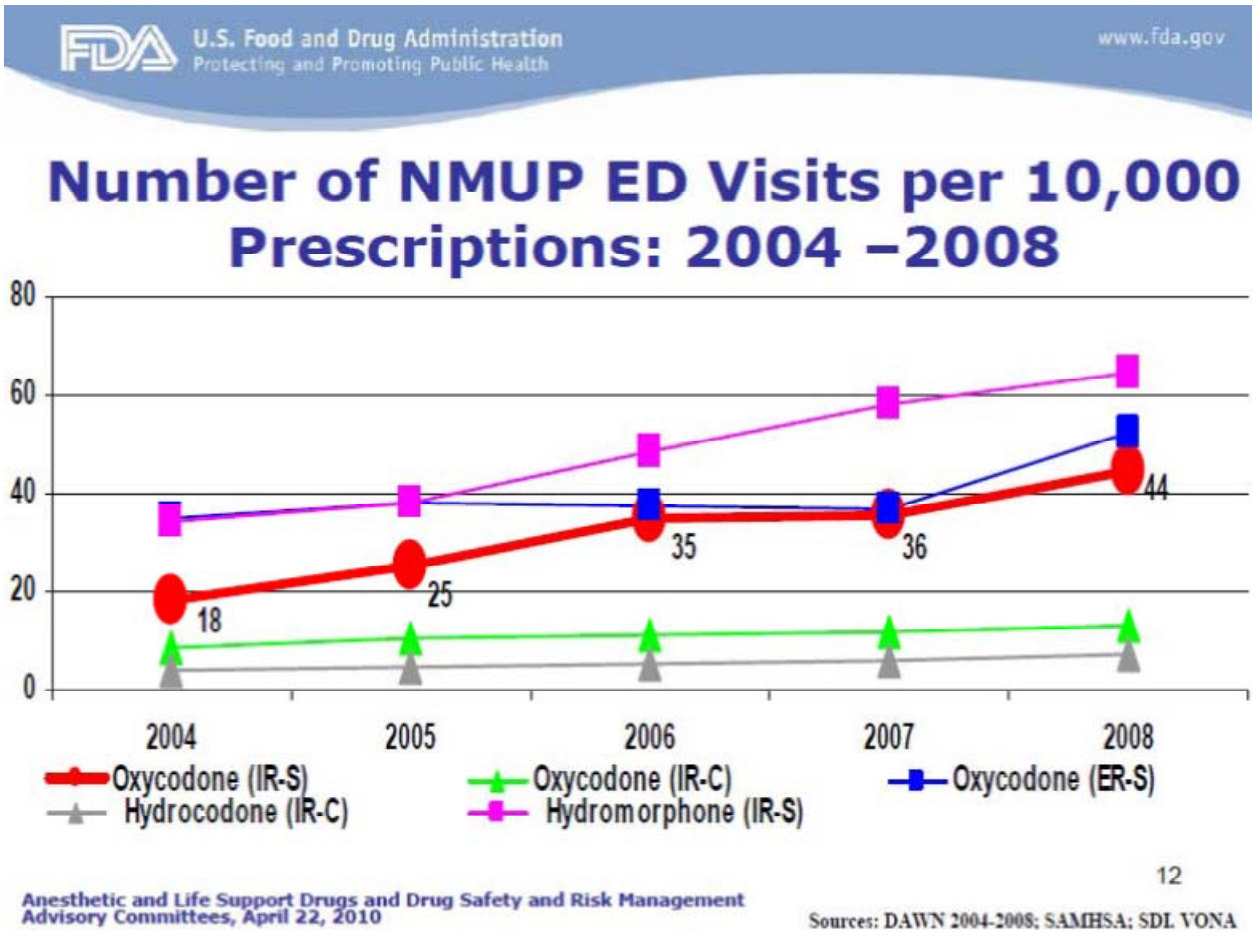
[27] *See* Powerpoint presentation, entitled "Misuse/Abuse of Opioid Analgesics: Findings from The Drug Abuse Warning Network (DAWN)," presented at the April 22, 2010 meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, at slides 8, 9, 10, 12, and 13, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM210854.pdf (the relevant presentation begins on page 36 of the linked collection of slide presentations) (hereinafter "April 2010 OSE Presentation" or "April 2010 OSE Slides").



