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June 30, 2009

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

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

To Whom It May Concern:

The American Society of Clinical Oncology thanks the FDA for the opportunity to provide comments on the proposed Risk Evaluation and Mitigation Strategy (REMS) for extended-release prescription opioids. With more than 27,000 members worldwide, the American Society of Clinical Oncology (ASCO) is the leading medical society for physicians involved in cancer research and treatment. ASCO has a seventeen year history of recognizing the appropriate treatment of cancer pain, and educating our member oncologists on this essential component of high-quality cancer care.<sup>1,2</sup> While ASCO supports the Agency's efforts to address the problems of abuse, misuse and drug poisoning, we are concerned that the proposed REMS may result in unintended consequences that lead to an increase in the under-treatment of pain for cancer patients. It is imperative that the Agency fully consider potential outcomes of all aspects of the proposed REMS, take meaningful steps to safeguard the interests of cancer patients who require these medications for pain management and implement an ongoing evaluation plan with appropriate, interpretable metrics.

**Summary of Recommendations**

- Fully implement NASPERS: the funding of NASPERS and its implementation by the states would help to fulfill the FDA's dual goals of preserving access to, while more carefully regulating, legitimately prescribed opioids

<sup>1</sup> [No authors listed]: Cancer pain assessment and treatment curriculum guidelines: the ad hoc committee on cancer pain of the American Society of Clinical Oncology. J Clin Oncol 10:1976-82, 1992.

<sup>2</sup> Ferris FD, Bruera E, Cherny N, et al: Palliative cancer care a decade later: accomplishments, the need, next steps—from the American Society of Clinical Oncology. J Clin Oncol 27:3052-8, 2009.



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- Education for Physicians and Patients: enhancing awareness of the correct and careful use of these drugs, as well as their potential for abuse and misuse, will decrease potential adverse events
- Data Centralization: centralize the educational resource which might contain both physician and patient educational modules and minimally burden the providers to be educated. ASCO’s “ASCO University” and *Cancer.Net* programs are illustrative models.
- Inclusion of Schedule II and III Opioids: inclusion of these classes of opioid drugs would bring this REMS more closely in line with NASPERS requirements, and extend the educational opportunities on these classes of drugs

**Background Information**

The US Food and Drug Administration (FDA) has announced plans to implement a Risk Evaluation and Mitigation Strategy (REMS) for long-acting opioids, pursuant to its authority under section 505-1 of the 2007 Food and Drug Administration Amendments Act (FDAAA). The FDA has held a series of meetings for stakeholders, in addition to well-attended public hearings. Throughout these meetings, the FDA has made clear that the Agency is interested in feedback from the community, especially specific and concrete suggestions that FDA may consider as it seeks to implement this new REMS program. The FDA has acknowledged that this REMS would be the largest program of its type yet undertaken by the Agency, and that the sheer scope of this program could be daunting.

The FDA has stated that such a program is necessary due to the concerning increase in both the number of people abusing or misusing prescription opioids—whether obtained legitimately or by illegitimate means—and in the number of unintentional drug overdose poisonings, the huge majority of which are caused by prescription drugs. Of these, the majority of deaths involve prescription opioids specifically. It is clear from the data presented by FDA that the number of legitimate prescriptions for opioids has been growing over the past few years, as have the numbers of patients seeking treatment for prescription drug abuse and the incidence of unintentional drug poisoning deaths.

**Discussion**

The growing number of deaths involving prescription opioids is of great concern to the medical community, including ASCO. Of equal concern, however, is the potential for mitigation programs, if not carefully constructed, to: 1) impede appropriate pain management for cancer patients, 2) impose additional administrative burden for oncologists already struggling to deal with today’s challenging regulatory environment, and 3) stigmatize either the cancer patients who receive these drugs or the oncologists who prescribe them.



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It is entirely within the normal and expected scope of practice for oncologists to prescribe opioids to a significant proportion of their patient population. The indications for these drugs are that the patient suffers from moderate to severe pain, and that such pain is expected to last at a minimum for a number of weeks; moreover, for many of the extended-release opioids, the approved indication refer specifically to cancer pain. The population of patients suffering from conditions such as painful bone metastases is the very population for whom such drugs are indicated. These patients may comprise half of the patient case load for medical oncologists, and are patients for whom prescribing of these drugs is highly appropriate.

