



Oncology Nursing Society

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June 26, 2009

Margaret A. Hamburg, MD
Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Request for Comment [Docket No. FDA-2009-N-0143]

Dear Commissioner Hamburg:

On behalf of the Oncology Nursing Society (ONS) – the largest professional oncology group in the United States, comprised of more than 37,000 nurses and other health care professionals dedicated to ensuring and advancing access to quality care for individuals affected by cancer – we appreciate this opportunity to submit comments to Docket Number FDA-2009-N-0143. We commend the Food and Drug Administration (FDA) for convening public meetings and for soliciting comments from individual health professionals, manufacturers, and patient advocates, as well as organizations representing various stakeholders, to ensure that concerns are addressed. We share the FDA's goal of balancing access for legitimate patients, with the need to prevent and reduce misuse, abuse, addiction, and overdose deaths associated with opioid analgesics. However, we have a number of concerns regarding the proposed Risk Evaluation and Mitigation Strategies (REMS) system currently under development.

ONS maintains a long-standing commitment to ensuring that all people with cancer-related pain have access to the quality pain and symptom management care, services, and therapies they need and deserve. Specifically, our organization believes that all people with legitimate need must be assured access to the pain medication and therapies that they and their health care providers deem most appropriate.¹ We recognize and appreciate that with the potential for abuse, our nation must develop and implement appropriate, yet reasonable, practices and regulations to ensure that these drugs do not fall into the wrong hands and are not abused. Please know that we stand ready to be a resource to you and your colleagues as you undertake

¹ "Cancer Pain Management." *Oncology Nursing Society Position on Cancer Pain Management*. Approved by the ONS Board of Directors, 4/98; revised 11/00, 6/02, 10/04, 10/06. <http://www.ons.org/publications/positions/CancerPainManagement.shtml>.

the development and implementation of a REMS for opioids. Thank you in advance for your attention to our comments and concerns.

Under-treated Pain - A Major Public Health Problem

As you know, pain is a major health problem in the United States, especially the kind of pain that is often experienced by individuals with cancer. The treatment and management of pain and accompanying symptoms, such as fear, anxiety, depression, weakness, nausea, and vomiting, need to be improved significantly. When pain is severe, it interferes with activities and quality-of-life; diminishing physical, psychological, and interpersonal well-being.

Under-managed pain often results in emotional and economic consequences, both of which have long-term costs to affected individuals and their families. Therefore, it is essential that improved quality-of-life, through expert pain control, be available to all, who experience pain. More must be done to ensure that appropriate pain management is the standard of care for the young, as well as the elderly, and for those with chronic illness or at end-of-life. ONS believes that the inadequate treatment of pain is a significant public health problem in the United States and requires the necessary public health response.

Cancer-related Pain

Despite significant breakthroughs in the treatment, early detection, and prevention of cancer, two-thirds of new cancer cases strike people over the age of 65, and the number of new cancer cases diagnosed among the elderly is projected to more than double by 2030, as the Baby Boom generation ages. As cancer risk increases with age, so does the risk and incidence of other chronic conditions. Therefore, many who develop cancer also suffer from other co-morbidities and underlying painful conditions associated with their other health problems, such as arthritis, diabetes, or prior trauma.

Additionally, concurrent advances in the treatment of cancer have yielded a growing population of patients who are living longer with cancer, as well as an increased number of people who are cured and transition to cancer "survivorship." Many of those patients, who live long-term, continue to experience pain that may be related to their treatment, rather than the malignancy itself. These patients often suffer moderate to severe pain on a daily basis, which compromises their ability to function in various life activities. Therefore, this cohort has more in common with the non-malignant pain patient, than the patient who has pain associated with advancing disease. For example, pain may be due to nerve injury or scar tissue formation from cancer-related surgical intervention.

Considerable progress has been made to improve the adequate treatment of pain through efforts at educating health care professionals and the public, but studies still show that some patients with cancer receive inadequate, or no treatment for pain.^{2,3} Much of the failure to

² Oldenmenger, W., Sillevs Smitt, P., van Dooren, S., Stoter, G., & van der Rijt, C. (2009). A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: A critical appraisal. *European Journal of Cancer*, 45(8), 1370-1380.

relieve cancer-pain stems from patient, provider, and family misconceptions and fears. Adequate pain control can also be complicated by regulatory agencies that scrutinize professional licensure and restrictively regulate controlled substances — practices that are well-intended, but unintentionally can obstruct legitimate use rather than stem diversion.

