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On March 25, 2015, the Food and Drug Administration (FDA) released the Draft Guidance entitled, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry*¹. When finalized, this guidance will represent the FDA's current position on the assessment of abuse potential for generic opioid analgesics formulated to be abuse deterrent (ADF). The Draft Guidance recommends that studies be conducted to "demonstrate that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse" (p.1). In particular, the Guidance specifies this demonstration should include "in vitro studies and, in some cases, pharmacokinetic or other studies" (p. 3).

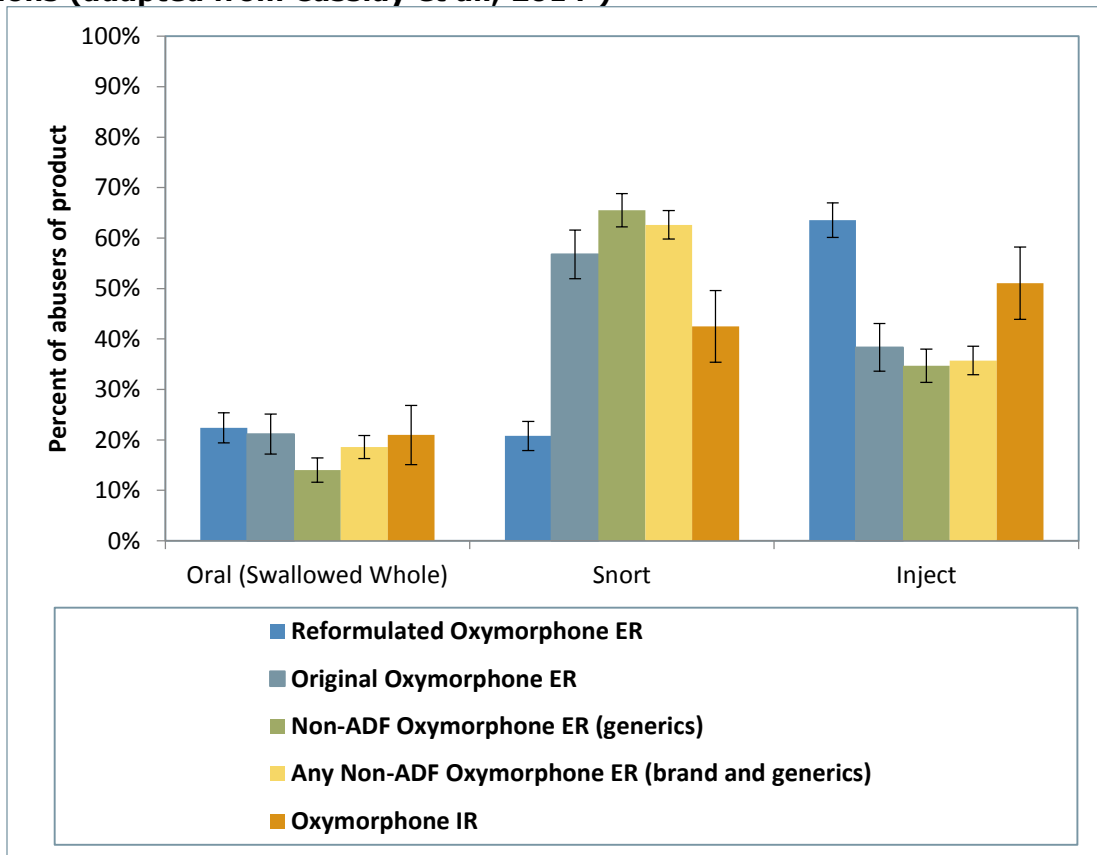
Inflexxion would like to address the absence of any reference in the Draft Guidance document to post-marketing surveillance or epidemiology studies of generic ADF products. Inflexxion has been involved with providing surveillance data and epidemiology studies for many major branded ADF products. Inflexxion operates NAVIPPROTM, the National Addictions Vigilance Intervention and Prevention Program², a unique, scientifically developed, comprehensive risk management program for prescription opioids, stimulants, and other Schedule II or III therapeutic agents. NAVIPPRO has been developed and tested with support from National Institutes of Health (NIH) most of this coming from National Institute on Drug Abuse (NIDA). NAVIPPRO data streams include substance abuse treatment center populations, analyses of American Association of Poison Control Center (AAPCC) data, and Internet monitoring. Together, these data streams can provide a real-time, real world picture of the relative rates of misuse, abuse and diversion of particular products along with product-specific routes of administration (ROAs). Careful analyses of such data can help understand how and to what extent a particular prescription opioid product (brand or generic) is used outside the laboratory once it is introduced to the market, unlike in vitro laboratory studies the goal of which is premarket prediction of abuse potential.