It is necessary to achieve a delicate balance between appropriate regulation of these powerful drugs and the avoidance of under-treatment of pain. According to the NIH,<sup>3</sup> the annual cost of chronic pain in the United States is estimated to be \$100 billion. Of concern to our members and their patients is the knowledge that under-treated pain co-exists with the problem FDA is trying to address; for example, studies have shown that over half of hospitalized patients experience pain in the last days of their lives, and more than half of these patients with cancer die in moderate to severe pain.<sup>4</sup>

Since there is significant evidence that prescriber behavior accounts for only a small portion of opioid misuse/abuse, it seems appropriate for the Agency to focus on the larger issue of diversion of these drugs after they have been legitimately prescribed by providers. According to the DEA, physician involvement in illegal drug activity is rare. Less than one-tenth of one percent of more than 750,000 physicians is subject to DEA investigations each year.<sup>5</sup> Research shows that the outright theft of narcotics unquestionably contributes to the problem of prescription drug abuse. One study of DEA data on the theft or loss of controlled substances in states with 53% of the US population showed that over a 4-year period (2000-2003), almost 28 million dosage units of all controlled substances were diverted from non-medical sources.<sup>6</sup> Obviously, much of the drug diversion activity arises from criminal enterprises, which falls under the jurisdiction of other authorities such as the DEA and federal and state law enforcement agencies.

<sup>3</sup> National Institutes of Health. NIH Guide: New Directions in Pain Research I. September 4, 1998. Available at <http://grants.nih.gov/grants/guide/pa-files/PA-98-102.html>. Accessed June 19, 2009.

<sup>4</sup> SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients: The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). JAMA.1995; 274:1591-1598

<sup>5</sup> Fact Sheet: Prescription Drug Abuse – a DEA Focus. U.S. Drug Enforcement Administration. Available at [http://www.usdoj.gov/dea/concern/prescription\\_drug\\_fact\\_sheet.html](http://www.usdoj.gov/dea/concern/prescription_drug_fact_sheet.html). Accessed June 19, 2009.

<sup>6</sup> Joranson DE, Gilson AM: "Drug Crime Is A Source of Abused Pain Medications in the United States," Journal of Pain and Symptom Management, 2005 Oct;30(4):299-301



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According to Congressional Testimony given by the DEA (May 2007)<sup>7</sup>, investigations have shown that Schedule II drugs are most commonly obtained illegally through “doctor-shopping” and other methods of illegal acquisition. This has not been the case, however, with Schedule III substances, which are being increasingly procured illegally in large amounts, via the Internet and the use of “rogue” pharmacies. The DEA testimony concluded that, “While studies such as National Survey on Drug Use and Health indicate that only a small percentage of youth get controlled pharmaceuticals via the Internet (the majority obtaining them from family and friends), it’s important to remember that when these individuals obtain these substances they generally acquire only a few pills at a time. In contrast, individuals ordering via the Internet frequently receive 100-120 pills at a time, making it a potentially much higher-volume source than friends or the family medicine cabinet.”

### Recommendations

ASCO acknowledges and shares the FDA’s concerns about abuse and misuse of opioid drugs. Below are specific suggestions that we believe will serve to mitigate inappropriate use of opioid drugs in the medical setting, while preserving oncologists’ ability to continue delivery of high quality cancer care.

#### *Implement NASPERS*

In August of 2005, the “NASPERS” (National All Schedules Prescription Electronic Reporting) Act was signed into law. This legislation provides for each state to either set up new prescription monitoring programs, or to expand and improve upon existing programs. Although this is intended as a national program, with interoperability between the states, each state is to be in control of its own program. Unfortunately, funding for this program never materialized. ASCO urges FDA to consider the merits of this legislation when considering the alternative of a new and burdensome national registry. NASPERS, if implemented as intended, would go a long way towards curtailing opioid abuse within the prescription setting. It has the added benefit of taking advantage of existing programs, thereby offering potential cost savings and faster start-up times.