While surgery, radiation, and chemotherapy may be used to control the pain by shrinking the tumor, drugs such as non-opioids, opioids, and adjuvant medications are the mainstay of pain treatment. Moreover, greater emphasis on quality-of-life for individuals at end-of-life and the growth of hospice care in this country has done much to validate the role of opioids in treating pain and suffering. It is, indeed, an unfortunate reality that the class of drugs that has the potential to alleviate pain and suffering also has the potential to be abused. However, while it is essential to strike a delicate balance between legitimate access and efforts to prevent diversion and abuse, it is critical to note that there is abundant evidence that the vast majority of those who use these drugs for their legitimate and intended purposes, do not go on to abuse them.

Opioid Treatment Essential to Managing Cancer-related Pain

For years, morphine has been the standard opioid of comparison to treat severe pain in cancer patients. However, as knowledge about pain physiology and pharmacology translates into better analgesics or new formulations of opioids with fewer side effects, morphine has not remained the drug of choice. Morphine has several active metabolites, including morphine 6-glucuronide and morphine 3-glucuronide that may accumulate in patients with renal disease, renal dysfunction, or elderly persons, because of decreased clearance and prolonged elimination half-life. When this occurs, patients taking morphine may become confused, disoriented, sedated, and may experience other side effects. Because of these problems related to morphine's active metabolites, the trend has been to use semisynthetic opioids, such as oxycodone, fentanyl, and hydromorphone.

Cancer patients typically have two types of pain — continuous, persistent pain that is always present and intermittent or breakthrough pain that occurs with activity. Patients, therefore, need to be treated with continuous release opioids (usually dosed twice a day) for the persistent pain and short acting opioids (usually dosed every two to four hours) for the breakthrough pain. At present the only continuous release opioids that are available are morphine (MS Contin®, Oramorph®, Kadian®), oxycodone (Oxycontin®), methadone and fentanyl (Duragesic patch® typically dosed every 72 hours). If continuous release oxycodone (Oxycontin®) were to be regulated strictly, this could pose a major problem, not only for people with cancer, but a multitude of patients with chronic nonmalignant pain who are enjoying an improved quality-of-life because of Oxycontin®.

Some cancer patients cannot tolerate morphine, because of the side effects of nausea and vomiting, while others need to take high doses of continuous release oxycodone, because they

³ Deandrea, S., Montanari, M., Moja, L., & Apolone, G. (2008). Prevalence of undertreatment in cancer pain. A review of published literature. *Annals of Oncology*, 19(12):1985-1991.

are not able to use the fentanyl patch, as they would need multiple patches to equal the Oxycontin® dose they are taking. With the availability of controlled release oxycodone, cancer patients are able to have access to another analgesic for relief of persistent pain. If access to opioids — such as Oxycontin® — is to be restricted severely, many patients would not be able to maintain a decent quality-of-life.

The percentage of the population who take prescription drugs for non-medical purposes has remained stable for the last decade at 1-1.5 percent, as has the percentage of the population with an illicit drug problem (6-7 percent). This suggests that while periodic hotspots develop around a particular drug in certain communities, overall, our nation's policies are working to minimize drug abuse. To that end, a study of opioid use and abuse published in the Journal of the American Medical Association concluded that the increase in medical use of opioid analgesics does not contribute to the increase in abuse.⁴ However, we unfortunately always have had to be aware that an individual's request for a certain drug could be based in real need/response, but could also be based on its street value. Yet, as noted above, we continue to see significant numbers of people with cancer dying in pain.

Risk Evaluation and Mitigation Strategies (REMS) for Certain Opioid Drugs

Again, ONS shares the FDA's goal of balancing access for legitimate patients, with the need to prevent and reduce misuse, abuse, addiction, and overdose deaths associated with opioid analgesics. As an evidence-based, outcomes driven organization, ONS believes that a key focus of the FDA's effort to create a REMS for opioids must begin with a clear understanding of where and how individuals are accessing opioids; this is essential to ensuring that the policies, programs, requirements, and other interventions the FDA designs and implements are targeted to the right areas. Moreover, we maintain that an overarching principle of an opioid REMS should be that it must protect – not interfere with – legitimate patient access to these important medications.

Following, please find our concerns and comments in response to the specific issues and questions posed in the request for public comment.

