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LETTER TO THE EDITOR

Comment on Mayock SP, Saim S, Fleming AB. In Vitro Drug Release After Crushing: Evaluation of Xtampza® ER and Other ER Opioid Formulations

Nancy Crudele[1] · Jennifer Giordano[1]

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Dear Editor,

The publication by Mayock et al. [1] provides incomplete information that may leave your readership with a false sense of security regarding the expected performance and impact that the Xtampza® ER formulation may have on abuse in the real world. In our opinion, the study authors present a biased and faulty study design that does not subject Xtampza ER to manipulation techniques most relevant to this product's wax-based formulation. This study describes the release-rate profiles following in-vitro dissolution of intact and crushed Xtampza ER capsules vs. OxyContin® tablets, which are two extended-release (ER) oxycodone formulations with US Food and Drug Administration (FDA)-approved labeling for physicochemical abuse-deterrent properties (ADP). The study included seven other ER opioid dosage formulations with *no* FDA-recognized ADP.

This comparative Collegium-funded study portrays Xtampza ER in a misleading and irresponsible manner and lacks proper disclosures and clarity. In the interest of public safety, we believe it is important to advise your readers of the need to evaluate the vulnerability of study design, as well as to identify bias in interpreting the reported results in this study, including:

- The Xtampza ER comparative study appears to have been designed to assess manipulation techniques most suitable to exposing the susceptibilities of *other* ER opioid formulations, particularly opioid formulations that resist crushing.
- The design of this study does not evaluate relevant susceptibilities of wax-based formulations such as Xtampza ER to chemical manipulation or rapid extraction such as dose dumping in common household solvents.
- The authors failed to acknowledge the need to study manipulation techniques other than physical manipulation (crushing).
- The authors made overstatements about the reported benefits of Xtampza ER given the fact that this study only evaluates the opioid release profiles of specific ER formulations, either those with ADP that resists crushing or those that have no ADP, *after* physical manipulation.
- The study includes misleading information about the ease of physically manipulating OxyContin, which contradicts the reductions in the abuse of OxyContin as evidenced in published real-world studies [2–5].
- There is repeated emphasis on how "Xtampza ER is the only opioid formulation available without a boxed warning against crushing or chewing," despite the fact that the Xtampza ER boxed warning is similar to that of other opioids in including warnings about the potential

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✉ Nancy Crudele
Nancy.Crudele@pharma.com

[1] Medical Affairs, Purdue Pharma L.P., Stamford, CT 06901, USA

for addiction, abuse, and misuse that can lead to overdose and death.
- The authors fail to acknowledge that Xtampza ER is susceptible to abuse and that the product's ADP do not address abuse via oral overconsumption.

Contrary to the insinuation of Mayock et al., vulnerabilities of Xtampza ER, as for *all* opioids with ADP, do indeed exist. This fact has been repeatedly emphasized by the FDA—opioid formulations with ADP are not "abuse proof" [6–8]. While we agree with the need to conceal specific details regarding the manipulation techniques used in these studies (so as to not provide a road map to abuse), readers must not be left with a false sense of security regarding the expected performance and impact that Xtampza ER may have on abuse in the real world.

In general, ADP are complex and differ between formulations; therefore, they must be studied in various ways that are tailored to the specific formulation or technology. It is important to reiterate to your readers that *all* opioids with ADP have limitations, regardless of the technology utilized. Some of these vulnerabilities are shared across all opioid formulations, such as the ability to abuse by swallowing multiple tablets/capsules intact or taking more than directed. Others are distinct to their specific formulations, such as exposure to particular solvents or heat and, as is the case with wax-based formulations, without the need for physical manipulation to achieve rapid extraction (data on file, Purdue Pharma L.P., Stamford, CT, USA). As such, *no* opioid product with ADP should be viewed as being abuse proof [8]. Careful consideration must be taken when comparing the effectiveness of ADP across formulations having differing physical and chemical approaches to deterring abuse.