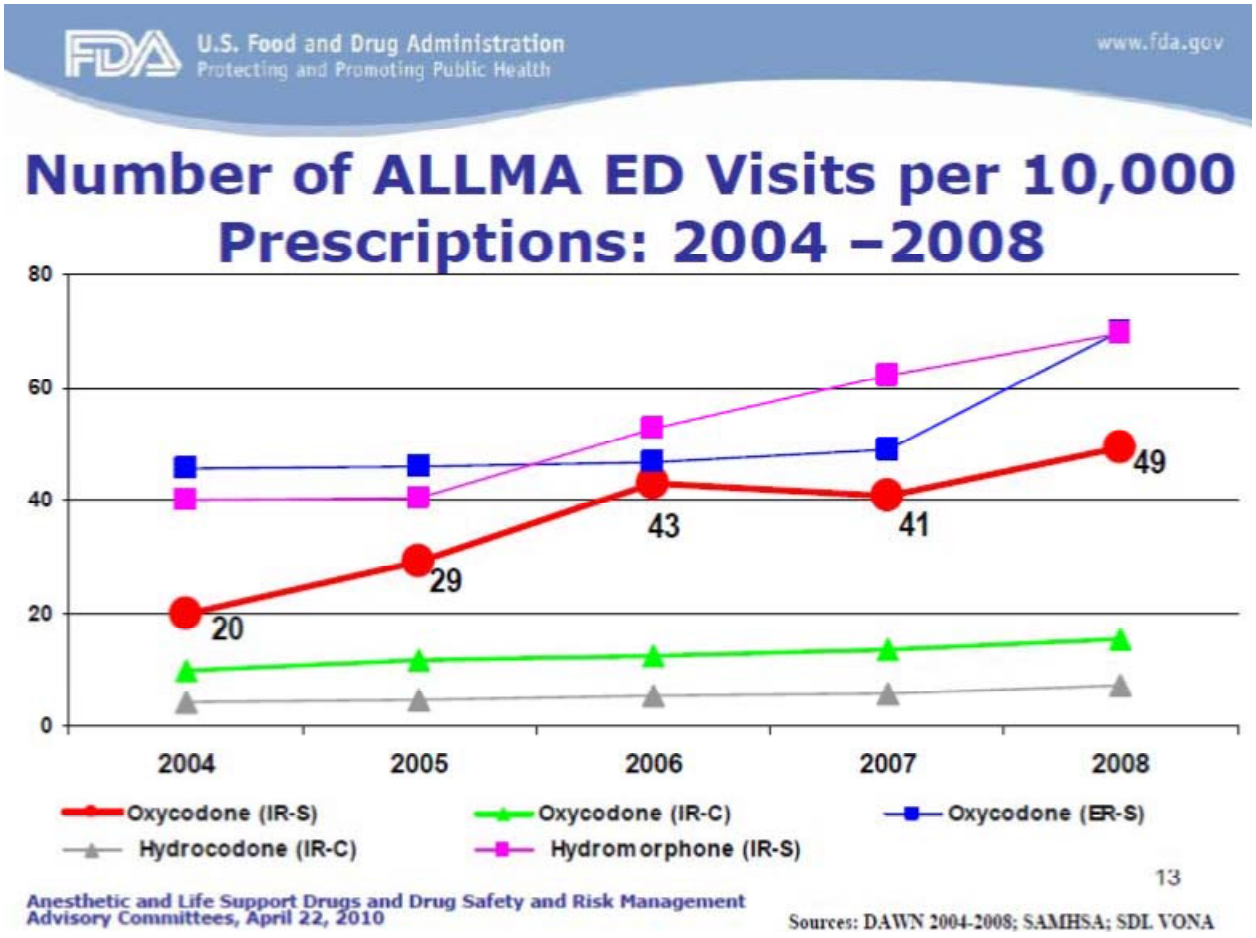
Comparing the above presentation to the corresponding NMUP ED visits per 10,000 prescriptions shown in Slide 15 of the July OSE Presentation reveals the following:

