June 30, 2009

Margaret Hamburg, MD
Commissioner
Food and Drug Administration
U.S. Department of Health & Human Services
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. FDA-2009-N-0143; Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs

Dear Commissioner Hamburg:

The undersigned national medical organizations respectfully submit the following comments in response to the Food and Drug Administration's (FDA) April 20, 2009, Federal Register Notice regarding Risk Evaluation and Mitigation Strategies (REMS) for certain opioid drugs (Notice). We strongly support initiatives that achieve the right balance between the risks and benefits in the utilization of the opioids and look forward to working closely with the FDA and other health care stakeholders to achieve such an outcome. We commend the FDA for seeking stakeholder input in light of the unprecedented use of REMS for a group of drugs and urge the agency to continue this engagement with the medical profession.

There is a significant and growing public health danger posed by the misuse and, in many cases, diversion of these opioids that must be addressed through a multi-pronged public health approach. While working to minimize the misuse and diversion of opioids, physicians have an equally compelling ethical obligation to remain mindful that they must preserve access to effective pain management options for patients—particularly in areas where physicians who manage chronic pain patients are already scarce. Achieving an optimal balance between risks and benefits is difficult because several concurrent and competing factors exist including:

- need for appropriate prescribing and pain management;
- patient misuse, diversion, or addiction;
- recognizing and monitoring aberrant behaviors;
- regulatory and law enforcement scrutiny; and,
- prescribers who contribute to non-medical use or diversion.

Each of these factors has a different dynamic, as well as a different solution.

Below we offer recommendations in response to the specific questions posed in the FDA's Notice. We also identify issues and concerns related to the scope of the potential REMS and the need for appropriate coordination among federal agencies to address the most significant causes and sources of diversion that extend beyond the FDA's existing authorities. Specifically, while strategies exist that manufacturers could implement to

mitigate risks associated with prescribing the listed opioids, federal agencies should pursue a number of coordinated steps to reduce diversion and inappropriate use of these opioids by individuals who have not been prescribed these drugs.

Recommendations for REMS Elements

In brief, we strongly support efforts to expand the tools and capabilities that the FDA has available to communicate risks directly to physicians. In prior communications to the FDA, Congress, and Institute of Medicine (IOM) Committee on Drug Safety, the American Medical Association (AMA) provided detailed comments concerning the general use of risk minimization action plans, the forerunner to REMS. Of note, the AMA convened meetings in 2006 and 2007 between the FDA and several medical specialty societies with the goal of identifying the most promising collaborative strategies that the FDA and specialty societies, individually or collectively, could utilize to improve the FDA's capacity and effectiveness in communicating risk and adverse events to physicians. We applaud and support the FDA's efforts to pilot a program so that the FDA and organized medicine can more effectively work together to address and mitigate new (and in some cases existing) drug safety concerns as they arise. A coordinated system for risk communication is needed in order to avoid fragmentation and confusion.

As the FDA evaluates what element(s) of a REMS are appropriate, we offer a number of observations and recommendations that we urge the FDA to consider and pursue.

Mandatory certification, substantially expanded counseling or record-keeping requirements, restricted use scenarios, and other intrusive REMS elements generally should be used only as a last resort to keep high-risk products with very unique and important benefits on the market when no other approach is sufficient to allow continued marketing of a drug product.

We favor the use of positive incentives to encourage physicians to complete educational requirements, such as a waiver of the $550 Drug Enforcement Agency (DEA) registration fee, for completion of voluntary course(s) to increase the number of physicians who obtain adequate training on pain management and the recognition of substance use disorders. Manufacturers should be required to absorb the cost associated with the DEA fee waiver in light of the relatively minimal DEA fee that they currently pay. Positive incentives, as opposed to mandatory requirements, are far more likely to increase the number of physicians who participate and will foster a better equipped physician workforce.

The AMA developed a 12-hour Pain Management continuing medical education (CME) Program in 2004 and revised in 2007. To date, approximately 155,000 CME certificates have been issued for the online version of this program, and 65,000 for the print version, with an additional 26,000 certificates issued to non-physicians, primarily physician assistants. The AMA plans to further revise this course to better address concerns which have recently been raised about the use of products that are the subject of the opioid REMS. Additional CME modules are being planned to provide enhanced focus on

physician education of patients and effective clinic-based prevention strategies. These modules will be designed to complement and incorporate a planned on-line CME developed by the U.S. Department of Health and Human Services Center for Substance Abuse Treatment for which the AMA is providing assistance. The AMA, in collaboration with a team of medical schools funded by through the National Institute on Drug Abuse, has coordinated the research and development of prescription drug abuse education modules for use with undergraduate medical students and residency programs. Assuming the availability of funding, these will be converted to on-line courses for practicing physicians.

