Testimony Before the FDA's Drug Safety and Risk Management & Anesthetic and Analgesic Drug Products Advisory Committees regarding

Reformulated Oxycontin

Creating Public Health Problems

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I have no financial conflicts of interest.

Three Groups of Opioid-Using Patients

- Individuals who require opioid analgesics for the treatment of pain, under the care of a healthcare provider (i.e., the intended population). *(Importantly, these individuals may simultaneously fit into another category described below.)*

- Individuals who misuse or abuse opioid analgesics but do not regularly manipulate these products for use by routes (e.g., snorting, injecting) other than the intended route.

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Not infrequently, during advisory committee meetings, an opioid company seeking approval would try to increase the meeting's focus on the benefits and risks on intended recipients of the opioid for pain relief, rather than on the broader public health concern for people in other groups who could later, if not sooner become opioid dependent and opioid abusers.

2017 National Academies' Opioid Recommendations and This Advisory Committee Meeting

In response to a 2016 FDA request for the National Academies "…to help us develop a regulatory framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of abuse and misuse," a major finding in the 2017 National Academies report was that the FDA has failed to adequately "incorporate public health considerations into opioid-related regulatory decisions."

This meeting inexcusably occurs almost 10 years from FDA's approval of abuse-deterrent Oxycontin, for which the FDA mandated that "the sponsor must conduct an epidemiological study to address whether the changes made to the OxyContin formulation...actually result in a decrease in misuse and abuse, and their consequences, addiction, overdose and death, in the community."

Advisory Committee Concerns About 2010 Reformulated Oxycontin

"[T]hose abusing or misusing the product by ingesting more intact tablets or higher doses of intact tablets would not be provided with any protection from overdose with this reformulated product… the committee members were generally in consensus that a post-marketing epidemiology study to assess the impact of the reformulation on actual abuse in the community is essential to fully understand the value of the product and the level of risk management it will need, and that this study should be required as a post-marketing requirement for approval."

(Dec 30. 2009 FDA Division Director summary review for regulatory action, p.6)

FDA January 17, 2003 Warning Letter to Purdue

"The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these advertisements… they are in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C.§§ 331(a) and (b), 352(n), and its implementing regulations. Your journal advertisements omit and minimize the serious safety risks associated with OxyContin, and promote it for uses beyond which have been proven safe and effective… your [JAMA] journal advertisements fail to present in the body of the advertisements any information from the boxed warning in the approved product labeling (PI) for OxyContin regarding the potentially fatal risks associated with the use of OxyContin and the abuse liability of OxyContin…and make unsubstantiated efficacy claims promoting the use of OxyContin for pain relief."

FDA 2003 Warning Letter to Purdue, cont'd

"Omission of material facts related to abuse liability and fatal risks

Specifically, your November Ad contains a two-page spread picturing a man fishing with a boy and featuring the prominent headline '**THERE CAN BE LIFE WITH RELIEF.'** The words **'LIFE WITH RELIEF'** are the largest in the advertisement. The ad also features a graphic of two paper medication dosage cups with '8 AM' and '8 PM' next to them. The logo for OxyContin is right below, with the prominent tagline '**IT WORKS.'** Your October Ad promotes '**WHEN IT'S TIME TO CONSIDER Q4-6H OPIOIDS…REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO**.' The claim '**REMEMBER, EFFECTIVE RELIEF TAKES JUST TWO'** is prominently highlighted in the middle of the ad, surrounded by comparative graphics of dosage cups which show only two dosage cups for OxyContin, as compared to six dosage cups for the other drugs."

FDA 2003 Warning Letter to Purdue, cont'd

"Minimization of risk in information presented

Your ads not only omit these important risks, but also understate the minimal safety information that you do disclose in the body of the advertisements, thus completely misrepresenting the safety profile of the drug. Your ads state that 'The most serious risk with opioids, including OxyContin, is respiratory depression.' This statement suggests that there are no specific safety considerations for OxyContin related to respiratory depression, which is false or misleading and could lead to prescribing of the product based on inadequate consideration of risk. This statement also fails to warn that this risk can be a fatal one.

…Immediately cease the dissemination of these advertisements and all other promotional materials that contain the same or similar violations outlined in this letter."

Purdue's $600 Million 2007 Criminal and Civil Penalty for Deceptive Oxycontin Marketing

"Purdue supervisors and employees sponsored training that used graphs that exaggerated the differences between the blood plasma levels of OxyContin as compared to immediate-release opioids. These graphs were used to falsely teach Purdue sales supervisors that OxyContin had fewer 'peak and trough' blood level effects than immediate-release opioids and that would result in less euphoria and less potential for abuse than short-acting opioids."

page 4 of the press the statement issued by the Justice Department on May 10, 2007 announcing the prosecution.

FDA Rejection 11/07 of Purdue Reformulated Oxycontin (just 6 months after $600 million DOJ penalty)

"The most significant inadequacies in the application were **the poor quality of the studies submitted to support the sponsor's proposed labeling claims…and the sponsor's plan to market the 60 mg and 80 mg higher-strength tablets in the original formulation at the same time and with the same name that they marketed the lower-strength tablets in the new formulation.** The Agency clearly informed the sponsor at their pre-NDA meeting that **this plan would be unacceptable due to the potential for a misconception among prescribers that the higher-strength tablets would also have abuse deterrent features. This misconception could lead to significant safety problems."** [Emphasis added]

(Dec 30. 2009 FDA Division Director summary review for regulatory action, p.3)

FDA's Overall Ask to the Committees

We are asking the committees to discuss and provide their viewpoints on broader public health impacts, both positive and negative, of OxyContin's reformulation within the complex and evolving landscape of opioid use, abuse, addiction, and overdose.

