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Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Dear FDA Officers:

We write to respond to the petition submitted by Physicians for Responsible Opioid Prescribing (PROP) requesting label changes from the FDA in connection with certain opioid products.

The American Academy of Pain Medicine (AAPM) shares the commitment of the petitioners to find ways to curb prescription pain medication harm. However, we have serious concerns about the petition and believe the rationale for the requested changes is seriously flawed, potentially harmful to patients with debilitating pain conditions for whom opioid therapy is indicated, and without substantive scientific foundation.

The petitioners request that the FDA strike the term "moderate" from the indication for noncancer pain. The AAPM believes there is no clinical method to differentiate moderate from severe pain other than patient report. Further there is often substantial variance over minutes, hours and days in pain intensity reports; pain is not a static condition. Nor is there any scientific evidence to show that moderate pain has any more or less adverse outcomes than the labeling of pain as "severe." Further, for years clinical trials leading to the approval of many of the currently available opioid formulations have used "moderate-to-severe pain" as the criterion in opioid efficacy studies, not severe pain only. Since the petitioners are basing their recommendations on what they believe is a lack of evidence, it seems reasonable to call for evidence to support this recommendation that the moderate-to-severe criterion now be changed to "severe pain."

The petitioners also suggest the FDA restrict labeled indications for the designated opioids to a maximum daily dose of 100 milligrams of morphine equivalents for noncancer pain. This dose limit is an arbitrarily chosen number that disregards pharmacokinetic, pharmacodynamic and pharmacogenetic differences among patients

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and inter-individual variability in opioid response and analgesia. As well, setting a 100 mg ceiling dose could be dangerously misleading, implying that doses below 100 mg are inherently safer than higher doses in any given individual or population of patients. The petitioners present as support for this restriction studies showing higher doses contribute to more deaths. Although these studies have flaws that are addressed below, it is certainly likely that there is an overall correlation between dose and morbidity. However, this correlation is not a simple one, with several likely confounding variables, including medical and psychiatric co-morbidities and drug-drug interactions, among other factors. These elements of clinical assessment, dose titration, monitoring and structured follow-up cannot be managed by designating an arbitrary dose ceiling. Rather, appropriate dosing requires education, training and experience, consistent with the larger sphere of complex chronic disease management. It is our respectfully stated view that the petitioners are seeking a simple solution to a complex problem, and in so doing, misdirecting the more appropriate course of action that is needed to rectify gaps in prescriber capacity to prescribe safely.

Very important additional factors that have been recognized to be associated with unintentional overdose deaths have not been addressed by the petitioners' requests. Initiating and/or rotating to methadone and other long-acting/extended-release opioids present key principles of prescribing not recognized in the 100 mg ceiling limit [Webster & Fine 2012:562-70; Webster & Fine 2012:571-4]. The Centers for Disease Control and Prevention (CDC) reports that a third of opioid-related overdose deaths involve methadone (CDC 2012). For instance, if every prescriber knew how to safely prescribe methadone, which has been associated with a disproportionate number of opioid-related deaths during the last decade, we could rapidly reverse the incidence of prescription opioid deaths. Similarly, there is substantial evidence that benzodiazepines, and perhaps co-administration of other central-nervous system depressants, are major contributors to the deaths associated with opioids. The petitioners' recommendations fail to address this evidence and thus may lead to a false sense that dose is the issue, not the problematic interactions of various drugs throughout a range of doses.

The petitioners request a maximum duration of 90 days for continuous (daily) use of opioids for noncancer pain. Pointedly stated, this change effectively eliminates the use of opioids for chronic noncancer pain. This is a radical position that would leave an untold number of pain sufferers with few treatment options given the on-label restrictions imposed by many insurers, including Medicare/Medicaid. The Washington Legal Foundation, a non-profit organization based in Washington, D.C., recently published a paper predicting an exodus of physicians from the pain-management specialty and a disproportionate negative impact on poorer citizens who need pain care as a result of new stricter opioid regulations in Washington State. The following paragraph is a quote from that paper:

"Washington Department of Health officials, recognizing that opioid therapy will become increasingly difficult to obtain, proposed that chronic pain patients

should explore alternative treatments for relieving pain, such as ‘physical therapy, yoga, massages or acupuncture.’ Unfortunately (and ironically), a majority of these alternative medicine options are not covered under Washington’s Medicaid program because they are not clinically proven, rendering these ‘choices’ financially unrealistic for many patients who suffer from chronic pain [Meringola 2011].”

Further, the Foundation averred that that the regulations impose a strong prejudicial bias, since they aim to deter opioid-related harm by targeting those with chronic noncancer pain, while ignoring problematic consequences of opioid prescribing in acute care venues, emergency departments, surgical settings, cancer pain treatment centers, and in palliative care.