- The program currently in place in Kentucky (“KASPERS”) has been widely cited as a model program for states across the country. Moreover, data has shown that, since the implementation of KASPERS, prescription drug abusers and larger-scale traffickers have moved their activity to adjoining states (many of which then implemented their own version of a

<sup>7</sup> DEA Congressional Testimony. Written Statement of Joseph T. Rannazzisi, Deputy Assistant Administrator, Office of Diversion Control, Drug Enforcement Administration, United States Department of Justice. May 16, 2007. Available at <http://www.usdoj.gov/dea/pubs/cngrtest/ct051607.html>. Accessed June 19, 2009.



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prescription monitoring program). Data on the Kentucky program<sup>8</sup> show that almost all of the thousands of inquiries to this database a month come from healthcare professionals. Kentucky’s program requires data collection every eight days, which then allows providers in the state to check this database in almost real-time to protect against either inadvertent over-prescribing or frank abuse (e.g., “doctor-shopping”). The program is having its desired effect of discouraging “doctor-shopping” and like activities. Secondly, the lack of a coordinated national program is taken advantage of by those who would abuse the system, as they simply move to states lacking such oversight.

- In California, prescription-monitoring program, CURES, originally evolved from the California Triplicate Prescription Program following numerous legislative enactments.<sup>9</sup> Created in 1940, the California Triplicate Prescription Program (TPP) was the oldest, longest running multiple copy prescription program in the nation. The TPP program regulated and monitored the distribution of Schedule II controlled substances through state-issued, serialized, triplicate prescription forms. In 1998, the TPP program moved forward into the 21st century establishing an electronic monitoring system capable of capturing all Schedule II controlled substance data throughout the state. This system became the Controlled Substance Utilization Review and Evaluation System (CURES), which captures Schedule II through IV, and provides patient activity reports (PAR) to the medical community, investigative referrals to BNE field offices, print out requests to outside law enforcement for assistance in investigations, specialized reports to researchers, and statistical data to determine drug trends either statewide or region specific. An example of an interstate network, between California and Nevada, is at [http://www.ijis.org/docs/success/case\\_study\\_pmix.pdf](http://www.ijis.org/docs/success/case_study_pmix.pdf).

We encourage the Agency to learn from these state experiments and systems, and build on the successes of these state’s programs. These programs are not only feasible, but they provide critical information to professionals prescribing and dispensing these drugs, and serve the regulatory needs about which the Agency is concerned.

*Education for Physicians and Patients*

Opioids can be a critical component of an overall pain management program. In addition to physicians’ knowledge of the appropriate use of these drugs, it is important that all physicians prescribing these agents are aware of the potential of

<sup>8</sup> National Alliance for Model State Drugs Laws: Kentucky’s Prescription Drug Monitoring Program. Available at <http://www.namsdl.org/resources/Kentucky1.pdf>. Accessed June 19, 2009

<sup>9</sup> See <http://www.ag.ca.gov/bne/trips.php>



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these drugs for abuse and addiction if misused, and the resultant individual suffering and cost to overall public health. ASCO supports an integrated educational program for physicians that covers these important topics and informs physicians on how to identify potential misuse or diversion. Such an educational program should be accessible via the Internet. While we are aware that, under the REMS authority, educational content is to be developed by the sponsor(s) and approved by the FDA, we feel strongly that the content of this program would benefit from input from professional societies, such as those representing physicians and other health care professionals in addiction, pain management, oncology, hospice, nursing care, and pharmacy. Many of these societies have existing high quality educational materials available on these topics, and it would be wise to take advantage of such materials where they exist.

In order to ensure the widest uptake of this educational program, we suggest that: a) successful application for, or renewal of, a prescriber's DEA registration be contingent upon successful completion of this program, and b) physicians successfully completing the module receive Continuing Medical Education (CME) credit. It is probably reasonable to require an every-two-year completion of this educational module.

ASCO has a seventeen year history of educating physicians on appropriate pain management. Most recently, ASCO has developed a patient-oriented website, *Cancer.Net*, which provides multiple resources on various methods of pain management for patients and those who care for them. We recommend that, in the setting of a first-time prescription, patients should receive education on the correct, intended use of these medications; safe techniques for storage and disposal; possible adverse events and what to do if they occur; and the potential dangers of misuse and diversion, whether intended or unintended. We suggest that patient education materials be accessible electronically, in a printer-ready format, at the same website with the physician education materials. (See below for fuller discussion of centralization of required materials.)