A. Elements of the REMS

1&2. Certification and Education of Prescribers and Certification and Education of Pharmacists, Prescribers, and Other Health Care Providers or Institutions that Dispense or Directly Administer Covered Opioid Products

The REMS should provide a curriculum – which has at its foundation proven-effective trainings and approaches – that ensures a core competency and understanding of myriad issues. Specifically, ONS recommends that the FDA consider educating prescribers, dispensers/health professionals by providing the following:

⁴ Data from 1990-96, Joransen DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA* 2000; 283(13):1710-1714.

- REMS logistical, operational, compliance, and implementation components, including the risk the REMS is seeking to mitigate;
- guidelines – developed in conjunction with a range of health professionals, including nurses – for practice that will assure access to opiates, based on sound clinical judgment and patient need, while increasing early recognition of problem behaviors;
- background on appropriate dosing and administration, as well as information on the therapeutic indication of the medication and any potential side effects;
- specific information regarding how to identify non-legitimate patients, patients who have addiction problems, and patients at-risk for abuse, addiction, or diversionary behavior;
- information related to misuse and safe storage, including how to effectively discuss with patients the importance of safe storage, safe disposal, and the responsibility that comes with opioid use – balancing the message of reassuring the legitimacy of opiates in treating pain, while giving guidelines regarding safe use and prevention of diversion and/or abuse;
- patient education and support information and materials to disseminate to the patients for whom they prescribe opioids – standard information provided to patients that is culturally appropriate (health literacy); and
- a system to return dispensed opioids that are no longer needed and education of providers about this mechanism.

The FDA needs to assure that any federal publications and REMS-associated information regarding opioids delineate clearly between substance abuse and legitimate pain management in acute pain, cancer pain, and chronic pain, as the evidence that “addiction and tolerance are not generally associated with effective cancer pain management.”^{5,6}

ONS recommends that a standardized set of education and training materials, tools, and modules be developed, with significant input from a multi-disciplinary group of experts and stakeholders, including patient advocates and health professionals who are the target audience. A panel of government and non-governmental experts, with representation from the various stakeholder professional organizations, should be convened to review and evaluate the educational and training materials to ensure that the goals of the curriculum are met. This panel, or another body, also could serve as an oversight entity to ensure that the information in the training and

⁵ Miaskowski, C., Cleary, J., Burney, R., Coyne, P., Finley, R., Foster, R., et al. (2005). *Guideline for the management of cancer pain in adults and children* [vol. 3]. Glenview, IL: American Pain Society.

⁶ Miaskowski, C. (2008). The use of risk-management approaches to protect patients with cancer-related pain and their healthcare providers. *Oncology Nursing Forum*, 35(6), 20-24. Retrieved June 25, 2009, from <http://ons.metapress.com/content/v1090053g3228v32/fulltext.pdf>.

certification is kept up-to-date and is modified, as necessary, to ensure timeliness and effectiveness. Existing oversight bodies, such as the state boards of nursing and pharmacy, should be involved, as appropriate. ONS suggests that a schedule and process for review, evaluation, and update be established to ensure that the training module continues to be appropriate and efficacious.

Ideally, the education and training session would be a readily accessible multi-media training, for which continuing education credit is given to all health professionals who dispense, prescribe, and/or administer. To help maximize compliance, the FDA could consider requiring that prescribers and dispensers complete the training module prior to receiving a DEA registration.

3. Patient Education

ONS appreciates that much of the focus of the May 27-28, 2009 public meetings was on patient education; it is vitally important to pain control and symptom management for cancer patients. Studies have found that individualized educational intervention for cancer pain management from a registered nurse is effective for patients with cancer being treated in outpatient and home-based settings.^{7,8} ONS recommends, to the greatest extent practicable, that patient education be provided in an oral, written, or electronic form that appropriately takes into account cultural and linguistic needs of the individual in order to make the information comprehensible to the individual and any caregiver (or caregivers).

The prescriber/individual administering the drug should discuss with patients the importance of safe storage, safe disposal, and the responsibility that comes with opioid use. In addition, patients and their caregivers should be given specific written patient education and support information and materials (culturally and literacy level appropriate) that reinforces this “teaching.” Another component of patient teaching that should be considered is the development of a template patient agreement, created and endorsed by stakeholder professional organizations. Such an agreement should be brief, easy to understand, and modifiable to meet the needs of particular practices and patients. Such a document should include recognition that the patient understands that “sharing of medications is an illegal activity.” The patient education “session” would include discussion and review of this document – similar to how informed consent typically is handled.

