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April 8, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

Re: FDA-2012-N-1172; Impact of Approved Drug Labeling on Chronic Opioid Therapy; Public Hearing; Request for Comments

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments in response to the Wednesday, December 19, 2012 notification in the Federal Register of a public hearing in February 2013 soliciting input on a number of questions pertaining to the use of opioid drugs in the treatment of chronic pain.[i] ASHP is the national professional organization whose over 40,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care services in hospitals, health systems, and ambulatory clinics. For 70 years, the Society has been on the forefront of efforts to improve medication use and enhance patient safety.

In the Federal Register notice referenced above, the FDA is soliciting information to the following questions related to opioid use.

A. Diagnosis and Understanding of Patient Pain

1. *What methods do professionals use to accurately distinguish between different types of pain (e.g., cancer vs. non-cancer) and their respective etiologies?*

   ASHP believes that the issue is more complicated than a "cancer vs. non-cancer" pain distinction. For example, how would a healthcare professional categorize chronic pain that is a result of a cancer that is currently in remission? The Society believes the more important issue is pain etiology (e.g., neuropathic, central, inflammatory).

2. *What are the definitions of the terms ``mild,'' ``moderate,'' and ``severe'' when those terms are used to describe symptomatic conditions such as pain?*

Based on published studies, ASHP suggests the following scale classifying pain scores:

Score	Pain Level
1-4	Mild
5-7	Moderate
8-10	Severe

However, it is important to note that experts have recommended slight variations in these breakpoints based on specific disease states or conditions.[ii] Additionally, limitations on activities of daily living may also dictate the impact of pain on patients.

3. *How do professionals accurately categorize a patient's pain as mild, moderate, or severe? For example, what tests or assessments do they use?*

   Primary care professionals usually use uni-dimensional assessments such as the numeric rating scale. Other professionals characterize pain using multidimensional scales that assess mood, sleep, concentration, disability, etc.

4. *What methods should and do professionals use to accurately distinguish between short-term pain and chronic pain?*

   a. *What are and should be the time periods that characterize short-term pain versus chronic pain?*
   b. *What are and should be considered the clinical differences between short-term pain versus chronic pain?*
   c. *What types of pain, if any, are presumed chronic versus presumed short term?*
      Based on published studies, ASHP believes that duration of pain can be classified as follows:

Duration of Pain	Pain Classification
<30 days	Acute
30 – 90 days	Subacute
>90 days	Chronic

B. *Understanding and Adhering to the Labels of Pain-Treating Products*

1. *How are the words ``indicated for the treatment of moderate to severe pain'' interpreted and used by practitioners when deciding what types of treatments (including opioids) are appropriate for treating patients with pain?*

   ASHP believes that many providers practice a "stepped care" approach vs. stratified care. Patients may initially rate their pain as moderate to severe, but that does not necessarily prompt opioid therapy as first line treatment

2. *If the indication for opioid drugs were restricted to the treatment of severe pain only, how would such a change impact:*
   a. *Prescribing practices?*
   b. *Patient access to pain medication and patient pain control?*
   c. *Abuse and misuse of opioid medicines?*

   Restricting treatment to severe pain only may create additional challenges for prescribers and patients as well as barriers to access. For example, if a patient with an initial pain score of severe reports a moderate pain score after initiation of opioid therapy, would the healthcare professional now be considered prescribing off-label? If this is indeed the case, patient access to necessary pain medications would be negatively impacted.

3. *If the pain threshold described in the indication (e.g., moderate, moderate to severe, severe pain) differed based on the pain's etiology, how would such an approach impact:*
   a. *Prescribing practices?*
   b. *Patient access to pain medication and patient pain control?*
   Abuse and misuse of opioid medicines?

   Patients with certain etiologies of pain are more apt to receive opioids, even with mild to moderate pain (i.e. cancer, burn, sickle cell)

C. *Limiting Opioid Prescription and Use*

1. *Limits on exposure to opioid drugs.*
   a. *What data, if any, exist that would support or oppose the establishment of a maximum daily dose for opioid drugs? FDA is interested in drug safety or efficacy data in particular.*

   In the Agency's Federal Register notice, the FDA states that "Over the past several years, the Agency has received comments, petitions, and informal inquiries concerning the extent to which opioid drugs should be used in the treatment of pain. In particular, members of the public and the regulated community have debated the presence or absence of evidence showing the safety and efficacy of these drugs as pain relievers in the various populations for whom they are prescribed."[iii]

