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EXPERT OPINION

Painful decision-making at FDA

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The FDA is critical in ensuring that medications are safe and effective. However, the FDA's decision-making process for opioid analgesics is complicated by the need to address patients with complex clinical pain syndromes while balancing public safety concerns involving opioid misuse and abuse. Several recent regulatory decisions by FDA have exposed the complexity of this regulatory tug of war. For example, the FDA's decision to include a requirement for tamper resistance for extended-release oxycodone products but not for extended-release oxymorphone or hydrocodone preparations is concerning. Although tamper resistance is an imperfect solution, it provides a modicum of abuse prevention. Additionally, the rewording of the labeled indication (from 'moderate to severe pain' to 'severe enough pain') for extended-release opioid analgesics, in an attempt to provide clarity, resulted in an equally if not more vague statement of appropriate use. Furthermore, the postmarketing requirement for continued data regarding safety and efficacy have been affirmed by FDA but some of the proposed means to acquire those data will likely result in unclear answers and may have undesired consequences. We fully support the important role of the FDA but raise concerns about the occasional lack of consistency and transparency.

Keywords: addiction, FDA, opioid, pain, safety

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FDA has the daunting responsibility of assessing the efficacy and safety of new drugs based primarily on data submitted by the sponsor. Not surprisingly, there are often aggressive attempts to influence FDA's decision-making process, most frequently from patient groups, professional medical organizations and the pharmaceutical industry. These constituencies generally advocate for favorable regulatory decisions, even for medications with little established efficacy or with serious safety concerns. Occasionally, drug approval is opposed by consumer advocacy groups, most often on the basis of safety concerns.

The decision-making process for opioid analgesics poses a unique situation for FDA. Advocates for more liberal drug approval are countered by an increasing number of vocal opponents, leaving FDA to navigate arguments on both sides of a highly polarized debate. Advocates for greater access to opioids argue that restricting availability may jeopardize treatment of pain, and that responsible patients should not be penalized for the inappropriate actions of those who misuse, divert or abuse these medications. Conversely, advocates for patients with drug addiction and relatives of those who have died from opioid overuse argue that the ready availability of opioids is the primary driver of the expansive prescription drug epidemic, and that the use of opioids for chronic pain is not supported by good evidence that the drugs' benefits outweigh their risks. Importantly, advocates on both sides of this issue claim to have the best interests of patients at heart.

Recent regulatory decisions by FDA have exposed the complexity of this regulatory tug of war. After years of advisory committee meetings, congressional inquiries and legal cases, FDA recently announced several decisions that are likely to confuse clinicians and disgruntle both constituencies. Here, we review several of these actions, highlight shortcomings and inconsistencies in FDA's decision-making

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and discuss the potential implications for public health. FDA does not typically release granular explanations for its decisions, leaving many to wonder if there should be greater consistency – perhaps through regulatory transparency – to this process. Paradoxically, in this particular situation, FDA's response to a Citizen's Petition provided some insight into their deliberations [1].

In August 2010, the manufacturer of extended-release oxycodone (OxyContin) replaced the product with a 'tamper-resistant' formulation designed to resist crushing and dissolution. In April 2013, FDA ruled that new generic formulations of extended-release oxycodone could not be marketed unless they mirrored the tamper-resistant properties of the new product. However, 1 month thereafter, FDA ruled that generic extended-release oxymorphone products need not contain the same tamper-resistant properties as the original product, Opana ER. These seemingly paradoxical decisions were based on FDA's determination that OxyContin was withdrawn by the manufacturer on the basis of safety concerns, whereas Opana ER was withdrawn for other, unspecified reasons [2]. FDA also accepted evidence that the reformulated OxyContin product merited classification as an 'abuse-deterrent' formulation [3], a lofty designation not previously granted to an opioid analgesic [4].

In September 2013, in an effort to address the overprescribing of opioids, FDA revised the labeling for all extended-release opioid products. Advocates for safer opioid use had encouraged FDA to remove 'moderate pain' from the indications for chronic opioid therapy, leaving only severe pain as a labeled indication. FDA did indeed strike the phrase, but revised the label in its entirety to indicate that opioids could be used for 'pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate'. The determination of pain severity is a complex and subjective task, but deciding whether pain is 'severe enough' is even more challenging. In this decision, FDA effectively took a step in both directions.