⁷ Yates, P., Edwards, H., Nash, R., Aranda, S., Purdie, D., Najman, J., et al. (2004). A randomized controlled trial of a nurse-administered educational intervention for improving cancer pain management in ambulatory settings. *Patient Education & Counseling*, 53(2), 227-237.

⁸ Aubin, M., Vézina, L., Parent, R., Fillion, L., Allard, P., Bergeron, R., et al. (2006). Impact of an educational program on pain management in patients with cancer living at home. *Oncology Nursing Forum*, 33(6), 1183-1188.

One challenge to delivering patient opioid education is that such a teaching requires time from the nurse or other health care provider (the amount of time depends on the learner/patient/family and the type of drug) and is not reimbursed; payment drives practice and with the existing pressures on health professionals, due to shortages of staff, limited time, and other challenges, few providers have the time and resources to provide such an educational session, short of being reimbursed specifically for it. ONS recommends reimbursing health professionals for their time doing education with patients and family members – coding and charting help build documentation for the provision of the education.

As with the educational materials for health professionals, ONS recommends that the patient education materials be developed with input from a multi-disciplinary group of experts and stakeholders, including patient advocates and health professionals. A panel of government and non-governmental experts, with representation from the various stakeholder professional and patient organizations, should be convened to review and evaluate the patient educational and training materials to ensure that the goals of the curriculum are met. Again, as with the provider education component, this panel, or another body, also could serve as an oversight entity to ensure that the information is kept up-to-date and is modified, as necessary, to ensure timeliness and effectiveness. A schedule and process for review, evaluation, and update of patient educational materials should be established, and existing oversight bodies (e.g., state boards of nursing and pharmacy) should be involved in these efforts, as appropriate.

4. Are other REMS elements necessary to support the safe use of approved opioids?

ONS urges the FDA to study the issue of opioid misuse and abuse further and to collect additional data, prior to launching a REMS nationwide. ONS believes we need to clearly identify the problem, before an intervention is developed and implemented. In the 2007 National Survey on Drug Use and Health data, referenced by the FDA, as the basis for the REMS, the survey found that of the individuals who reported that they took an analgesic for non-medical use (not prescribed for the person or taken only for the experience/feeling it caused):

- 56.5% received the pain reliever from a friend or relative (for free);
- 14.1% bought (8.9%) the drug from a friend or relative; and
- 5.2% took/stole (5.2%) the drug from a friend or relative.⁹

The Survey did not specify/report what percent of the individuals, who were the “source” for the pain medications, had obtained them for legitimate purposes.

⁹ Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Results from the 2007 National Survey on Drug Use and Health: National Findings. <http://www.oas.samhsa.gov/NSDUH/2k7NSDUH/2k7results.cfm>.

Our representative at the May 4th stakeholder meeting asked whether or not the FDA had additional information about the “sources” of the opioids and/or if the FDA had plans for additional study in this regard. We are concerned that no one from the agency, who was present, indicated that there were plans for additional research. ONS believes that additional research should be conducted in advance of the design and implementation of an opioid focused REMS. We believe that additional follow-up questions should be asked of individuals reporting non-medical use of prescription analgesics to determine the particular diversionary paths, which in turn, would help identify the necessary points for public policy interventions.

First, if the friends/relatives “source” had legitimate needs/uses for these analgesics, and were in turn, giving their prescription drugs to their friends or relatives, or were having their drugs stolen from them, then these patients with legitimate use likely need additional education regarding: (1) how to ensure the safe storage of their medications, and (2) the dangers of providing the drugs to others. However, if these friends/relatives were misusing or abusing the system to secure drugs for their friends and relatives, there are different policy solutions and interventions necessary to ensure that these prescription drugs only are provided to patients with legitimate needs.

In addition, we feel strongly that the issue of safe and appropriate disposal of opioids is one that must be addressed. ONS recommends that disposal and/or “take back” programs must be developed to help patients/family members with unused opioids dispose of them in a safe way that ensures the left-over drug does not fall into the wrong hands. A program, combined with patient education, should decrease the number of unused opioids remaining in people’s medicine cabinets, where they can be accessed by non-legitimate users.

