

# A Review of FDA's Action Plan to Proactively Reduce Prescription Opioid Abuse

The increasing rates of opioid abuse and dependence, as well as the alarming rise in the number of prescription opioid-related overdoses and deaths in the US (19,000 overdose deaths which now exceed deaths caused by motor vehicle accidents<sup>1</sup>) has caused government agencies around the globe to launch various initiatives in an attempt to stem the tide of this devastating public health crisis. In response to this, as well as harsh criticism of regulatory bodies for some recent opioid approvals, and unprecedented mounting political pressure from lawmakers, the US Food and Drug Administration (FDA) has recently outlined a comprehensive action plan to reduce prescription opioid abuse. Although policy updates such as this are typically presented in a federal register, the immediacy and severity of this wide-reaching problem necessitated a much more public setting of a special report written for a widely-read medical journal<sup>2</sup>. This action plan consists of several wide-ranging proactive strategies; the successful implementation of which will greatly impact pharmaceutical companies attempting to gain approval, not just for opioid medications but possibly for any analgesic medications. These strategies include a reexamination of opioid labelling and monitoring; the prioritisation of abuse-deterrent formulations and non-opioids; the expansion of reversal medications; a more complete assessment of paediatric issues; and a plan to provide better evidence for chronic pain treatment. The purpose of this CNS Watch article is to review this action plan and highlight these strategies and their potential impact on the development and approval of analgesic medications.

## Reexamination of Opioid Labelling and Monitoring Strategies

In an effort to curb this devastating epidemic and address past criticisms, the FDA intends to launch a wide-ranging reexamination of the policies and practices that are currently in place in terms of opioid approvals, labelling and monitoring strategies. To this end, the FDA have sought out assistance from the National Academy of Medicine to help develop an enhanced regulatory framework for the review, approval and ongoing monitoring of opioid medications. Additionally, in March an independent panel of experts will meet publicly to advise the FDA on these important issues and to make detailed recommendations on the development of alternative analgesics and post-marketing surveillance commitments, especially in terms of extended release/long-acting (ER/LA) opioids. Although last updated in 2013, a general reevaluation of ER/LA opioid labelling will be undertaken which will not only include wide-ranging descriptions of risks, monitoring requirements, and continual reassessment of the ongoing need for opioids (which will only be dispensed in limited quantities), but also the requirements for extensive post-marketing

research. This post-marketing requirement will be in addition to the existing risk evaluation and mitigation strategy (REMS) programmes which require funding of medical education initiatives at low to no cost, covering the appropriate use of such medications<sup>3</sup>. The advisory committee will also offer specific guidance regarding the expansion of the scope and content of prescriber education, as well as the advice on the expansion of these programmes to the entire class of opioids.

## Prioritise Abuse-Deterrent Formulations and Expand Access to Overdose Medications

The agency's strong support for the development of abuse-deterrent formulations has generally followed the interests and progress in technology pioneered by numerous pharmaceutical companies<sup>4</sup>. Despite the fact that five of these abuse-deterrent formulation products have already been approved to date, there remains a great need for more widely-available, less costly and more effective abuse-deterrent opioids. To support this, the FDA will issue draft guidance on generic abuse-deterrent opioids. Importantly, opioid medications that do not have abuse-deterrent properties may also face modified criteria for review and approval, and will likely also require advisory committee review as lawmakers have requested such a comprehensive review to inform all of its opioid approval decisions. Further, the agency will prioritise the development of non-opioids that do not have the hallmark opioid addictive properties by expediting the regulatory process for these drugs. This includes non-pharmacologic treatments as well as other more traditional pharmaceutical products. In addition to this, there is also strong support for both the development and marketing of drugs such as naloxone that can efficiently counteract the effects of opioids and reverse the effects of overdose. Recent approvals of intramuscular and intranasal naloxone formulations are cited as important measures in combatting opioid-related deaths, so much so that the expansion of these reversal drugs is being considered for over-the-counter use, which would greatly increase their availability and use.

## Strategies to Assess Paediatric Pain

The recent labelling changes for OxyContin for use in paediatric patients aged 11 and older generated substantial controversy from lawmakers and patient advocacy groups. For many years, opioids such as this were prescribed off-label to children in severe pain (e.g., from cancer, trauma or following surgery) and fears stemming from practice changes anticipated after such an approval have emerged. Of note, this approval came without convening an advisory committee and although arguable, several prominent lawmakers and pain researchers have opined that had there been an advisory committee



meeting, there would not have been an approval. To help remedy this, the FDA will proactively assemble a paediatric advisory committee on two occasions to specifically address issues related to the use of opioids in children and adolescents including providing further guidance for labelling, the development of high-quality evidence to guide treatment, and methods to improve practice patterns in order to reduce opioid abuse and diversion. Importantly, in terms of post-approval commitments, the FDA will require sponsor companies to conduct multiple studies as well as mandate annual reporting of adverse events, including accidental exposures and overdoses in children and adolescents. This will be done in an attempt to provide more comprehensive analyses of side-effects, medication errors and prescribing patterns (including types of prescribing physicians and various types of pain indication), and help to identify factors important in creating and maintaining adolescent opioid use disorders, so that these can be successfully addressed in future development programmes.

#### **Providing Better Evidence for Chronic Pain Treatment**

Finally, the FDA plans on tackling issues surrounding the dearth of evidence surrounding the long-term benefits of opioids in chronic pain patients. The lack of efficacy is

evidenced by numerous safety and usage trials in which the long-term effectiveness of opioids cannot be clearly established empirically<sup>5</sup>. It is also commonly acknowledged that chronic use of opioids may paradoxically induce pain, cause diminished tolerance for pain, reduce pain thresholds and actually result in higher doses of pain medication<sup>6</sup>. In order to more firmly establish the long-term benefits of opioids, the FDA is demanding that post-marketing studies derive evidence over at least one year for subjects who are randomly assigned to continue opioid therapy or to be weaned from opioid therapy according to a predefined schedule.

Of course, all of these strategies and their associated efforts need to be carefully balanced against drug developers' sustained obligation to ameliorate the devastating impact of acute and chronic pain suffered by millions of patients around the globe. In addition to these strategies, regulatory bodies should also take the lead in educating all physicians on the biological underpinnings of pain and providing prescribers with a stronger understanding of the appropriate use and management of pain medications with an eye toward curbing inappropriate prescribing patterns through the reinforcement of evidence-based pain management

approaches. Physicians and clinical trialists should also be made more aware of methods that proactively address the potential for opioid abuse amongst their patients. Tools such as the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) or the Opioid-Related Behaviours In Treatment (ORBIT) scale were developed to help determine how much monitoring chronic pain patients on long-term opioid therapy might require in terms of addiction and misuse, as well as the other aberrant medication-related behaviours such as diversion. These useful and easy-to-use measures enable clinicians and sites to identify patients who may have greater difficulty modulating their own use of opioids requiring extra monitoring and management, quantify aberrant behaviour, and importantly, assess changes over time. Finally, all physicians who prescribe pain medications



or are involved in analgesia clinical trials should also be trained, not only to identify, but also to treat opioid use disorders using already approved medications such as buprenorphine alone or in combination with naloxone. This is especially important given the possibility that policy-driven reductions in the availability of prescription opioids with accompanying increases in abuse-deterrent opioids may unfortunately lead to an unintended upturn in the rates of illicit drug use in some populations.

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