ASHP is aware of one such petition submitted to the FDA on July 25, 2012 by the Physicians for Responsible Opioid Prescribing (PROP)[iv]. The petitioners in this case make several claims including one that "Three large observational studies published in 2010 and 2011 found dose-related overdose risk in CNCP patients on COT.[v,vi,vii]"

The Dunn et al. (2010) study, the Bohnert et al. (2011) study, and the Gomes et al. (2011) study cited by the petitioners in support of this point have been thoroughly critiqued. [viii,ix,x]

These large observational studies are retrospective exercises in data mining, involving initial sample sizes running well over 100,000 in two cases, with opioid-related fatality rates well under 1 percent. The studies do not control for a variety of potential confounding factors, such as the concomitant use of other central nervous system depressant medications, population factors that may increase the risk of overdose and death, and determination of the extent to which decedents used their medications in ways other than as prescribed.

The elevated risk of death is cited in relative terms based on arbitrary dosage ranges (e.g., patients using <20 mg morphine equivalent per day had a death rate of X, while those using 21-90 mg per day had a death rate of 2X). As noted above, fatality rates are relatively small in absolute terms.

Additionally, even if these figures were statistically significant, the lack of important contextual information only signals that there is a problem. It does not describe the nature of the problem, leaving only one possible solution; i.e., removing the one known factor — opioid analgesics. Data mining studies are useful for generating hypotheses but should not be inappropriately used to test those hypotheses.

The petition also claims that "COT at high doses is associated with increased risk of overdose death, emergency room visits and fractures in the elderly."[xi]

The petition cites a report by Braden et al. on risk factors associated with emergency room (ER) visits among people using opioids long-term.[xii] The subjects come from two different populations; Arkansas Medicaid (n = 10,159) and a private insurance plan covering parts of 14 states (n = 38,491). Among other things, the study determines average daily opioid dose in mg morphine equivalent dose (MED) per day, and then divides the sample into three categories: a) those taking less than the median dose (35 mg and 32 mg MED in the two samples, respectively); b) those taking between the median dose and 120 mg MED; and c) those taking more than 120 mg MED.

The authors note that a cut point of 120 mg MED was arbitrarily chosen because it is the threshold recommended in dosing guidelines issued by authorities in Washington state. Data analyses determined that the two higher-dose groups had an elevated risk of ER visits in the Arkansas Medicaid sample (RR = 1.30 and 1.08, respectively), but not in the private insurance sample (RR = 1.03 and 0.97). It should be noted that, despite the modest relative risk elevation in absolute terms, the Arkansas Medicaid findings reach statistical significance because of the very large sample size.

However, given that the private insurance sample is nearly 4 times as large, the failure to find significant results in that group suggests that there really is no difference to be found, and there may be something specific about the Arkansas Medicaid sample that changes the findings. Methodologically, one also wonders what the findings would have been if a more traditional analysis comparing only groups above and below the median had been conducted.

Third, a study by Saunders et al. is cited in the petition as examining the occurrence of bone fracture in people 60 years of age and older who had previously been prescribed opioids three or more times in a 90-day period.[xiii] They examined risk of fracture as a function of current dose, including in one group that had discontinued opioid use and thus served as a no-current-opioid control.

In a sample of 2,341 subjects followed for 6,379 person-years, 320 fractures were confirmed. Median daily dose of opioids was 7.6 mg MED. Groups based on opioid dose were arbitrarily established as: 0 mg MED; 1 – <20 mg MED; 20 – <50 mg MED; and 50+ mg MED.

Compared to patients no longer taking opioids, patients currently taking any dose of opioids did not display a significantly elevated risk of fracture; although, there was a clear *trend* in the direction of more fractures (hazard ratio = 1.28, CI 0.99-1.64). Within the dosage levels, only the group taking 50+ mg MED displayed a significantly elevated fracture risk (hazard ratio = 2.00, CI 1.24-3.24); although, the confidence interval here overlapped with the overall, non significant results for those taking any opioids.

Therefore, in order to display an elevated risk of fracture, patients needed to be taking an average opioid dose roughly **6 times** the median dose for the population. The authors control for a number of confounding factors, but exclude perhaps the most obvious one: the patients' underlying diagnoses.

Those patients who continue to take opioids at elevated doses, compared to those who started opioids but were able to discontinue them, might well have painful conditions that necessitate the use of opioids. Those painful conditions themselves might create or mark an elevated risk of fractures.

b. What data, if any, exist that would support or oppose a difference in maximum daily dose for opioid drugs based on pain etiology (e.g., cancer vs. non-cancer pain)? FDA is interested in drug safety or efficacy data in particular.