While we believe that there is a need to balance risks to patients with pain and potential harms to the general public, we construe the terms requested by the petitioners as weighing excessively against the target population (patients with moderate-severe chronic debilitating pain) for whom the currently approved long-acting opioid analgesics are indicated, insofar as prescribers will seek safe harbor for prescribing within these limits (dose and duration) since labeling has become the *de facto* standard of care, defining “legitimate practice.” Under the highly interpretable language of the Controlled Substances Act, which speaks of “legitimate medical purpose,” it creates additional risk for prescribers to deviate from language within the labeling. Therefore, even though neither the FDA nor the DEA regulate the practice of medicine, in this particular sphere, they powerfully and pointedly affect the practice of medicine.

The petitioners cite that, over the past decade, a four-fold increase in the prescribing of opioid analgesics has been associated with a four-fold increase in opioid-related overdose deaths and a six-fold increase in individuals seeking treatment for addiction to opioid analgesics. We acknowledge the problem with opioid-related harm and agree that more must be done to reverse these problems. However, there are two separate populations that need different solutions: the population of patients treated with opioids for pain and the population of nonmedical users of opioids. Evidence from the National Survey on Drug Use and Health suggests more than two-thirds of nonmedical users get opioids from family or friends [SAMHSA 2010]. Much of society’s problem with nonmedical use is due to leftover medication stemming from the prescribing of more opioids than necessary for acute and trauma pain, not chronic noncancer pain. [Bates 2011, SAMHSA 2010]. The measures proposed by the petitioners will not address this problem. It would be an error to try to solve the problem of nonmedical use by denying people with pain access to medication.

The petitioners state that the prescribing of opioids increased over the past 15 years in response to marketing efforts that minimized risks of long-term use for chronic noncancer pain and exaggerated benefits. AAPM believes the marketing issue needs ongoing vigilance, but making medications more difficult to obtain by people who benefit from them will not address the marketing issue. A clear distinction must be

made between the very important public health campaign over recent years to increase awareness about the adverse consequences of undertreated chronic pain and the critical elements of assessment and optimal management, versus marketing and promotion of opioids by pharmaceutical companies. These issues are sadly conflated in the petition, and as the foundation for the requested changes in labeling, lead to specious conclusions and solutions. There is truly a “throw the baby out with the bathwater” approach. We suggest that there are better means to the mutually agreed-upon salutary ends of safe and effective use.

The petitioners contend that long-term safety and effectiveness of managing chronic noncancer pain with opioids has not been established. Indeed, little research has focused on the question of long-term effectiveness of opioid therapy for chronic noncancer pain. The majority of recommendations from a practice guideline endorsed by the American Pain Society and the American Academy of Pain Medicine are based on lower-quality evidence [Chou et al 2009]. At best, the literature has shown inconsistent effectiveness of opioids for chronic pain [Trescot 2008].

A systematic review of patients with chronic back pain by Martell et al found opioids relieved pain for up to 16 weeks but that long-term benefit was uncertain; furthermore, patients exhibited a high incidence of substance-use disorders [Martell 2007]. However, co-morbid conditions are frequent with chronic back pain, including major depression in 18% to 32% of patients [Ballantyne 2007]. Therefore, it may be unwise to use these patients as a yardstick by which to measure the likelihood of success with opioids in all patients. Some evidence suggests that patients with depression, regardless of pain condition, do not respond as well to opioid therapy as non-depressed patients [Middleton & Pollard 2005]. Perhaps it is patients without co-morbid disorders who achieve the most benefit from opioid therapy. Therefore, screening of patients for mental-health and substance-use co-morbidities may be the most important step in assuring proper candidate selection for long-term opioid therapy.

However, it is clear from clinical experience and the literature that there are many patients who do benefit. Even though opioid trials are plagued by high dropout rates due to adverse effects or ineffective analgesia, a subset of patients continues to achieve meaningful pain control long term [Noble et al 2010]. In patients who had been taking opioids for chronic pain for an average of two years, when the treatment was suddenly stopped, the patients experienced more pain and a reduced quality of life – not an uncontrolled craving for drugs [Cowan et al 2005]. Furthermore, the degree of pain relief that is meaningful to the patient must be taken into consideration. If patients do not achieve effective pain relief with one opioid, rotation to another frequently produces greater success [Quang-Cantagrel 2000]. For many of these patients, other treatments have failed and restrictions on the availability of opioids within a full potentially therapeutic range sentence them to suffer needlessly. In other words, it is equally detrimental to generalize from successes as it is from failures. In the absence of highly sensitive and specific predictive factors, clinicians must rely on well-defined risk

mitigation practices that have emerged in order to create the most propitious benefit-to-harm ratio for each patient under treatment. This cannot be adjudicated through *a priori* constrained dose and duration parameters.