*Data Centralization*

All physician and patient educational materials, all required forms and documents, and any additional information should be placed as electronic modules in one central database, with one website interface. The sponsors of each of the affected drugs should work together with DEA and FDA to create one physician module and one patient module, minimizing the numbers of educational materials and required forms needing to be accessed. The goal of developing overarching electronic modules (including the use of a single, all-inclusive verification form) is to convert the current DEA and FDA RiskMAP requirements into the new streamlined REMS requirements, avoiding duplication of effort and minimally keeping regulatory burden at status quo. The agency should make every effort to ensure that REMS requirements do not result in an increased burden on



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physicians or the patients they treat, increased fear of prescribing by doctors who treat patients experiencing moderate to severe chronic pain or other unintended consequences that would result in an increase in the number of patients being undertreated for pain.

If FDA decides that a specific informed consent document is necessary, this document should be available at the same central website and should be adaptable for state-specific needs (e.g., certain states have requirements that patients agree not to perform certain activities while taking these drugs).

*Expanding the Proposed REMS to Opioids on Schedules II and III*

The proposal put forward by the FDA for a REMS program is specific to the extended-release opioid drugs. Although much of the coverage, especially mainstream media coverage, on prescription opioid abuse has focused on extended-release oxycodone (i.e., Oxycontin®), it is in fact the case that the most-abused opioid is the immediate-release form of hydrocodone (e.g., Vicodin®).

It is ASCO's position that any action the FDA takes within the context of the proposed REMS should include the short-acting opioids. Otherwise, experience has shown us that, in certain states that enacted prescription monitoring programs (PMPs) only for Schedule II drugs, the rate of prescribing for Schedule II drugs decreased, but the rate of prescribing for Schedule III drugs conversely increased. Implementation of the proposed REMS presents an opportunity for education on all drugs in the opioid class, as to omit certain drugs from this class only due to their more immediate bioavailability could lead to lack of necessary education on this specific class of opioids and also the potential for greater abuse if these drugs fall outside of this REMS. Moreover, NASPERS mandates coverage of drugs on Schedules II-IV, so requiring short-acting opioids to fall within the proposed REMS would result in more seamless integration of data on prescribing and use practices.

*Evaluation Plan and Metrics*

In order to ensure that a REMS for opioids does not have the unintended consequence of increasing the under-treatment of pain of a cancer patient, and is successful in addressing abuse, misuse and drug poisoning issues, the Agency needs to carefully select metrics for a REMS program evaluation. The metrics should be chosen in such a way as to ensure the Agency fully understands the impact of the REMS. For instance, using a metric such as an overall decrease in prescriptions written for opioids only proves that doctors are writing fewer prescriptions. It may in fact mean that the REMS has created an undue burden on oncology physicians and patients or created an environment of fear surrounding prescribing these drugs leading to a decrease in pain management for cancer patients. If the Agency were to use the prescribing habits of medical specialty



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subgroups, it may gain more valuable information. For instance, if oncologists' prescription habits remained steady or even increased while the prescribing habits of medical specialties that typically do not see patients who have intractable, long-term pain decreased, more valuable insight may be gained. If accidental drug poisonings decrease, the education aspect of the REMS may be having a positive impact. ASCO is experienced in identifying appropriate evaluation metrics and would be happy to assist the Agency in its development of an evaluation program. The Agency should request public comment on any program before it is implemented.

**Conclusion**

ASCO supports the FDA's efforts to ensure safe prescribing of prescription opioid drugs. In common with the FDA, we do not wish to erect unreasonable barriers to patients who have legitimate needs to access these drugs as part of their medical treatment. We support efforts to educate physicians, patients, and the public about the valuable role these drugs can play in pain management, as well as their potential for abuse and diversion. Taking full advantage of the NASPERS program will play a large role in the oversight of the use of these drugs in the legitimate medical setting. And the implementation of an evaluation plan using appropriate, interpretable metrics will assist the Agency in its mission to improve public health.

Sincerely,

Douglas W. Blayney, MD  
ASCO President