Additionally, the development and more widespread implementation of physician-mentoring programs must be supported and adequately funded. For example, the Physician Clinical Support System (PCSS) Buprenorphine, managed by the American Society for Addiction Medicine, with the support and assistance of the AMA and other medical specialty societies and treatment experts, is a clinical mentoring program that has trained and provided assistance to hundreds of physicians around the nation. A similar mentoring program focusing on methadone has just gotten underway, but has received very limited funding compared to the size of the task it faces. Physician behaviors are most likely to change when prompted and assisted by other physicians. This makes a peer mentoring model particularly effective. The FDA should evaluate alternative strategies to manufacturer based activities, and promote voluntary provider education and ascertain whether other approaches to risk mitigation can be utilized that do not hinge on manufacturers to implement and maintain the system.

In this area, we strongly urge the FDA to work closely with Substance Abuse and Mental Health Services Administration (SAMHSA) and the DEA to implement positive incentives that will increase and assist the number of physicians who are willing and able to provide appropriate pain management to patients. Decreasing access to specific Schedule II drug products is likely to have a deleterious impact on the most vulnerable, underserved communities across the country, further stigmatize those who suffer from moderate to severe pain, and increase suffering across the pain care spectrum from patients with chronic pain to those with cancer or who are receiving hospice/end-of-life care.

Any education requirements for opioid REMS should include the input of practicing physicians. Better information is needed on the factors contributing to overdoses, inappropriate patient selection or prescribing, and the pathways to non-medical use. A well designed, web-based CME course on responsible prescribing of controlled substances is an option.

When risk management beyond product labeling for a specific drug is needed, we can support additional REMS elements. However, less intrusive elements as specified in the Food and Drug Administration Act Amendments of 2007 (FDAAA) must be tried first, including a “Communications Plan.”

Restricted distribution tools such as mandatory education and certification can only be used as a last resort to keep high-risk products with unique and important benefits on the market. Mandatory certification and restricted distribution may have several unintended consequences, including:

- physicians opting out of prescribing Schedule II controlled substances with fewer primary care physicians willing to manage patients with chronic pain;
- reduced access for some patients, particularly those in underserved communities, to medically necessary drugs; and,
- a shift in prescribing from Schedule II to Schedule III opioid products.

Previous prescription monitoring or process-related restrictions for Schedule II products have fostered such behaviors. The following are specific examples of where this occurred:

- when New York mandated government-issued serialized forms for benzodiazepines;
- states with prescription monitoring programs (PMP) that track only Schedule II substances;
- states that have "proactive" versus "reactive" PMPs; and,
- when highly restrictive limitations were placed on permits for providing methadone maintenance (for opioid dependence treatment) and then for the number of patients allowed for each physician to prescribe buprenorphine for opioid maintenance or detoxification (e.g., the same number applied to a solo practitioner as applied to a group practice).

In all instances, the policy greatly limited patient access and effectively limited the desire of physicians to participate in providing treatment and maintenance. These also had the unintended effect of reinforcing the concept that substance use related treatment and effective prescribing are not major physician concerns or part of basic medical practice. In the end this makes identification and effective interventions with substance use disorders less likely and more prone to patient management problems.

In addition, given the unprecedented reach of this REMS, we do not support extending the REMS to all opioids, including immediate release products. The FDA has acknowledged in published accounts that REMS would be a “relatively massive new program.” The public reporting states that the current proposed group covered by the REMS involved “21 million prescriptions [and] is ‘orders of magnitude’ greater than any other program in place.” Equally significant, in an annual survey by the National Center for Health Statistics/Center for Disease Control it was reported that 20 percent of patients presented in emergency departments with severe pain and another 25 percent presented in moderate pain, (24 million and 30 million visits, respectively). If physicians face significant barriers to prescribing time release opioids, more patients will come to emergency rooms for pain relief—even though time release opioids are rarely prescribed in the emergency room. For the foregoing, reasons we would have significant concerns with efforts to expand yet further the REMS.

REMS elements to assure safe use must be implemented based on evidence of their effectiveness. Appropriate patient counseling and adherence monitoring, and the tools to implement these behaviors, should be part of the education process. However, we oppose (as mandatory) practices that are already considered appropriate in certain patients including the use of patient-physician agreements, specific monitoring schedules, or urine tests.