The petitioners cite recent surveys of chronic noncancer pain patients receiving chronic opioid therapy showing that many continue to experience significant chronic pain and dysfunction. The same could be stated about the plight of most patients with chronic progressive conditions treated with well-accepted therapies, including those with COPD, heart failure, or neurodegenerative diseases, among many others. For patients living with chronic pain, the goal of opioid therapy is not to eliminate all pain – which is currently impossible in most instances – but to help improve and restore function and optimize quality of life to the greatest extent possible. Expecting any treatment, including opioids, to eliminate intractable pain is unrealistic, as much so as expecting miraculous recovery of muscle control in multiple sclerosis patients given the limitations of current treatments.

The petitioners argue that recent surveys using DSM criteria found high rates of addiction in chronic noncancer pain patients receiving chronic opioid therapy. However, the interpretation of the data depends on the definitions and meanings of aberrant behaviors, misuse, use, and addiction. All of these terms do not have the same clinical implications. Boscarino et al 2011 compared diagnostic criteria for opioid dependence contained in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) with those in the updated DSM-V for an opioid-use disorder. This analysis was accomplished by combining the prior categories “abuse” and “dependence” into a single opioid-use disorder category and then grading the severity. This move away from indistinct categories, such as “abuse,” reflects evolution in neuroscience and empirically-based understanding of the relationships among a given chemical, an individual’s genetic and environmental circumstances, and the disease of addiction. However, many of the criteria investigators used to identify opioid-use disorders resemble common behaviors of patients with uncontrolled pain (e.g., taking more than intended, unsuccessful attempts to cut down intake), casting doubt on the reported signs of “addiction.” Each of the criteria in the DSM-V could result from an entirely different cause or motivation when observed in patients with pain than in nonmedical users seeking the same drugs. If the study is interpreted to say 35% of patients may have trouble managing opioid intake, it is consistent with prior studies assessing problematic opioid use behaviors. Some of these behaviors can be managed with structured approaches to care and appropriate monitoring. But it is false to conclude that this number equates with the prevalence of “addiction,” or that addiction is an inevitable consequence of chronic opioid therapy in patients without predisposing factors. This distinction is of great importance, because it implies very different approaches to care in distinct populations of patients (based upon risk assessment) and prognoses.

Fleming and colleagues conducted two-hour interviews with 801 patients receiving long-term opioid therapy who were being treated by 235 Wisconsin physicians. They found rates of 26% for purposeful oversedation, 39% for increasing dose without prescription, 8% for obtaining extra opioids from other doctors, 18% for use for purposes other than pain, 20% for drinking alcohol to relieve pain, and 12% for hoarding pain medications [Von Korff 2011].” The sum of these aberrant behaviors is troublesome. Yet the study cited in the excerpt by Fleming et al has also frequently been cited as showing that opioid-use disorders – a term usually equated with “addiction” – were 3.8% in the sample studied [Fleming 2007]. For patients who are able to sustain long-term benefit from opioid therapy, the risk of addiction appears low in some studies. In a review of 26 studies (total enrollment of participants: 4,893) that reported data after six months of chronic pain treatment with opioids, signs of iatrogenic addiction were reported in 0.27% of participants [Noble et al 2010]. Such results suggest that chronic opioids cannot be assumed to be the wrong treatment for all patients at the start.

Again, we conclude that the changes requested by the petitioners do not address the far more salient issue of prescriber education and adherence to principles of practice, including ongoing monitoring for aberrant behaviors and early signs of addiction, while it provides a false sense of security for patients and practitioners that lower doses or durations of treatment are protective.

The petitioners also argue that patients who remain on opioids for extended periods justify a need to change the label. They cite a large sample of medical and pharmacy claims records showing that two-thirds of patients who took opioids on a daily basis for 90 days were still taking opioids five years later. It is unclear what this statement of finding is meant to indicate. How does this differ from patients on insulin, statins, antihypertensives, etc.? Chronic pain is in most cases just that, a chronic disorder that may be life long, often due to damage sustained to tissues or the nervous system. We fail to see the rationale behind a delimiting label change for the specific treatment of any chronic condition in patients who are using their prescribed medication safely and effectively (i.e., meeting defined goals of treatment), regardless of the chronic condition, including chronic pain.