While the Draft Guidance is thorough and specific with regard to the nature of in vitro and pharmacokinetic studies, the unstated assumption is that these laboratory studies alone will be sufficient to gauge future public health and societal impacts once a new prescription opioid formulation is marketed. Omission of a requirement to monitor abuse of ADF generics runs the risk of missing unanticipated reactions of abusers once a product is available in the community. What we have learned is that product-specific abuse and product-specific ROA patterns reflect a complex interplay of local prescribed availability (i.e., the amount of a medication in the community), alternatives (i.e.,

other products, heroin), molecule, cost, abuser preferences, and tablet/capsule formulation (ADF versus not ADF). Generic versions that are less costly and/or more likely to be on formularies may change the equation in ways that are not predictable from the experience of the RLD or from laboratory studies alone. Without the requisite empirical investigations, it may be difficult to rapidly detect an emerging, unanticipated public health problem.

There are examples where post-market monitoring of ADF products revealed ROA profiles that were other than expected prior to launch. For example, data by Cassidy and colleagues³ examined past 30-day abuse and ROA patterns for reformulated crush-resistant oxymorphone ER and other categories of oxymorphone (both ER and IR formulations) among a sample of 77,175 adults assessed for substance abuse treatment planning at centers located in the United States over an 18-month period during October 2012 through March 2014 using data collected from the Addiction Severity Index-Multimedia Version (ASI-MV[®]), part of the NAVIPPRO surveillance system (see Figure 1). As can be seen, the reformulated or ADF version of oxymorphone ER (first bar in the series) yielded lower insufflation (snorting) when compared with original formulation as well non-ADF generics. However, the reformulated version yielded greater levels of injection than either the original extended-release formulation or generic oxymorphone ER non-ADF versions. Without post-marketing surveillance or studies of any kind, it may be difficult to detect the reaction of abusers to a generic ADF formulation that is not identical to the RLD (i.e., does not impinge on the intellectual property protection of the listed reference drug). An ADF generic might provide greater deterrence than its RLD or less.

Figure 1. ROA for Reformulated Oxymorphone ER and non-ADF Oxymorphone ER Formulations (adapted from Cassidy et al., 2014³)



NOTE: Respondents select all that routes that apply, so percentages do not add to 100%
These data suggest that post-marketing data may be critical for evaluating and monitoring the impact of any ADF that is introduced to the market, whether brand or generic. Published or presented data suggest that abusers have responded differently to the different branded ADFs. For instance, in Figure 1, insufflation (snorting) for original, branded oxymorphone ER was reported by about 57% of those who abused the product, which reduced to 21% of the reformulated product. Injection of the original product was reported by 38% of abusers of the product, but the reformulated product was reportedly injected by 64% of those who abused the ADF version³. This pattern was not observed for similar ASI-MV substance abuse treatment data for the reformulated OxyContin⁴. For OxyContin, the reformulated product reduced snorting from about 53% to 25% and injection from 37% to 16%. Thus, across molecule, the ADF formulations had very different impacts in terms of ROA use by abusers in treatment. At this point, it is unknown whether a similar or different ADF version within molecule would have similar or different public health impacts in a post-marketing study. Without post-marketing data, it would not be possible to confirm, as the Draft Guidance states, “that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse” (p. 1)¹.

A further point is that post-marketing surveillance/studies have revealed that abusers actively attempt to defeat abuse deterrent formulations and share their recipes and results online. Systematic collection of posts discussing reformulated OxyContin were captured from seven online forums that discuss substance abuse between January 1, 2008 and September 30, 2013⁵. Posts were evaluated before and after the introduction of reformulated OxyContin on August 9, 2010. A total of 5,677 posts were identified as referring specifically to the reformulated version of OxyContin. Within this reformulated OxyContin-specific discussion, recipes related to reformulated OxyContin were mentioned 1,052 times within 825 posts (14.5% of reformulated OxyContin-related discussion) and evidence of feasible manipulation of reformulated OxyContin (i.e., use of the product other than swallowing the tablet whole) was observed 576 times within 498 posts (8.8% of reformulated OxyContin-related discussion) across the approximately 3-year period. While these numbers may appear relatively small, it is important to remember that most visitors to these Web forums do not post, but merely read the posts (aka “lurkers”)⁶. Immediately following the release of reformulated OxyContin, a thread emerged on one of the drug discussion forums titled, “Defeating the new OC time release.” In the first 70 days, 278 unique individuals had posted on this thread. During the same time, this thread was viewed more than 80,000 times⁷. This study and others^{8,9} suggest that a more or less libertarian community of individuals interested in substance use actively engages in discussion around the abuse of prescription opioid in general and efforts to defeat abuse deterrent formulations in particular. It may be unwise to simply assume that laboratory results alone can be generalized to this active and creative population.