B. Systems Issues

1. How restrictive a system should be designed?

This is the key issue – we are not certain that a REMS will “solve” the problem. We maintain that REMS is unproven, and we are concerned that the burdens will outweigh any benefits and create a new problem for a frail population. ONS feels strongly that pain management must be individualized to the patient and that health professionals should have access to the full-range of FDA-approved medications, so they can appropriately address patient needs, as determined through a thorough assessment. Oncology health professionals must be able to choose from among various pain medications, formulations, and dosages to ensure that individual patient pain needs are met continuously, over the course of their treatment and through survivorship or end-of-life.

Given significant concern about how a REMS might restrict access to legitimate opioid use and the adverse impact that could have on people with pain, ONS urges the FDA to pilot a REMS first – possibly within a circumscribed geographic location,

or limiting the implementation to a certain patient cohort – before nationwide implementation. This would allow the FDA to determine the validity and appropriateness of health professional and patient educational materials and modalities and permit for modifications and improvements to ensure effectiveness and continued access for legitimate patients.

ONS recommends that a patient registry not be included as a component of the REMS. We are concerned that if patient registries are included in the REMS, they could be burdensome to prescribers and patients and could pose a barrier to legitimate access to opioids.

3. What existing systems already exist that could be used to implement a REMS?

We encourage the FDA to consider leveraging existing prescription monitoring programs to ensure that there are not duplicative or conflicting systems in place related to opioid prescribing. For example, ONS recommends that the FDA consider tying prescriber and dispenser education to the existing DEA registration process, which should help encourage and maximize participation while also allowing for system efficiencies and coordination.

In addition, we feel that state prescription drug monitoring systems should be reviewed/studied and evaluated for lessons learned and other factors that might be useful in the design of the REMS. This review would identify benefits and harms of existing systems and make clear areas in which changes, corrections, or other improvements should be made to achieve the balance between legitimate access and reducing/preventing misuse and abuse. While imperfect, with improvements, additional resources, and continual evaluation, existing state prescription drug monitoring systems potentially could be an efficient starting point for this effort, rather than allocating scarce resources to create an entirely new national system for opioid medication use. To that end, ONS recommends that the FDA consider allocating resources to evaluate, improve, and support the 38 existing programs and allow for the development of systems in the remaining states.

4. What metrics used to assess the success of the REMS?

ONS strongly recommends piloting any REMS first, before nationwide implementation, in order to develop, define, and refine metrics to evaluate effectiveness and to identify challenges and allow for corrections and improvements to be made.

Specifically, we need to determine the areas/types of patients where diversion is occurring and then monitor those areas for change. For example, we need baseline data from surveys about the number of legitimate patients who are giving prescription pain drugs to friends and families and then do follow-up surveys after implementation of education and other REMS elements to determine if the percentage/numbers change over time.

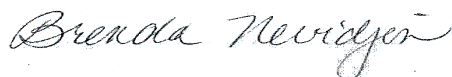
Overall, REMS elements should be designed so they can be measured to determine if the system is fulfilling its purpose in reducing abuse, misuse, and overdose. All metrics and measures should be evaluated periodically and modified, updated, and/or retired if proven to be inaccurate, or ineffective, in capturing desired information. Again, baseline data will be critical to help ensure that the REMS is making a measurable difference and achieving its goals, while also protecting against unintended consequences, such as undertreated pain, barriers to access for legitimate need, prescribers' fear of prescribing appropriate medication, or of the burden any training may cause, and other challenges that patients may face as an unintended consequence of the REMS. Creating and maintaining a "feedback" loop is essential in ensuring that any opioid REMS addresses public health concerns while sustaining access for legitimate patients in need.

Summary

ONS very much appreciates the opportunity to submit comments on this important public health issue. We recognize that the FDA is in a challenging position, with groups and individuals advocating for and against differing levels of regulation. We understand the difficulty in balancing the need to act quickly to stem the tide of abuse and misuse of opioids, with the desire to act in a way which will not cause harm to those patients who have legitimate pain needs. Patients with cancer pain cannot afford missteps; as such, we believe acting in a cautious and deliberative manner, including piloting a new system, will help to achieve, in the long-run, the FDA's goal of ensuring that the benefits of these drugs continue to outweigh the risks.

Thank you very much for your consideration of our comments. If we can be of any assistance to you, or the FDA, on this important matter, please do not hesitate to contact our ONS Health Policy Manager, Leslie Greenberg (412/859-6401, lgreenberg@ons.org).

Respectfully Submitted,



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