In Mayock et al., the authors have made various misleading and incomplete statements that, when taken together, seem to imply that OxyContin, with FDA-approved ADP, is not having a meaningful or sustained impact on deterring its abuse in the real world, and that Xtampza ER could be a better alternative, even though real-world studies for Xtampza ER do not yet exist. In particular, the authors make incorrect statements implying that OxyContin has not impacted the extent of its oral abuse. However, reductions in abuse, including reductions in oral abuse, of OxyContin have been demonstrated in real-world studies, and are consistent across various data sources and surveillance systems—some up to 5 years after the introduction of reformulated OxyContin [2–5].

Furthermore, Mayock et al. appear to overestimate the ability or willingness of an abuser to physically manipulate OxyContin in the real world. The authors overstate the ease of physically manipulating OxyContin and they artificially remove the real-world components of ability and desire by utilizing laboratory-derived knowledge to govern the best method of physical manipulation, which may not be understood or routinely applied by abusers. As noted earlier, published studies support reductions in abuse with reformulated OxyContin, and these reductions have been shown to be sustained. Severtson et al. set out to assess so-called "feasible methods" to circumvent the OxyContin ADP posted on Internet forums and studied the notion of how, if these methods became widespread, abuse and diversion could increase. Rates of opioid analgesic abuse and diversion were analyzed across four programs for the 5 years following introduction of OxyContin with ADP to determine whether initial reductions in OxyContin abuse persisted, despite the availability of purported methods to overcome ADP. The authors found that OxyContin abuse and diversion declined significantly each quarter after reformulation and persisted for 5 years. In addition, abuse through both oral and non-oral routes declined following its reformulation [3].

Currently, abusers appear to be more focused on techniques that involve crushing, as that has been the common method of opioid extraction with available ER formulations for the last two decades [9]. However, as it relates to newer ER formulations with ADP introduced to the market, with the passage of time and increased utilization and availability, abusers can be expected to become more informed as to how to overcome specific ADP. This has been the case with Xtampza ER and its wax-based formulation. Our intent with this letter is not to inform on the proposed or known methods to overcome the ADP of Xtampza ER, but instead, to emphasize that no opioid with ADP is abuse proof, a fact that the FDA has repeatedly emphasized. The FDA and others knowledgeable in the area of opioid abuse recognize that opioid abuse is a highly complex and multifactorial problem, where formulations with ADP are one potential tool to help address this problem. They are not a total solution to the problem or a treatment for opioid addiction [6, 7].

Another message of concern in this paper is a repeated emphasis on how "Xtampza ER is the only opioid formulation available without a boxed warning against crushing or chewing." The authors are silent on the fact that the Xtampza ER boxed warning, as for all opioids, *does* include warnings about the potential for addiction, abuse, and misuse, as well as the following: "As extended-release products such as Xtampza ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present" [10].

Given the importance of addressing the US opioid abuse and overdose crisis, we are pleased to see that the FDA continues to support the innovation of opioids having ADP. Yet, the manner in which Xtampza ER has been portrayed

in this publication presents certain public safety concerns. This is particularly concerning because this collegium-sponsored study evaluating the "effectiveness" of ADP (1) does not use extraction techniques vulnerable to wax-based formulations; (2) ignores reductions in abuse, including reductions in oral abuse, of OxyContin seen in real-world studies up to 5 years after introduction of the reformulation; (3) overstates the ease of physically manipulating OxyContin; and (4) fails to acknowledge the fact that ADP are not abuse proof and do nothing to address abuse via oral overconsumption or the risk of addiction.

It is important that physicians, patients, and society are not given a false sense of security, as it relates to the anticipated impact that these formulations may have on abuse and its related outcomes in the real world. Physicians, patients, and society need to fully understand the risks of addiction, abuse, misuse, and overdose with opioid medications, including those with ADP.

Compliance with Ethical Standards

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Conflict of interest Nancy Crudele and Jennifer Giordano are full-time employees of Purdue Pharma L.P., Stamford, CT, USA.

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