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April 9, 2013

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket FDA-2012-P-0818

Dear Commissioner Hamburg:

On behalf of the physician and medical student members of the American Medical Association (AMA), I am writing to urge the Food and Drug Administration (FDA) to reject the petition from Physicians for Responsible Opioid Prescribing (PROP) seeking changes to the labeling of opioid analgesics. Specifically, the PROP petition calls for the agency to label immediate and extended release opioids only for severe non-cancer pain in place of current labels indicating these medications can be used to treat moderate-to-severe pain. It also calls for a maximum daily morphine equivalent dose of 100 milligrams and a maximum duration of 90 continuous days when opioids are indicated for non-cancer pain.

The AMA recognizes that there is an epidemic of prescription opioid abuse and diversion and strongly supports many efforts that are underway to address this crisis, including the FDA's recent call to action to physicians. Current efforts to address the epidemic and improve prescribing include recent changes in the labeling of most opioid analgesics. These changes made the labeling consistent among extended-release and long-acting products and increased the prominence of information regarding risks and precautions, such as those for abuse and misuse, respiratory depression, and accidental exposure. We believe these labeling changes, which were done as part of the FDA Risk Evaluation and Mitigation Strategy for extended-release and long-acting opioids, address the Drug Enforcement Administration's recommendation in its comment on the PROP petition that the FDA "implement suitable measures, such as labeling revisions, to help mitigate the adverse impact on the public health resulting from abuse of these products."

The PROP petition, in our view, is not an appropriate basis for any of the labeling changes it seeks. In the absence of additional studies that examine specific clinical questions, retrofitting labels that were based on clinical trials using "moderate-to-severe" pain as the criterion for opioid efficacy and arbitrarily setting a maximum daily limit through regulatory edict is not a sound approach. The AMA has longstanding policy that:

- (a) an FDA decision to approve a new drug, to withdraw a drug's approval, or to change the indications for use of a drug must be based on sound scientific and medical evidence derived from controlled trials and/or post-market incident reports as provided by statute;
- (b) this evidence should be evaluated by the FDA, in consultation with its Advisory Committees and expert extramural advisory bodies; and
- (c) any risk/benefit analysis or relative safety or efficacy judgments should not be grounds for limiting access to or indications for use of a drug unless the weight of the evidence from clinical trials and post-market reports shows that the drug is unsafe and/or ineffective for its labeled indications. (AMA Policy H-100.992)

As required by the Patient Protection and Affordable Care Act, the Institute of Medicine (IOM) recently conducted a major study, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." The IOM concludes that health professionals "should increasingly aim at tailoring pain care to each person's experience." The AMA shares the IOM's view that the treatment of pain cannot be fit into a one-size-fits-all approach. The AMA is especially concerned, therefore, about PROP's recommendation to limit the labeled indications for opioid analgesics to "severe" instead of "moderate-to-severe" non-cancer pain. Pain intensity assessments are entirely subjective and rely upon patients' own reports. One person's "moderate" is another person's "severe," and an individual patient's experience with and self-reported pain levels may fluctuate between "moderate" and "severe" levels. AMA policy does not regard a drug label as a standard of accepted medical practice nor a substitute for clinical judgment, but such a labeling change clearly would affect patients seeking medically necessary pain relief and increase the risk that prescribing physicians could be branded as practicing outside of accepted medical standards based on subjective and inconsistent measures.

The AMA also opposes PROP's call for a maximum daily dose of 100 milligrams. While it seems clear that the risks of harm from opioid analgesic use increase with the total daily dose and duration of therapy, no bright line exists to demarcate thresholds that would be widely applicable on a population basis and could meet the scientific rigor required for labeling decisions. Patients demonstrate extraordinary variability in their response to opioid analgesics. Several confounding variables exist that can be best managed by clinical assessment, dose titration, monitoring and structured follow-up, not by designating an arbitrary dose ceiling. Additionally, some patients may be prescribed an immediate-release opioid analgesic for use as a rescue dose to manage acute exacerbations of persistent pain conditions being managed with a long-acting opioid. On days that they need to take the rescue dose, the total dose could easily exceed 100 milligrams, even if the maintenance dose is substantially lower. The petition itself provides no randomized controlled trial data for a 100 milligram maximum in morphine equivalents, or for the other labeling changes it seeks, yet it relies on the premise that if a medical practice has not been fully validated, it should not be used or is inherently harmful.

The AMA agrees with the IOM's finding that more scientific research should be undertaken to improve our knowledge regarding the comparative effectiveness of alternative treatments in reducing

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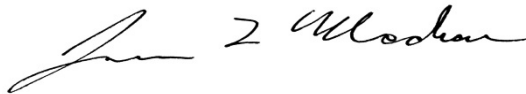
pain and pain-related disability. The IOM also recommends that the FDA work with other agencies, industry, and researchers to develop new and faster ways to evaluate and approve new pain therapies, such as novel forms of patient stratification in clinical trials and novel investigative endpoints. The AMA supports these efforts. The PROP petition, conversely, is not based on valid, scientific data from new studies, nor does PROP suggest that there are better, proven treatment options for these patients that ought to replace opioid analgesics on the 91st day of pain therapy. This change would effectively eliminate the use of opioids for chronic non-cancer pain.

Physicians work hard to balance their ethical obligation to treat patients with legitimate pain management needs against the need to identify drug seekers and prevent abuse, overdose, and death from prescription drugs. Much of this discussion is occurring without regard to the actual patient experience. The evidence is mired in an arena in which virtually no uniform, reliable, or reproducible metrics exist around the perception of pain. As noted above, this is a subjective experience on the part of patients and we have yet to fully understand all of the factors that influence the individual pain experience. In our view, the PROP petition essentially asks the FDA to modify the labels for opioid analgesics in order to take treatment decisions about pain care outside of the physician-patient relationship in many cases. Clearly, a subpopulation of chronic pain patients exists for whom the risk-benefit balance is better for opioids than other treatments. In such patients, the PROP labeling recommendations would shift the balance away from the sometimes negative consequences of opioids (by limiting their availability) to increase patient suffering with no valid scientific basis.

The AMA urges the agency to reject the PROP petition.

Thank you for your consideration of our views on this important issue. If you have any questions, please do not hesitate to contact Sandy Marks in our Washington, DC office at sandy.marks@ama-assn.org or 202-789-4585.

Sincerely,

A handwritten signature in black ink, appearing to read "James L. Madara". The signature is fluid and cursive, with a large initial "J" and "M".

James L. Madara, MD