

“Abuse-Deterrent Opioid” is an Oxymoron FDA’s “Action Plan” preserves its “No Help Wanted” status quo

Summary: Starting with FDA’s 1995 approval of the original OxyContin — widely recognized as the starting point for the prescription opioid and heroin overdose epidemic — claims that an opioid is “abuse-deterrent” have time and again been proven oxymoronic. FDA’s own guidance recognizes the inherent contradiction in the term “abuse deterrent,” explaining: “It should be noted that [abuse-deterrent] technologies have not yet proven successful at deterring the most common form of abuse — swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse.”¹ In many cases, FDA approved so-called abuse-deterrent opioids despite warnings from the medical community about the potential for abuse — concerns borne out by subsequent experience with the drugs.

Nevertheless, in its February 2016 announcement of an “Opioid Action Plan,” FDA said that it would not convene advisory committees before approving a new opioid classified as abuse-deterrent. That position continues the deadly status quo: Of eleven opioids with abuse-deterrent properties that FDA has approved since 2010, the agency convened advisory committees for only four of them (and in one of those instances, FDA ultimately approved a re-formulated version of the opioid following its withdrawal from the market, without further advisory committee consideration). Instead of routinely convening advisory committees and availing itself of outside expertise, FDA has turned a blind eye to expert advice and approved opioid after addicting opioid without any independent advice whatsoever. Under FDA’s new action plan, it will continue to do so.

Timeline of FDA Approval of Abuse-Deterrent Opioids

1995: FDA approved the original version of OxyContin, an extended release opioid, believing that it “would result in *less* abuse potential, since the drug would be absorbed slowly and there would not be an immediate ‘rush’ or high that would promote abuse.”²

ADVISORY COMMITTEE: No.

OUTCOME: “Purdue’s promotion of OxyContin for the treatment of non-cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670,000 in 1997 to about 6.2 million in 2002, whereas prescriptions for cancer-related pain increased about fourfold during that same period.”³

2010: FDA approved a new version of OxyContin designed to deter abuse associated with crushing the tablet. According to FDA’s press release at the time, “[t]he reformulated

¹ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>

² <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm>

³ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/>

OxyContin is intended to prevent the opioid medication from being cut, broken, chewed, crushed or dissolved to release more medication.”⁴

ADVISORY COMMITTEE: No.

OUTCOME: A subsequent study found that “[u]p to one-fourth of people entering drug rehabilitation programs say they have abused the newer version of OxyContin ‘There are still some people who have figured out how to circumvent abuse-deterrent formulation,’ said lead researcher Theodore J. Cicero, PhD of Washington University School of Medicine in St. Louis. . . . Researchers found at the time the drug’s abuse-deterrent formulation was introduced in 2010, 45 percent of study participants entering drug treatment said they had used OxyContin to get high at least once in the last month. Two years later, 26 percent said they got high using the abuse-deterrent formulation of the drug in the month before entering treatment.”⁵

2010: FDA approved an abuse-deterrent formulation of Exalgo ER (crush and extraction resistant).

ADVISORY COMMITTEE: Yes (no vote).

OUTCOME: A member of FDA’s Controlled Substance Staff stated at the advisory committee meeting: “Based on the data presented, our conclusions are hydromorphone [the opioid active ingredient in Exalgo] has a high abuse potential comparable to oxycodone. . . . [W]e predict that Exalgo will have high levels of abuse and diversion.”⁶

2011: FDA approved an abuse-deterrent formulation of Nucynta ER (crush resistant).

ADVISORY COMMITTEE: No.

OUTCOME: Upon approval, Nucynta ER’s manufacturer Janssen Pharmaceuticals, Inc. noted in a statement: “NUCYNTA® ER contains tapentadol, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit.”⁷

2011: FDA approved an abuse-deterrent formulation of Oxecta (containing sodium lauryl sulfate, which makes snorting the medication unpleasant, and an excipient that causes the tablet to form a gel if any attempts are made to dissolve it).

ADVISORY COMMITTEE: Yes, initially. No advisory committee convened on reformulation.