Moving forward, we strongly support ongoing rigorous evaluation of the effectiveness of any opioid REMS. Accordingly, the FDA must have the appropriate metrics in place to evaluate not only potential harm to patients from opioid medications, but also harm to those patients who will suffer from inadequate pain management. The latter could result from a lack of certified physicians, shifts in prescribing patterns, the resurrection of widespread opioid phobia on the part of physicians, or a clinical practice environment that emphasizes preventing the misuse and abuse of pain medications at the expense of providing adequate and humanitarian pain relief. Other metrics that the FDA should consider utilizing include tracking the number of physicians taking CME pain management courses and participating in mentoring programs, percentage and number of DEA licenses issued annually, and before and after surveys of pain patients concerning their satisfaction with pain management and access to care.

In contemplating the need for an opioid REMS, we urge the FDA to view the development of such a program through the lens of FDAAA which requires that REMS "not be unduly burdensome on patient access to the drug, considering in particular (i) patients with serious or life-threatening diseases or conditions; and, (ii) patients who have difficulty accessing health care; and to the extent practicable…minimize the burden on the health care delivery system."

Diversion Generally and the Need for Coordinated Government Response

The increase in opioid misuse, diversion, and deaths has been well documented and represents a significant public health problem. Nonetheless, evidence is lacking that the primary driver for these trends is an increase in opioid diversion by patients who rely on them therapeutically for pain relief; the same argument applies to trends observed with other controlled substances such a benzodiazepines or stimulants. Drug diversion can occur anywhere along a line from the manufacturer/wholesale distributor to the prescriber, hospital or retail pharmacy, or the patient. The actual contribution that poor prescribing practices or fraudulent activity on the part of prescribers makes to the supply of diverted controlled substances is unknown. Based on National Survey on Drug Use and Health (NSDUH), drugs used for non-medical purposes are usually obtained for free or taken or purchased from friends or relatives. Among persons aged 12 or older who used pain relievers non-medically in the past 12 months, 57 percent reported that the source of the drug was from a friend or relative for free. Another 18 percent reported they got the drug from a single prescriber. Only 4 percent obtained the pain reliever from a drug dealer or other stranger, and 0.5 percent reported buying the drug on the Internet. Among those who reported getting the pain reliever from a friend or relative for free,

more than 80 percent reported in a follow-up question that they believed their source had obtained the drugs from a single prescriber. Less than 3 percent reported "doctor shopping" to obtain controlled substances. The figures derived from NSDUH are relevant for a portion of the "supply" side of prescription drugs for non-medical use, but offer no information about the motives for such use.

Physicians generally believe the three main mechanisms of diversion to be "doctor shopping," patient deception, and forgery or altered prescriptions. Among individuals seeking admission to substance use treatment programs for OxyContin® addiction, 78 percent of subjects reported the drug had not been prescribed for them, and a similar percentage reported prior treatment for a substance use disorder.

In addition to outright prescription fraud, thefts from the distribution chain and access to illegal online pharmacies are significant sources of controlled substances diverted into the illicit market. Sources of fraudulent prescriptions include legitimate prescription pads that are stolen from physicians' offices, alteration of original prescriptions, computer-generated prescription pads or fictitious prescriptions, and various scams involving the use of fake patients. The National Center on Addiction and Substance Abuse at Columbia University, in an update of a previous report, identified 159 Internet sites selling prescription opioids, sedative-hypnotics, and stimulants during a one-week period in 2008; 85 percent of these sites did not require a valid prescription (i.e., either they explicitly stated that no prescription was needed, made no mention of a prescription (47 percent), or offered an "online consultation" in lieu of a prescription (38 percent)).

When the illicit marketplace and subgroups of users are examined, numerous sources of diversion are revealed, including: prescribers and pharmacists; parents, relatives, and friends; "doctor shopping;" leftover medications; personal visits to non-US countries; burglaries; and "sneak thefts."

In light of the foregoing, a concerted and coordinated set of responses are required across agencies including the DEA, the SAMHSA, and FDA. Furthermore, we strongly urge the FDA to be measured in seeking development of acceptable REMS elements that manufacturers must design, implement, and administer.

In the background materials for the FDA meetings, and in previous pronouncements on this subject, drug diversion and non-medical use of pain medications have been cited as factors that contribute to the need for an opioid REMS. However, opioid REMS are not intended to directly address diversion. The most effective approach to reducing diversion is the development of real-time, state-based, PMPs that can interface with each other. Accordingly, we reiterate our support for funding and implementation of the National All Schedules Prescription Electronic Reporting (NASPER) Act. Despite passage a number of years ago, Congress did not appropriate funding until this fiscal year. We believe that this provides a much needed tool in the arsenal to combat the rising public health problem associated with misuse of opioids, and if implemented appropriately, will address both patient and prescriber-based inappropriate behavior.