- In the July 2010 OSE Slides, the 2008 NMUP rate (ED visits per 10,000 prescriptions) for IR oxycodone is shown as 12.4. In the April slides, the 2008 NMUP rate for IR single-entity oxycodone is stated to be 44 and the 2008 NMUP rate for IR combination oxycodone is graphically depicted as between 10 and 20.
- In the July 2010 OSE Slides, the 2008 NMUP rate for ER oxycodone is shown as 84.5. In the April slides, the 2008 NMUP rate for ER oxycodone is graphically depicted as between 50 and 60.
- The NMUP rates for 2004 to 2007 also show these same type of significant discrepancies between the April and July 2010 presentations.
- In the April 2010 OSE Presentation, the hydromorphone data are properly labeled as representing "IR-S" (immediate-release, single-entity) products.
- It appears that the "Oxycodone IR" category in the July 2010 OSE Presentation corresponds to the data shown for oxycodone IR combination products in April 2010, while the "Oxycodone ER" category in the July 2010 OSE Presentation

corresponds to the data shown in April 2010 for single-entity oxycodone in both IR and ER formulations.

- The NMUP rates for IR and ER products depicted in the April 2010 OSE Presentation indicate that abuse/misuse-related risks are not disproportionately associated with ER/LA opioids.

Slide 13 from the April 2010 OSE Presentation displays ALLMA ED visits per 10,000 prescriptions as follows:



Comparing the above presentation to the corresponding ALLMA ED visits per 10,000 prescriptions shown in Slide 16 of the July OSE Presentation reveals the following:

- In the July 2010 OSE Slides, the 2008 ALLMA rate for IR oxycodone is shown as 14.3. In the April 2010 OSE Slides, the 2008 ALLMA rate for IR single-entity oxycodone is stated to be 49 and the 2008 ALLMA rate for IR combination oxycodone is graphically depicted as between 10 and 20.

- In the July 2010 OSE Slides, the 2008 ALLMA rate for ER oxycodone is shown as 106.8. In the April slides, the 2008 ALLMA rate for ER oxycodone is graphically depicted as between 60 and 80.
- The ALLMA rates for 2004 to 2007 also show these same type of significant discrepancies.
- In the April 2010 OSE Presentation, the hydromorphone data are properly labeled as representing "IR-S" (immediate-release, single-entity) products.
- It appears that the "Oxycodone IR" category in the July 2010 OSE Presentation corresponds to the data shown for oxycodone IR combination products in April 2010, while the "Oxycodone ER" category in the July 2010 OSE Presentation corresponds to the data shown in April 2010 for single-entity oxycodone in both IR and ER formulations.
- The ALLMA rates for IR and ER products depicted in the April 2010 OSE Presentation indicate that abuse/misuse-related risks are not disproportionately associated with ER/LA opioids.

It is inappropriate for the Agency to make regulatory decisions relying on the DAWN ED data presented in the July 2010 OSE Slides. Information disseminated to the public by FDA, including the July 2010 OSE Presentation and the publicly disseminated September 2013 letter to sponsors citing those slides, is subject to specific standards intended to ensure and maximize the quality of such information.[28] The July 2010 OSE Presentation does not satisfy the standard of "utility" because the slides do not reflect the true number of ED visits associated with ER/LA and IR opioids, and therefore they are not useful to the intended users of the information. Nor do the July 2010 OSE slides satisfy the standard of "objectivity," because the information is not accurate, clear, complete, or reliable. Because the July 2010 OSE Slides do not meet these quality standards, they should not be used as a basis for significant regulatory decisions impacting a large number of widely prescribed medicines.[29]

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[28] Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554, Appendix C), 114 Stat. 2763A-153 (2000) (the Data Quality Act). *See* Guidelines for Ensuring the Quality of Information Disseminated to the Public, Food and Drug Administration, at §§ V.A. and V.B., available at: http://aspe.hhs.gov/infoquality/guidelines/fda.shtml; HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public (Sept. 30, 2002), at Part I § D, available at: http://aspe.hhs.gov/infoquality/Guidelines/part1.shtml#a; Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, Office of Management and Budget, 67 Fed. Reg. 8452 (Feb. 22, 2002), at § V, available at: http://www.whitehouse.gov/omb/fedreg_reproducible.

[29] In light of the material descrepancies between the April and July 2010 OSE Presentations and the significant regulatory decisions resting on the July OSE Presentation, the actual data underlying both presentations should be publicly released. Kleinfeld, Kaplan and Becker, LLP has submitted a FOIA request seeking these data, but they have not yet been released.