OUTCOME: King Pharma originally submitted this opioid to FDA for approval under the name Acurox, with an additional method of abuse deterrence — niacin — that was intended to cause unpleasant side effects if too much of the drug was ingested. Acurox went before an advisory

⁴ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480.htm>

⁵ <https://www.ncadd.org/blogs/in-the-news/entry/reformulated-version-of-oxycontin-can-still-be-abused>

⁶

<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anestheticandanalgesicdrugproductsadvisorycommittee/ucm187490.pdf> at 157-58

⁷ <http://www.jnj.com/news/all/fda-approves-nucynta-er-tapentadol-extended-release-oral-tablets-for-the-management-of-neuropathic-pain-associated-with-diabetic-peripheral-neuropathy>

committee, which voted it down because niacin was considered an insufficient deterrent.⁸ King Pharma removed the niacin from the formulation, changed the name to Oxecta, and received approval without further advisory committee review. Upon approval, the drug's manufacturer Pfizer noted in a statement that "there is no evidence that Oxecta has a reduced abuse liability compared to immediate-release oxycodone."⁹

2011: FDA approved a reformulated, abuse-deterrent version of Opana ER (crush and intravenous-use resistant).

ADVISORY COMMITTEE: No.

OUTCOME: In 2013, FDA found that "[w]hile there is an increased ability of the reformulated version of Opana ER to resist crushing relative to the original formulation, study data show that the reformulated version's extended-release features can be compromised when subjected to other forms of manipulation, such as cutting, grinding, or chewing, followed by swallowing. Reformulated Opana ER can be readily prepared for injection, despite Endo's claim that these tablets have 'resistance to aqueous extraction (i.e., poor syringeability).' It also appears that reformulated Opana ER can be prepared for snorting using commonly available tools and methods."¹⁰ In June 2015, the Centers for Disease Control and Prevention reported "that a formulation of . . . Opana ER — that's supposed to be difficult to crush — is responsible for an outbreak of HIV in southern Indiana, because the changes made it easier to prepare the drug for more dangerous intravenous or subcutaneous injection. Time reports that drug addicts prefer the formulation to heroin even though it is more expensive and doesn't last as long. HIV spread through the sharing of needles, resulting in at least 135 HIV infections in a rural Indiana county of 4,200 people."¹¹

2013: FDA approved updating labeling allowing reformulated Oxycontin to be labeled as an abuse-deterrent drug. FDA also announced it would not allow generic versions of the original non-abuse-deterrent formulation.¹²

2014: FDA approved an abuse-deterrent formulation of Targiniq ER (containing the opioid antagonist naloxone which is released only if the tablet is crushed, snorted, or dissolved).

ADVISORY COMMITTEE: No.

OUTCOME: FDA's own press release stated: "Targiniq ER can still be abused, including when taken orally (by mouth), which is currently the most common way oxycodone is abused."¹³ In criticizing the approval, the coalition to end the opioid epidemic, Fed Up, wrote: "Just last month FDA approved another extended-release opioid called Targiniq, which contains a high

⁸ http://www.drugs.com/nda/acurox_100423.html

⁹ <http://press.pfizer.com/press-release/pfizer-and-acura-announce-fda-approval-oxectatm-oxycodone-hcl-usp-cii>

¹⁰ <http://www.fda.gov/Drugs/DrugSafety/ucm351357.htm>

¹¹ <http://www.fiercedrugdelivery.com/story/abuse-endos-second-generation-opana-er-formulation-implicated-indiana-hiv-e/2015-06-16>

¹² <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm>

¹³

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm406407.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

dose of oxycodone combined with naloxone. Although the addition of naloxone may deter misuse by injection and snorting, it cannot exert its effect when taken orally. This means that when chewed, extended-release Targiniq tablets will immediately release the entire dose of oxycodone and the naloxone will have no effect. It is likely that FDA's scientific advisory committee would have voted against Targiniq approval because it contains the same active ingredient found in OxyContin but unlike OxyContin, which was reformulated to be crush-resistant, Targiniq can be easily chewed for release of the full dose.¹⁴

2014: FDA approved an abuse-deterrent formulation of Embeda (containing the opioid antagonist naltrexone which is released only if the tablet is crushed, snorted, or dissolved). Embeda was first approved on August 13, 2009, but was voluntarily withdrawn from the market in March 2011 due to testing that found stability concerns in the manufacturing process. In November 2013, FDA confirmed that these issues were resolved with its approval of a manufacturing supplement.¹⁵

ADVISORY COMMITTEE: Yes, in 2008, when the new drug application was first submitted, but not after the drug was reformulated.¹⁶ According to press reports, the Advisory Committee was not asked to vote on approval of the drug.¹⁷

OUTCOME: FDA's own press release described how Embeda could still be abused: "Embeda has properties that are expected to reduce, but not totally prevent, abuse of the drug when crushed and taken orally or snorted. . . . When swallowed intact, however, Embeda can still be abused or misused because the naltrexone is not expected to substantially block the euphoric effects of the morphine."¹⁸

2014: FDA approved an abuse-deterrent formulation of Hyslinga ER (crush and intravenous-use resistant).