It is correct, as the petitioners argue, that some evidence shows that patients with mental-health and substance-abuse comorbidities are more likely to receive chronic opioid therapy than patients who lack these risk factors, a phenomenon referred to as *adverse selection*. However, people with pain and mental-health disorders also deserve to have their pain treated. This is an increased risk population that requires vigilance and more medical involvement, not less. It is acknowledged that this population is more difficult to treat largely because it is hard to know when the drug is being used for pain or for the mental disorder or both. Some of these patients need strict monitoring, and some should not receive long-term opioids. This is where we need more research and medical training, but it is not a reason to deny people with pain an opioid if it is appropriate.

The petitioners cite three large observational studies published in 2010 and 2011 that found a dose-related overdose risk in chronic noncancer pain patients on opioid therapy. Close examination of these studies fails to show evidence that dose alone was the reason for overdose deaths. In one of the cited studies, Bohnert et al 2011, investigators retrospectively studied the Veterans Health Administration (VHA) database and reported that the rate of fatal overdose among patients treated with opioids was 0.04% with a higher risk among patients prescribed doses of ≥ 100 mg per day compared with those prescribed 1 to < 20 mg per day. In Gomes et al 2011, a study of Canadians on public assistance, doses of > 200 mg morphine equivalent per day were associated with nearly three times the risk of opioid-related mortality compared with doses of < 20 mg [Gomes et al 2011].

These reports contain a high number of confounding factors that include a high prevalence of benzodiazepine involvement in fatalities in the Gomes study and a heterogeneous population with many comorbid psychiatric and substance-use disorders in the Bohnert study [Leavitt April 7, 2011]. In criticizing the “data mining” approach used by investigators, Leavitt wrote, “It also is curious in the [Bohnert] study that the greatest absolute number of overdose deaths (43.5%) occurred when the maximum prescribed daily opioid dose was listed as 0 mg/day. The authors had little explanation for this, other than many patients might have obtained opioids from non-VHA healthcare providers, and some might have saved opioids from a prior prescription or obtained them from illicit sources [Leavitt April 7, 2011].”

Furthermore, the studies failed to analyze methadone as a medication shown by the CDC to contribute to a disproportionate number of overdose deaths when compared to the quantity of methadone prescriptions [CDC 2012]. Both studies specifically excluded methadone from analysis, explaining that methadone equates poorly to morphine equivalents and that it is used more frequently (in Canada, the setting of the Gomes study) for addiction treatment than pain.

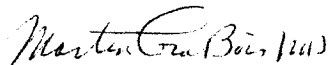
Importantly, there is no comparative data presented on the risk or incidence of suicide resulting from inadequate pain control, recognizing that this risk in patients with chronic pain is double the control population rate. We infer that it is premature to conclude that an arbitrary dose limitation in opioid labeling will beneficially reduce mortality, but there is good cause for concern that such a maneuver, well intended as it may be, could have serious unintended consequences, including inciting morbidity and mortality among chronic pain sufferers due to uncontrolled pain. This remains an important area for much needed research and professional education.

Finally, the petitioners cite studies reporting that at high doses, opioids are associated with increased risk of overdose death, emergency room visits, and fractures in the elderly. Indeed, higher doses of opioids are associated with increased risk of harm in a subset of the pain population. However, as we have cited above, dose is only one factor contributing to the harm associated with opioids. In the study the petitioners cite,

associating high dose to increased risk of fractures in elderly, propoxyphene was the opioid most commonly prescribed. This opioid is not considered highly potent and is no longer on the market. In addition the study cited by the petitioners has been aptly criticized for serious flaws in the analysis of the data. On balance, great caution should be exercised in interpreting conclusions. We advocate opioids generally be limited to patients that have failed other safer and more effective therapies. But specifically, physicians involved in the care of older individuals need to understand the unique aspects of geriatrics and pharmacotherapy, and through this understanding provide informed, salutary treatment options and monitor appropriately to prevent adverse events. This is a population at risk for falls and fractures, including as a result of under-treated pain. It is the compact between physician and patient (or proxy) to determine how best to strike the optimal balance in ascertaining treatment decisions. When an approved drug is deemed appropriate based upon a patient's specific circumstances, and in the absence of any contraindications, the treating physician must have the latitude to determine what serves the best interest of her patient. This is the essence of the practice of medicine.

We welcome the opportunity to participate in a dialogue with FDA and other interested parties, including prescribers, pharmacists, behavior health practitioners, other healthcare professionals, the scientific community, government agencies, and patients, in reaching a positive outcome for those Americans who suffer unnecessarily with chronic pain.

Sincerely,

A handwritten signature in cursive script that reads "Martin Grabois, MD".

Martin Grabois, MD
President

Additional signatures on separate page

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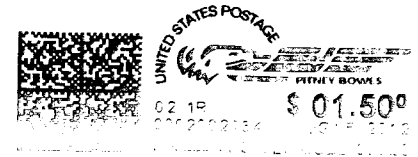
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