We agree with other commenters that existing and emerging state PMPs should be based on a public health approach designed to identify problem behaviors, help promote responsible prescribing, and be more efficient and timely in their operation. **This is a far superior strategy than creating REMS elements featuring restricted distribution that are designed, implemented, and monitored by manufacturers.** The majority of states have PMPs, but they vary by state. Nonetheless, the purpose of PMPs, in part, is to prevent "doctor shopping" and track prescriptions of controlled substances to help address drug abuse, misuse, and diversion. With enhancements, this existing PMP infrastructure can be a helpful tool for prescribers (as well as law enforcement) to promote responsible prescribing and reduce misuse and diversion. PMPs should be available for prescriber and dispenser use in all 50 states. We agree with the recommendations of other commenters that the PMPs should be improved by:

- making the data available in "real time" to all prescribers (and dispensers);
- developing a system of interstate connectivity to the databases;
- incorporating into the PMP core training for prescribers, law enforcement, and other PMP users about the purpose and use of PMPs as a means of promoting responsible prescribing and dispensing and reducing misuse, abuse, and diversion of controlled substances;
- evaluating effectiveness of PMPs in promoting responsible prescribing and reducing misuse, abuse, and diversion; and,
- increasing federal funding to help pay for these improvements.

We strongly urge the FDA to consider that, although NASPER has been authorized since 2005, it has never been funded until now. The agency should provide a sufficient time for the implementation of this strategy to ensure that legitimate users of these prescription drugs are not adversely impacted through more restrictive measures. The FDA should work in coordination with other federal agencies to ensure utilization of strategies that are more likely to effectively address misuse and diversion.

FDA Authorities and Class-wide REMS

FDAAA confers the FDA with additional authorities to improve the safe use of prescription drugs. The FDAAA does not have express provisions authorizing class-wide REMS. There are particular challenges to implementing a REMS for a group of drugs because manufacturers are responsible for design, implementation, and monitoring of the REMS elements. The public health issues presented by opioids are best addressed in a coordinated effort among federal and state agencies with significant participation by those in the health care community. Also, this REMS proposal comes at time when physician-industry interactions, including manufacturer funded CME units, are subject to rigorous scrutiny yet the FDA now proposes to vest "regulatory" authority over appropriate uses of the opioids with manufacturers. Utilizing REMS for a category or group of drugs is a novel use of the FDA's authority and presents significant implementation challenges.

Furthermore, to the extent that the FDA utilizes the element formerly known as restricted distribution—now dubbed "conditions for safe use"—the agency could run afoul of the statutory requirements that mandate individualized findings that other REMS elements have not been successful. FDAAA did not establish new authorities vis-à-vis restricted distribution, it merely codified existing regulations promulgated by the agency.

One individual who presented at the May 27-28, 2009, FDA Public Meeting stated that many of the safety issues with opioid products could be attributed to the FDA's failure to include appropriate dosing information in the product labeling. We strongly urge the FDA to consider the recommendations offered by this commenter and immediately initiate a plan to address labeling information concerning appropriate therapeutic ranges for methadone, which clearly fall within the scope of the agency's authorities.

In summary, there are significant public health challenges that must be addressed. We commend the FDA for soliciting input from stakeholders concerning the appropriate elements of a REMS. **We urge the FDA to solicit public comment once a proposed REMS has been developed and submit it to the agency's advisory committee(s) for formal review. The reach and scope of this REMS regardless of the elements will represent a marked expansion of the use of REMS and could have numerous unanticipated consequences without rigorous review and systematic input.**

Finally, a coordinated effort that includes a meaningful and positive engagement of physicians and other prescribers can produce substantial benefits for patients. We urge the FDA to work closely with other federal and state agencies as they develop a comprehensive approach, and implement NASPER. We urge the FDA prior to the meaningful implementation of NASPER to avoid fashioning policies that restrict access to those in greatest need of medical assistance.

Sincerely,

American Academy of Dermatology Association
American Academy of Family Physicians
American Academy of Orthopaedic Surgeons
American Academy of Physical Medicine and Rehabilitation
American Association of Neurological Surgeons
American College of Emergency Physicians
American College of Physicians
American College of Preventive Medicine
American Gastroenterological Association
American Medical Association
American Osteopathic Association
American Psychiatric Association
American Society for Gastrointestinal Endoscopy
American Society of Anesthesiologists
American Society of Plastic Surgeons
Congress of Neurological Surgeons