ADVISORY COMMITTEE: No.

OUTCOME: "Dr. Andrew Kolodny, the chief medical officer at Phoenix House, a group of nonprofit addiction-treatment centers, said he was disturbed by the drug's approval and disappointed that the F.D.A. did not seek input from an advisory committee of experts. Dr. Kolodny said that addicts knew how to break down abuse-deterrent products for oral use, and that the 120-milligram tablets were particularly dangerous because they 'pack an enormous amount of hydrocodone.'"¹⁹

2015: FDA issued non-binding guidance to industry related to abuse-deterrent opioids, stating: "It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse — swallowing a number of intact capsules or tablets to achieve a feeling

¹⁴ <http://feduprally.org/wp-content/uploads/2014/09/Burwell-Letter-completed-with-signature-Final.pdf>

¹⁵ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm>

¹⁶ <http://www.medpagetoday.com/ProductAlert/Prescriptions/15540>

¹⁷ *Id.*

¹⁸ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm>

¹⁹ http://www.nytimes.com/2014/11/21/science/fda-approves-hysingla-a-powerful-painkiller.html?_r=0

of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse.”²⁰

2015: FDA approved a modified version of Zohydro ER, with abuse-deterrent properties (a viscous gel is created when the medication is crushed and dissolved in a liquid or solvent) but did not approve an abuse-deterrent labeling claim. In 2013, FDA approved the original non-abuse-deterrent formulation of Zohydro over the 11-2 vote of an advisory committee against recommending its approval. FDA’s own staff had also raised concerns about abuse potential: “Two members of the FDA’s controlled substance staff warned about the potential for abuse in materials presented to the advisory committee. ‘If approved and marketed, Zohydro ER will be abused, possibly at a rate greater than that of currently available hydrocodone combination products,’ wrote medical officer Lori Love, MD, PhD, and pharmacologist James Tolliver, PhD.”²¹

ADVISORY COMMITTEE: No.

OUTCOME: Zohydro’s manufacturer, Zogenix, was expected to submit clinical data supporting claims of abuse deterrence in late 2015, but in March 2015 sold its Zohydro ER business to Pernix Therapeutics for \$100 million.²²

2015: FDA approved OxyContin for pediatric use.

ADVISORY COMMITTEE: No.

OUTCOME: FDA ignored its own guidance calling for an advisory committee when a question of “pediatric dosing” is involved.²³ Criticism was widespread. “Manufacturers don’t pursue regulatory approvals simply to provide prescribers and patients with additional information,” said Dr. G. Caleb Alexander, an internist and a director of the Center for Drug Safety and Effectiveness at Johns Hopkins Bloomberg School of Public Health in Baltimore. “This approval allows Purdue Pharma to market and promote this product for use in children, and the obvious concern is this approval will change the pattern of use.”²⁴

2015: FDA approved an abuse-deterrent formulation of MorphaBond (crush and intravenous-use resistant).

ADVISORY COMMITTEE: No.

OUTCOME: In its approval letter, FDA required Morphabond’s manufacturer, Inspiron, to “[c]onduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products.”²⁵

²⁰ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>

²¹ <http://www.webmd.com/pain-management/news/20140226/new-painkiller-zohydro-criticized>

²² <http://ir.zogenix.com/phoenix.zhtml?c=220862&p=irol-newsArticle&ID=2024400>

²³ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125651.pdf>

²⁴ <http://www.nytimes.com/2015/10/09/health/fda-approval-of-oxycotin-for-children-continues-to-draw-scrutiny.html>

²⁵ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/206544Orig1s000ltr.pdf

FDA stated that “MorphaBond has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and snorted or injected.”²⁶

2015: FDA tentatively approved an abuse-deterrent formulation of Xtampza ER — intended for patients with difficulty swallowing (although its capsules can be opened and mixed with food, properties make it difficult to abuse nasally or intravenously).²⁷

ADVISORY COMMITTEE: Yes, by a 23-0 vote.

OUTCOME: FDA’s approval was tentative, and the drug’s manufacturer has delayed its marketing, because of pending patent-infringement litigation brought against it by OxyContin’s manufacturer, Purdue Pharma.²⁸

²⁶ <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm>

²⁷ <http://www.medpagetoday.com/PainManagement/PainManagement/54653>

²⁸ *Id.*