Finally, we acknowledge and agree with recent reviews that data sources currently used in post-marketing studies of prescription opioids, including the ASI-MV and poison control center data, have significant limitations¹². We concur that the limitations of such data sources’ underlying methodologies and statistical demographic and regional representativeness need to be taken into account. The ASI-MV substance abuse treatment center data cited here, for instance, is not a representative sample of substance abuse treatment in the US. Since treatment centers within the ASI-MV system are not randomly recruited to join the network, data collected from these treatment centers cannot and should

not be generalized to all substance abuse treatment centers. Such limitations are inherent in this country's substance abuse landscape, rendering any data stream for this population susceptible to bias and limitations. Despite its limitations, it is important to not lose sight of the strengths of data collected from the ASI-MV data stream. For example, this data stream is designed for active data collection, and as such, is not dependent upon passive, retrospective, and often anecdotal data characteristic of other, commonly used data streams. Secondly, the ASI-MV system yields data in near real time: the majority of patient assessments (85%) are uploaded within the same day. Data are uploaded within two weeks for 95% of all assessments. While representative data are always preferable, when available, the public health importance of near-real time data from a sentinel population of those most involved with substances, such as the ASI-MV data, are likely to reflect use patterns of "early adopters". Data sources like the ASI-MV could prove invaluable for estimating the impact of tamper-resistant formulations, with respect to emerging trends in drug abuse indicators. The ASI-MV data stream is consistent with the types of data sources specifically described in the *Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry* that was finalized by FDA last year¹⁰. Evaluation of the impact of tamper-resistant formulations on specific ROAs requires prospectively collected data on ROAs used by abusers of the ADF and any comparator product(s). To our knowledge, the ASI-MV is the only existing data stream that systematically collects product-specific ROAs for each product endorsed by a respondent. Finally, the broad distribution of treatment sites in the ASI-MV network yields a sample that is similar in some respects to other, more comprehensive data streams. Demographic characteristics of patients within the ASI-MV data set are comparable to patients in the Treatment Episode Data Set (TEDS), suggesting that the ASI-MV data may be tapping a sample that is generally reflective of the larger population of substance abuse treatment centers.

In conclusion, we endorse the aim of the Draft Guidance on evaluating the abuse deterrence of generic opioid products. These products should certainly demonstrate that they are no less abuse deterrent than is RLD. When addressing this complex issue, Inflexxion respectfully recommends that the FDA consider some form of post-marketing requirement/study be proposed as part of the abbreviated new drug application (ANDA) when an opioid ADF generic is seeking approval. Specifically, we recommend:

- Post-market surveillance and/or an epidemiology study be required to validate findings from in vitro laboratory and from in vivo pharmacokinetic studies. The studies might be similar, in some respects, to the Category 4 post-marketing studies as outlined in the *Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*¹⁰.
- That generic prescription opioids be required to have a distinctive size, shape or other appearance from the RLD, and preferably from other prescription opioids, brand or generic. We recognize that this recommendation is counter to the Draft Guidance on size, shape and other physical attributes of generic tablets and capsules recently issued by the FDA¹¹. However, generic prescription opioids present a unique challenge for a post-marketing study when attempting to differentiate abuse patterns in the real world (i.e., outside of the laboratory). If generic ADF versions are made to look like the RLD, it will be impossible for self-report systems like the ASI-MV to differentiate what product abusers actually used. Identical size, shape and color of tablets and capsules will likely also impact the ability of reports to poison control centers to differentiate exposure of specific products. Reports to poison centers by lay people (i.e., individuals, family or friends) and perhaps even first responders will have difficulty

differentiating RLD from its generic or differentiating a generic product from other generics, unless a labelled bottle is available.

- We encourage the FDA to consider endorsing continued monitoring of social media. In particular the Web forums where discussion of prescription drugs for abuse purposes, including recipes for defeating specific abuse deterrent formulations continue. While other forms of social media (e.g., Twitter and Facebook) are certainly popular in recent years, the anonymity allowed by the Web forum format continues to support the popularity of this type of social media exchange among the subpopulation of recreational drug abusers.

We appreciate the opportunity to provide comments on this Draft Guidance and would welcome the opportunity to discuss our comments further. Thank you.

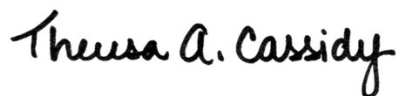
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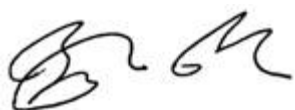
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