3. The Relative Risk Of Overdose And Death Associated With ER/LA and IR Opioid Analgesics Cannot Be Properly Evaluated Using NMUP And ALLMA ED Visits Per 10,000 Prescriptions

The FDA analyses prepared in connection with the Agency's recently announced decision to recommend upscheduling of hydrocodone combination products discuss appropriate means of comparing risks associated with abuse and misuse of opioid products. The July 2010 OSE Presentation relied upon by the Agency to differentiate between the risks of IR and ER/LA opioid analgesics is inconsistent with this current approach. Therefore, even if the July 2010 OSE Slides had correctly reflected the underlying DAWN data, those slides should not be relied upon, particularly when other data indicate the risks are actually comparable.[30]

Typically, to evaluate the relative levels of abuse FDA relies upon comparisons of abuse ratios. To calculate these ratios, a measure of abuse-related events is used as the numerator, and a measure of drug availability is used as the denominator. Because there is no single national data system from which both numerator and denominator data are available, the Agency uses data from separate sources.[31] To evaluate hydrocodone abuse, FDA primarily relied upon DAWN ED data as the numerator.[32] As noted above, both the April and July 2010 OSE Presentations also used DAWN ED data as the measure of abuse-related events.

For the denominator data, both the April and the July 2010 OSE Presentations use retail prescriptions as a proxy for drug availability.[33] OSE also used retail prescriptions as the denominator in its 2008 review of hydrocodone abuse. However, in its more recent analysis of hydrocodone abuse, OSE rejected the use of retail prescriptions for this purpose and, instead, used a measure of the total number of extended units dispensed.[34]

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[30] FDA's recommendation to upschedule hydrocodone combination products, all of which are immediate-release, by itself suggests a recognition of the significant risks of abuse, misuse, and overdose of those drugs.

[31] *See* Memorandum to Douglas Throckmorton, M.D., Deputy Director, CDER from Silvia Calderon, Ph.D., Team Leader, Pharmacology, Controlled Substances Staff, *Summary Review of the Controlled Substances Staff (CSS) Assessment of the Abuse of Hydrocodone Combination Products, From* FDA Briefing Document, Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting – January 24-25, 2013, at p. 19, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM334276.pdf (Dr. Calderon's memorandum begins on page 6 of the linked pdf) (hereinafter "CSS Memorandum").

[32] CSS Memorandum, p. 21-22.

[33] *See* slide 12 of July 2010 OSE Presentation and slide 6 of April 2010 OSE Presentation.

In this respect, OSE agreed with the view expressed by the Drug Enforcement Administration in its analysis of hydrocodone abuse that a comparison of abuse potential should take into account any differences in (1) average days of therapy per prescription, (2) composition type (single-entity vs. combination product), (3) total dosage units per prescription, (4) potency-adjusted drug amounts per each dose unit, and (5) clinical indications. OSE determined that no single denominator can account for all of the pertinent differences between hydrocodone products and the comparator oxycodone products. OSE further concluded that retail prescriptions do not adequately reflect drug availability because the measure does not account for differences in the number of dosage units per prescription or the average days of therapy between hydrocodone products and the comparator oxycodone products.[35] Instead, OSE concluded that drug abuse-related health outcome rate estimates using Extended Units Dispensed as a denominator provided the best metric of patient exposure-based risk for hydrocodone products and the comparator oxycodone products because this denominator accounts for the variability in days of therapy and dosage units per prescription.[36] Likewise, there are also significant differences between ER/LA opioids and IR opioids that necessitate use of a denominator other than retail prescriptions to adequately compare abuse-related risks (*e.g.*, composition type (single-entity vs. combination product), total dosage unit per prescription, drug amounts in each dose unit, and in therapeutic use).[37]

In addition, OSE has also concluded that the evaluation of the public health impact and risk profile associated with abuse/misuse of opioids properly includes not only the patient-based risk profile, but also the population exposure-based risk profile.[38]

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[34] CSS Memorandum, p. 23.