In October 2013, in response to pressure from the Drug Enforcement Agency and consumer advocacy groups, and in accordance with the advice of its own advisory committee, FDA moved to reschedule hydrocodone combination products from Schedule III of the Controlled Drugs Act to Schedule II. This change makes hydrocodone more difficult to obtain by restricting prescribing; it also carries greater regulatory scrutiny. FDA's decision, more than a decade in the making, was hailed by many as sensible because it harmonized the status of these products with those of similar products containing other opioids, and because combination hydrocodone products (such as Vicodin and Lortab, which contain acetaminophen) are the most widely prescribed drugs in the USA. Indeed, such products often constitute the initial opioid exposure among patients who eventually become addicted to opioids [5], and overuse is an important cause of acetaminophen-induced hepatotoxicity. What remains unknown is whether the move will have any of the predicted unintended consequences, such as more difficult access for patients using the drug responsibly or the increased use of heroin (an easy to obtain and inexpensive replacement) or other Schedule II opioids that will now be in the same regulatory schedule [6]. Of additional concern, many of these other opioid options are single-entity products that may be more readily abused because they do not contain acetaminophen.

One day following the decision to 'upschedule' hydrocodone combination products, FDA announced approval of an extended-release (but not tamper-resistant) formulation of hydrocodone – Zohydro ER. Interestingly, the product had been soundly rejected in an 11 – 2 vote by an FDA advisory committee, largely because the formulation offered no tamper resistance or deterrent to abuse. In other words, those intent on abusing hydrocodone through a means other than simply ingesting an excess amount, can now (as with the original OxyContin) crush and insufflate or inject pure opioid. The move also raised alarm from public safety advocates. Despite evaluating Zohydro ER in a clinical trial designed to maximize efficacy and minimize safety concerns, there were several deaths, including one from pill hoarding [7]. The eventual safety profile of Zohydro will almost certainty be less favorable in clinical practice, an observation made by FDA staff in 2012 [7].

Increasingly, FDA compels drug sponsors to perform post-marketing studies as a requirement for continued approval of potentially dangerous medications. Indeed, this was mandated for Zohydro ER, 'to assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose and death associated with long-term use beyond 12 weeks'. However, this approach disregards the poor completion record for such studies [8]. Moreover, and of greater consequence, FDA's decision exposes thousands of patients to these very risks while the data accrue.

Given the limited evidence for the use of opioids for chronic pain – most studies compare opioids to placebo, and not a single randomized trial exceeds 6 months in duration – and the conflicting priorities of access to treatment and patient safety, it is clear that innovative approaches are required to study this complex problem. But this creativity is itself subject to biases. We suggest that regulatory decisions should be informed by pragmatic clinical trials comparing opioids to active comparators (e.g., naproxen) rather than placebo, with assessment of clinical meaningful outcomes such as quality of life, functional outcomes and safety end points after at least 6 – 12 months of treatment.

These studies are best implemented at the initiation of analgesic therapy, rather than attempting to study it in a 'controlled withdrawal' model in which worsening pain after discontinuation of therapy would 'confirm' the need for such therapy [9]. Most patients on chronic opioid therapy exhibit pharmacologic dependence, and pain upon cessation may simply represent opioid withdrawal rather than untreated pain per se. Conversely, some suggest that it is best to use 'enriched

enrollment' studies as a means of maximizing efficiency and safety in early clinical studies [9]. This approach, used in the Zohydro study mentioned above, involves studying carefully screened patients to identify those most likely to benefit and least likely to be harmed. This approach is unquestionably efficient, but it will cast the drug in the best possible light. The resulting conclusions, however, simply cannot be generalized to clinical practice. We suggest that 'enriched enrollment' studies are unsuitable to inform regulatory decisions regarding opioids and should not be accepted by FDA.

We have worked closely with FDA and other government organizations and fully support their mission of bringing effective and safe medication to patients, in an objective and deliberate manner. At the same time, we must view these decisions with a critical eye and apply practical reasoning and clinical insight into the process. We believe that the lingering doubts about long-term effectiveness of opioids [10] should be aligned with the increasingly apparent risks to public health. The risks extend to patients with chronic pain, who, like physicians, have been systematically misled about the addictiveness and effectiveness of chronic opioid therapy by both health care providers and the pharmaceutical industry [11]. We believe that given the current state of affairs, regulatory decisions regarding opioids should be guided primarily by patient safety considerations and supported by high-quality evidence of therapeutic benefit. FDA should support the enhancement and interstate collaboration of prescription drug-monitoring programs, pharmacy- and insurer-based diversion detection programs, provider-level screening programs for potential opioid misuse, patient provider agreements for chronic, and perhaps short-term, opioid use, development of non-conflicted prescribing guidance, and mandated education through its risk evaluation and mitigation strategies [12,13]. In addition, we advocate for greater transparency in FDAs decision-making to explain why these decisions, such as those involving two nearly identical long-acting opioid formulations, are sometimes contradictory. Given that the needs of patients with chronic pain and addiction are two looming public health concerns, everyone deserves a full accounting of the considerations and influences that bear on the regulatory process.

Declaration of interest

The authors have no competing interests to declare and have received no funding in preparation of the manuscript.

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