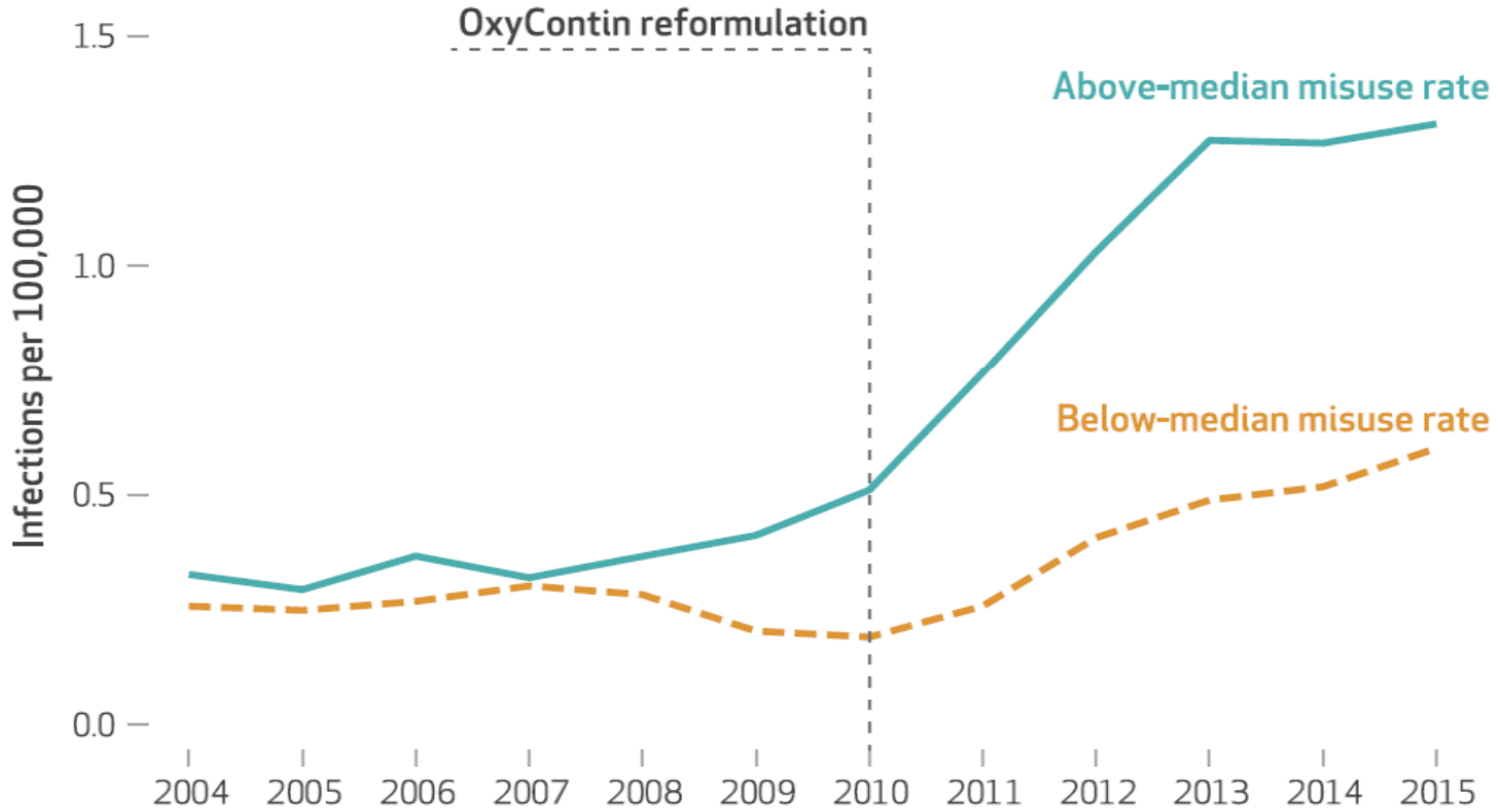
FDA Analyses of the Four PMR Studies

- 350-1 NAVIPRO The evidence for a reduction in overall OxyContin abuse (via any route) in this study was not compelling even though non-oral abuse decreased.
- 350-2 RADARS Poison control findings do not provide robust evidence that the observed decline in overall (i.e., via any route) abuse call rates for OxyContin is attributable to its reformulation rather than to broader secular trends.
- 350-3 RADARS Treatment Center Study findings were mixed and did not provide compelling evidence that the reformulation meaningfully reduced OxyContin abuse among adults enrolling in OUD treatment.
- 3051-4: Claims-based Overdose Study The results do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall.

Decrease from 2011 to 2019 in Percentage of Opioid Prescriptions that are Abuse-Deterrent

- Abuse-deterrent formulations were introduced to the market in 2009. The utilization of ADF formulations peaked in 2011 (5.6 million out of 258 million prescriptions or 2.2%), followed by a decline of 51% (to 2.7 million out of 154 million prescriptions or 1.8%) in 2019.
- Is the net effect of ADF opioids positive or negative?
- More recent published studies discussed in the briefing package looking at public health effects after vs before reformulation raise serious questions about whether the net effect is positive, as in the Powell study published last year.

Figure 5: Rate of Acute Hepatitis C Infection per 100,000, by State Rate of Nonmedical OxyContin Use Pre-reformulation, 2004-2015, U.S.



Source: Powell, D., A. Alpert, and R.L. Pacula, A Transitioning Epidemic: How the Opioid Crisis Is Driving the Rise In Hepatitis C. Health affairs (Project Hope), 2019. 38(2): p. 287.