[35] *See* Memorandum to Michael Klein, Ph.D., Director, Controlled Substances Staff from Catherine Dormitzer, Ph.D., MPH, *et. a.l*, Division of Epidemiology, Office of Surveillance and Epidemiology, *Evaluation of the validity of the epidemiological methods and approaches that were used in the DEA's petition for rescheduling of hydrocodone combination products from Schedule III to II, from* FDA Briefing Document, Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting – January 24-25, 2013, at p. 42, 51-53, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM334276.pdf (Dr. Dormitzer's memorandum begins on page 41 of the linked pdf) (hereinafter "OSE Memorandum").

[36] OSE Memorandum at pp. 44, 46, 50-54.

[37] *See, e.g.,* Powerpoint presentation, entitled "Outpatient Drug Utilization Patterns For Selected Opioid Analgesics in the U.S., Years 2007-2011," presented at the December 7, 2012 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM333218.pdf.

[38] OSE Memorandum, pp. 44, 46.

Population exposure-based rates provide a way to describe a product's abuse/misuse risk profile from a community perspective by assessing the health-related burden on the community as a whole. Patient exposure-based rates, in contrast, provide a metric to describe the risk/benefit profile of a product from the patient's perspective by assessing the health-related burden in relation to the level of corresponding medicinal (beneficial) use.[39] NMUP and ALLMA ratios as shown in the July 2010 OSE presentation only address patient-based risk profile and, even then, only in a crude fashion. The July 2010 OSE Slides relied upon by the Agency for its decision to impose class labeling changes on ER/LA opioids but not IR opioids do not address population exposure-based risk. In contrast, the NPDS data provided in this Petition do address population exposure-based risk. As discussed in Section II.A.2. above, exposure rates per 100,000 population were significantly lower for OxyContin than for IR single-entity oxycodone for all exposure categories. Moreover, the Market scan, NPDS, and NAVIPPRO data above are provided with adjustments for patient exposure, indicating that the patient-based risk profile for ER opioid analgesics is comparable to, or more favorable, than that for IR opioid analgesics.

C. Even If There Were Demonstrable Differences In Degree Between The Risks Posed By ER and IR Opioid Analgesics, The Risks Are Not Different In Kind Or In Any Other Relevant Respect

While the Agency relied primarily on the July 2010 OSE Presentation to justify its intention not to require class labeling changes for IR opioids similar to those required of ER/LA opioids, the Agency also asserted that the higher doses of ER/LA opioids increase the risk of a fatal outcome in the event of an overdose and also make ER/LA opioids more desireable for abuse, compared to IR opioids. While abuse of a single, high-dose ER tablet may result in greater risk to the abuser than abuse of a single, low-dose IR tablet, that difference does not justify omission of appropriate warnings from the labels of a large sub-class of opioids. For at least three reasons, these theories fail to justify differing regulatory approaches to IR and ER/LA opioids, particularly when the available data show the actual risks are quite comparable.

First, not all ER opioids are formulated in higher doses than IR opioids. For example, IR oxycodone is available in a number of single-tablet strengths, including 30 mg, whereas OxyContin is available in 10, 15, 20, and 30 mg, as well as in 40, 60, and 80 mg. Hydromorphone is available in 8 mg strengths in both IR and ER formulations. IR oxymorphone is available in 10 mg and ER oxymorphone is available in 5, 7.5, and 10 mg tablet strengths. Tapentadol IR is available in 50 and 100 mg tablets and tapentadol ER is available in 50 and 100 mg tablets. Moreover, regardless of the per-tablet dose, those intent on abusing these medications can simply take additional tablets of IR

[39] OSE Memorandum, pp. 50-52, 55-56.

formulations, resulting in opioid doses that equal or exceed the doses available in single ER tablets.

Second, the FDA rationale ignores the fact that certain ER and IR products contain the same active ingredients – and that it is the active ingredient which causes the effects which lead to the various identified risks of these drugs. Moreover, regardless of the per-tablet strengths of ER and IR formulations, the same daily dose of the active ingredient is required to achieve the same therapeutic effect, whether in IR or ER form. The risks of prescribing an ER or IR formulation to a patient in the same total daily dose adequate to control his or her pain are therefore exactly the same.

