In July of 2012, Physicians for Responsible Opioid Prescribing (PROP) submitted a petition to the Food and Drug Administration (FDA) asking the agency to update labeling of opioid analgesics. According to a copy of the letter submitted to the FDA, the group stated that: “an increasing body of medical literature suggests that long-term use of opioids may be neither safe nor effective for many patients, especially when prescribed in high doses.” The group wanted the FDA to “exercise its regulatory responsibility over opioid manufacturers by prohibiting the marketing of opioids for conditions in which their use has not been proven safe and effective.” The petitioners suggested specific action should be taken by the agency:

- Strike the term “moderate” from the indication for non-cancer pain
- Add a maximum daily dose, equivalent to 100 mg of morphine for non-cancer pain
- Add a maximum duration of 90 days for continuous (daily) use for non-cancer pain

In response to the PROP petition, a multidisciplinary group of clinicians involved in pain management formed Professionals for Rational Opioid Monitoring and Pharmacotherapy (PROMPT). According to the group's Web site, the motivation for forming PROMPT was to address some of the concerns raised by PROP—the safe use of chronic opioids—“by mitigating these risks with appropriate proactive and ongoing validated interventions intended for the benefit of the patient care and public safety,” noted Jeffrey Fudin, BS, PharmD, and one of the founders of PROMPT.

FDA Ruling

After over a year of debate, petitions, and hearings, in September the FDA announced class-wide safety labeling changes and new post-market study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain. The actions of the FDA “demonstrates its resolve to reduce the serious risks of LA/ER opioids while still seeking to preserve appropriate access for those patients who rely on these medications to manage their pain,” noted FDA Commissioner Margaret A. Hamburg, MD. Given the serious risks of using ER/LA opioids, the class-wide labeling changes, when final, will include important new language to help physicians tailor their prescribing decisions based on a patient's individual needs, noted the agency in a press release.

Some aspects of the FDA ruling pleased members on both side of the debate. The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The updated FDA indication further clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief.

In addition, the FDA recognized that more information is needed to assess the serious risks associated with long-term use of ER/LA opioids. Therefore, the agency is requiring the drug companies that make these products to "conduct further studies and clinical trials. The goals of these postmarket requirements are to further assess the known serious risks of misuse, abuse, increased sensitivity to pain [hyperalgesia], addiction, overdose, and death."

The FDA is also requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening and require management according to protocols developed by neonatology experts. NOWS can occur in a newborn exposed to opioid drugs while in the mother's womb. Symptoms may include poor feeding, rapid breathing, trembling, and excessive or high-pitched crying.
In response to the citizen petitions submitted by PROP and PROMPT, Douglas Throckmorton, MD, deputy director for regulatory programs in the FDA’s Center for Drug Evaluation and Research, noted that “the FDA remains committed to improving the safety of opioids and to continuing to engage in efforts to evaluate and mitigate the risks associated with opioid use. The safety labeling changes reflect the FDA’s current understanding of the risks and benefits of these products. The FDA will evaluate the results of the postmarket studies, continue to monitor relevant safety data, and take further safety action, as warranted,” he added.

**PROP Response**

Andrew Kolodny, MD, President of PROP, told *Practical Pain Management* that he was “disappointed that the FDA left the door wide open for drug companies to continue to promote opioids for conditions where the risks of use are likely to outweigh benefits.” For example, he noted that “the bulk of patients receiving opioids long-term for chronic pain suffer from low back pain, fibromyalgia, and chronic headache. Leading experts agree that opioids are a lousy treatment for these problems, and the risks of using opioids are likely to outweigh benefits.” Federal law, he added, is supposed to prohibit drug companies from promoting products for conditions where the risks are likely to outweigh benefits. “What PROP wanted was a narrower indication and more specific instructions on labels, such that use for these conditions [low back pain, fibromyalgia, chronic headache] would have been off-label—that is, allowed to be used by prescribers, but not allowed to be promoted by drug companies. That is what we were aiming for.”

On the other hand, Dr. Kolodny was pleased that the FDA agreed with their main argument—that evidence is lacking to support long-term and high-dose use of opioids. However, he noted that “since [the FDA] agreed with us that long-term use may be neither safe nor effective, they should have made chronic opioid therapy off-label now instead of asking drug companies to perform long-term trials and report back. What happens if the research proves that far more patients are harmed by chronic opioid therapy than helped? While the FDA waits for the drug companies to conduct trials, 100,000s of people may be started on a therapy that can be harmful and difficult to get off of.”