Typically cancer patients are much more sensitive to opioids for analgesia and require lower doses.

c. What method(s), if any, should be used to establish a maximum daily dose of opioid drugs?

For a number of factors, there is no universally accepted definition of what defines a "high dose." Current definitions of what may constitute a "high dose" range from mg MED> 100 to dosages often in excess of 200mg of oral morphine equivalents.

ASHP does not believe a maximum daily dose should be established as this is a clinical decision that is best made by the prescriber and to impose a mandatory maximum duration limit would be contrary to the practice of medicine.

d. What effect(s), if any, would a maximum daily dose for opioid drugs have on the following:

i. Prescribing practices?

Little to no effect as most prescribers limit doses without specialist followup

ii. Patient access to pain medication and patient pain control?

Access will likely be more restricted. Maximum daily doses, if established too conservatively, would have a crippling effect on treating some patient populations (e.g., advanced cancer, palliative and hospice care) where providers would be hesitant to prescribe the doses needed for pain control for fear of litigation.

iii. Abuse and misuse of opioid medicines?

While this is difficult to predict, but imposing a maximum daily dose for opioid drugs is likely to limit the quantity of drugs in the community,

2. *Limits on duration of use of opioid drugs.*
   a. *What data, if any, exist that would support or oppose the establishment of a maximum duration of continuous treatment with opioid drugs? FDA is interested in drug safety or efficacy data in particular.*

At least one systematic review of long-term opioid treatment for NCP has been published. Devulder et al. presented the results of 11 studies that evaluated long-term treatment with opioids in patients with chronic NCP and also assessed quality of life (QoL; n=2877)[xiv]. Six of the studies were randomized trials and the remaining five were observational studies.

Of the four randomized studies in which baseline QoL was reported, 3 showed an improvement in QoL. Similarly, of the five observational studies, a significant improvement in QoL was reported in four of them. The authors found that there is ample evidence suggesting that long-term treatment with opioids can lead to significant improvements in functional outcomes and QoL in patients with chronic NCP. However, the authors suggest, further investigations will help to confirm the long-term QoL benefit of opioid therapy in such patients, and to clarify any effects of physical tolerance, opioid withdrawal syndrome, and/or addiction — all potentially associated with long-term use of opioids — on patients' continued functional status.

This is not intended to endorse long-term opioid therapy; however, it is necessary to remember that the absence of evidence for long-term opioid safety and efficacy does not equal evidence of absence of long-term opioid safety and efficacy. Unless and until FDA changes the standard on which it bases its labeling decisions, and adequate data are collected to demonstrate the contrary, the current labeling should stand, based on the absence of evidence to the contrary.

   b. *What data, if any, exist that would support or oppose a difference in maximum duration of continuous treatment with opioid drugs based on pain etiology (e.g., cancer vs. non-cancer pain)? FDA is interested in drug safety or efficacy data in particular.*

N/A

   c. *What method(s), if any, should be used to establish a maximum duration of continuous treatment with opioid drugs?*

ASHP does not believe that a maximum duration of continuous treatment with opioid drugs should be established. This is a clinical decision that is best made by the prescriber and to

impose a mandatory maximum duration limit would be contrary to the practice of medicine.

The Society appreciates the opportunity to provide input on the questions posed by the FDA on opioid therapy. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,

Christopher J. Topoleski
Director, Federal Regulatory Affairs

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[i] Federal Register Volume 77, Number 244 Pages 75177 – 75179

[ii] See http://www.rehab.research.va.gov/jour/07/44/2/pdf/jones.pdf

[iii] Federal Register Volume 77, Number 244 Page 75179

[iv] See http://www.citizen.org/documents/2048.pdf

[v] Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of Internal Medicine 2010;152:85-92.

[vi] Bohnert AS, Valenstein M, Bair MJ, et al. (2011). Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA, 305:1315-21.

[vii] Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med 2011;171: 686–91.

[viii] http://updates.pain-topics.org/2010/02/do-higher-opioid-doses-increase.html

[ix] http://updates.pain-topics.org/2011/04/do-higher-rx-opioid-doses-raise-death.html

[x] http://updates.pain-topics.org/2011/10/more-myths-about-high-dose-opioids.html

[xi] http://www.citizen.org/documents/2048.pdf

[xii] Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 2010;170:1425-32.

[xiii] Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med 2010;25:310-5

[xiv] Devulder J, Richarz U, Nataraja SH.Impact of long-term use of opioids on quality of life in patients with chronic, non-malignant pain.Curr Med Res Opin. 2005;21:10 1555-68.