Third, by taking action to strengthen the labeling of ER/LA opioid analgesics, but not of the corresponding IR opioid analgesics, the changes proposed by FDA could have the effect of moving patients in pain to higher doses or longer courses of IR opioid analgesics, including increased quantities of pills prescribed for administration on a daily basis. Increased numbers of IR dosage units increases opportunities for diversion, *e.g.,* there may be a delay in the detection of opportunistic diversion from households, or even a failure to detect such diversion at all, if greater quantities are dispensed. Such a switch to IR opioid analgesics is particularly likely if the final class labeling for ER/LA opioid analgesics includes language suggesting that IR opioid analgesics are a safer or preferred option, or are otherwise a better first line therapy.[40]

Indeed, the potential resulting shift to IR dosage forms could actually cause an increase in adverse effects associated with medication errors or deliberate misuse of IR forms when the same dose of an ER form (particularly an ER form that resists tampering with the controlled release mechanism) would release the drug more slowly.

D. FDA Should Apply Its Standards In An Even-Handed Manner, And Extend The September Action To IR Opioid Analgesics

The five analyses described above, as well as the April OSE Presentation of DAWN ER data, indicate that there are not disproportionate safety concerns associated with ER/LA opioid analgesics compared to immediate-release opioid analgesics. Instead, immediate-release opioid analgesics are associated with the same potential adverse consequences as ER/LA opioid formulations generally, including the cited risks of abuse, misuse, and overdose, with comparable incidences and public health ramifications.

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[40] *See, e.g.,* CSS Memorandum, pp. 25-27 (discussing potential unintended shifts in prescribing, were hydrocodone drug products moved to Schedule II).

The Agency should apply its regulatory standards even-handedly to similarly situated products, or classes of products. In *Bracco Diagnostics, Inc. v. Shalala*, plaintiffs challenged FDA's decision to subject their applications for injectable contrast imaging agents to different, more onerous, standards of review than were applied to another similar product. The court granted plaintiffs' motions for a preliminary injunction, holding that FDA's unexplained failure to treat similarly situated products in the same way was arbitrary and capricious in violation of the APA. The court determined that FDA could either regulate the products as drugs or devices, but could not impose disparate standards on the two products. In the words of the court:

> What the FDA is not free to do, however, is to treat them dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason.

963 F.Supp. 20, 27-8 (D.D.C. 1997).[41]

Because both IR and ER/LA opioid analgesics present the same recognized risks, in a directly and obviously comparable manner, the public health is best served by similarly descriptive indication statements, and enhanced warnings and precautionary information, in the labeling of both ER and IR opioid analgesic products. In short, there is no justification for a "more treacherous" and onerous approach to the labeling of ER/LA opioids versus IR opioids. Indeed, adopting disproportionate labeling may encourage the prescribing of non-abuse deterrent IR opioid analgesics over abuse-deterrent ER formulations, to the detriment of the public health. Accordingly, FDA should extend the action on ER/LA class labeling announced September 10, 2013 to also include immediate-release opioids indicated for analgesia.

Conclusion

For the reasons discussed above, the appropriate message for class labeling is that all opioid analgesics present a risk for addition, abuse, misuse, overdose, and death. The labeling for ER/LA and IR opioid analgesics should be consistent with each other in conveying those risks. Purdue therefore respectfully requests that FDA promptly exercise its authority under Section 505(o) of the Federal Food, Drug and Cosmetic Act to seek and, if necessary, impose safety labeling changes on immediate-release opioid

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[41] *See also United States v. Diapulse Corp.*, 748 F.2d 56 (2d Cir. 1984) (holding that FDA must "apply its scientific conclusions evenhandedly" and cannot "'grant to one person the right to do that which it denies to another similarly situated'." (citation omitted)); *Allergan, Inc. v. Shalala,* No. 94-1223, 6 Food and Drug Rep. 389 (D.D.C. Nov. 10, 1994) (holding that FDA enforcement must be conducted in a fair and even handed manner against similarly situated parties; otherwise agency conduct is arbitrary and capricious in violation of the APA).

analgesics that parallel the final safety labeling changes resulting from the completion of the 505(o) procedures initiated for ER/LA opioid analgesics on September 10, 2013, and assure that the indications for use and other safety labeling information for IR and ER/LA opioid analgesics convey the same warnings and precautions regarding the risks of opioid use and misuse.

Environmental Impact

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

Economic Impact

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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