**PROMPT Response**

“For the most part, PROMPT couldn’t be more pleased,” Dr. Fudin told *Practical Pain Management*. “Interestingly much of the mainstream media has focused on the ‘major’ changes to FDA labeling for ER/LA opioids. The truth is that the new label changes decreed by the FDA are an extension of REMS [Risk Evaluation and Mitigation Strategies] and are more likely a result of that ‘Evaluation’ than any citizens’ petition put forth by PROP. Moreover, while helping to mitigate risk moving forward, the new labeling is more patient-friendly than previous,” he noted. By changing the labeling for ER/LA opioids from “moderate to severe” to “severe enough to warrant around-the-clock opioids,” the FDA is “basically allowing patients and providers the latitude to decide if constant daily pain that otherwise precludes activities of daily living is in fact ‘severe enough’ to warrant continuous around-the-clock opioid therapy. The difference is that now it is not necessarily based on a number scale or one that ranges from low-moderate-severe. This decision by the FDA is practical, fair, and responsible,” he stated.

After carefully reviewing and outlining available literature, or lack thereof, noted Dr. Fudin, the FDA sent a clear message:

- They denied change to a maximum 100 mg daily morphine equivalent (MEQ) dose
- Denied a 90-day limit for non-cancer pain
- Denied a differentiation between cancer and non-cancer pain.

According to Dr. Fudin, “The heart of FDA’s final decision is that they were quite responsible, clearly were looking out for the patients, and intend to employ a ‘strategy’ that employs continuous monitoring to assess risk, evaluate data, and mitigate harm. That is what the FDA promised, and that is what they are doing. Hats off to the FDA! I thank you; patients thank you; and PROMPT thanks you!”

PPM recently surveyed our editorial board members and asked for their opinions on the subject. A sampling of board’s responses can be found on page 15.

**References**


If you would like to weigh in on the subject, please go to the PPM Survey at PracticalPainManagement.com and vote. Results of the survey will appear in upcoming issues.
PPM's Editorial Board Response to FDA Ruling

FDA Did Well
Gary Jay, MD
Raleigh-Durham, NC

I think the FDA did well. They obviated the absurd 90-day use limit. They determined to stop using “mild, moderate, and severe” descriptors of pain, therefore doing what PROP wanted. However, what they did is make an area open to interpretation that shouldn’t hurt patient care: “ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.” If the physician feels that the patient needs ER/LA opioids, and has no appropriate alternative treatments that are adequate, the patient may get the medications if indicated. Their requests for other postmarketing studies are, I believe, reasonable. All in all, I think the agency did a great job with their determination.

It Could Have Been Worse
Joseph Shurman, MD
La Jolla, CA

I am okay with the FDA release. It could have been worse if they followed the recommendations of the PROP Group. By mandating that opioid companies conduct postmarketing studies, we may finally get the long-term study results we have needed. We need these long-term studies of patients with non-malignant pain on opioids (extended release) to demonstrate improvement of function, quality of life, and pain relief as well as to show what is the frequency of interpretative that shouldn't hurt patient care: “ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.” If the physician feels that the patient needs ER/LA opioids, and has no appropriate alternative treatments that are adequate, the patient may get the medications if indicated. Their requests for other postmarketing studies are, I believe, reasonable. All in all, I think the agency did a great job with their determination.

PPM Invites You to Take a Survey

Variability in Opioid Equivalence

Patients are often switched to different opioids in an effort to improve analgesic efficacy, increase tolerability, diminish side effects, and/or mitigate hyperalgesia. In some cases, lack of efficacy may be due to improper conversion. We know that up to 80% of patients experience a positive response when switching agents appropriately, even at a lower than “equivalent” dose because of reduction for cross-tolerance. However, despite providing successful symptomatic improvement, opioid analogues are involved in 75% of prescription drug overdose deaths, accounting for 16,651 deaths in 2010. Improper opioid conversions can put patients at an increased risk of under-dosage or overdosage.

In consideration of these issues, a survey has been created to analyze the variability among various clinician types (physicians, pharmacists, physician assistants, and nurse practitioners) in their calculations for five preselected opioids at fixed doses. The primary hypothesis is that there will be statistically significant differences in the average response and ranges of responses to these requested conversions. We invite you to participate in this anonymous survey to determine disparity and variability in opioid conversions among clinicians. Please go to PracticalPainManagement.com and take the survey.

References