PAIN & POLICY STUDIES GROUP
WHO Collaborating Center for Policy and Communications in Cancer Care

June 25, 2009

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

RE: Docket No. FDA-2009-N-0143

To Whom It May Concern:

The Pain & Policy Studies Group (PPSG) respectfully submits the following comments in response to the Food and Drug Administration's (FDA's) April 20, 2009, *Federal Register* notice regarding a Risk Evaluation and Mitigation Strategy (REMS) for 24 long-acting opioid analgesics and the public meetings that took place on May 27-28, 2009.

As members of a university-based research group with a mission to improve international and federal policy, as well as state drug control and professional practice laws governing pain management and the use of prescription opioid analgesics, we always have been concerned about the extent that these medications are used non-medically and play a role in deaths. To minimize the increasing non-medical use of prescription opioid analgesics, and the associated impact on public health and welfare, we support the idea of a REMS if it is both effective (i.e., successfully reduces non-medical use and diversion) and safe (i.e., does not restrict access and negatively affect patient care). These objectives are in keeping with the principle of "Balance" established by the United Nations' Single Convention on Narcotic Drugs of 1961 (Single Convention).[1] The Single Convention establishes a number of basic requirements for a country's laws and regulations to institute measures to control abuse and diversion. A government that is a party to the Single Convention, such as the U.S., also is obligated to take steps to ensure that controlled substances, including opioid analgesics, are available in adequate amounts for medical and scientific purposes.[2,3] The FDA has made public statements that clearly seem to support these dual objectives when considering REMS development. Obviously, any moratorium on long-acting opioids, even when allowing for their use if a patient has the disease of cancer or is being treated in a comprehensive care program, fails to consider a deleterious impact on the care for all patients who may need these medications. As a result, even though a moratorium was proposed during the public meetings in May, this is an unbalanced and therefore inappropriate policy response to prescription opioid abuse and diversion.

The PPSG promotes a public health approach to the issue of the non-medical use of prescription opioids, which requires the comprehensive identification of vectors (or sources) so that effective interventions can be targeted successfully.[4,5] To this end, before implementing a REMS, we recommend that the FDA consider the following issues:

(1) Thoroughly understanding the non-medical use of prescription opioids,
(2) Authority to regulate medical practice,
(3) Possible unintended effects of the REMS,
(4) Determining "success" of the REMS, and
(5) Better utilizing already-existing drug control programs.

(1) The FDA should thoroughly understand the non-medical use of prescription opioids. These comments are submitted because we are convinced that, while the FDA's commitment to requiring a REMS to reduce prescription opioid abuse and diversion is laudable, there is insufficient understanding of this public health issue to guide development of an effective and safe REMS. Such a conclusion is supported by a recent report from the Drug Enforcement Administration's (DEA's) National Drug Intelligence Center, entitled *National Prescription Drug Threat Assessment*, which details multiple known diversion sources including in-transit robberies, thefts from pharmacies and healthcare facilities, and "rogue" Internet pharmacies.[6] These criminal enterprises are the sources of substantial amounts of opioids that are subsequently used non-medically, but none of these are addressed by a REMS that focuses solely on the practitioner-patient relationship (see Appendix A for a schematic we developed to aid in understanding the multiple sources of diversion). In fact, there is no published evidence of the extent that registrant prescribing practices contribute to non-medical opioid use or the mortality that is often reported. In addition, findings from the most recent National Survey of Drug Use and Health (NSDUH) demonstrated that most (71%) people reporting non-medical opioid use receive the drug from a friend or family member, making it difficult to conclude that a prescriber or patient was at fault.[7] Thus, although the FDA currently is considering a "patient education" component for the REMS, it is unclear how the REMS would address this source of diversion and how the effectiveness of patient education will be determined. Security of the medications, once they are dispensed to the patient, remains a foundational issue that requires attention.

In the FDA's *Federal Register* Notice of Public Meeting, a list is provided of serious adverse events associated with opioid pain medications, including addiction and death. While certainly it is true that such adverse events can result from "improper dosing, indication, and patient selection" (p. 17968), there again is little evidence that these clinical practices are principal causes of such adverse events. The extent that these adverse events involve patients who are provided legitimate prescriptions, rather than those who have acquired the drug for illicit purposes, is unknown and difficult to determine. Poly-drug use, which occurs frequently for people who are using opoiods non-medically or who have an addictive disease, is another complicating factor when explaining adverse events and devising solutions.[8]

(2) The FDA lacks authority to regulate healthcare practice. When contemplating the elements of the REMS that is being considered, important questions of statutory authority arise. For example, does the authority within the Controlled Substances Act to register practitioners extend to a REMS requirement for practitioner certification as a prerequisite to DEA-registration? In addition, there has been discussion about requiring a prescriber-patient agreement as a key element of the REMS. It has been proposed that such an agreement would obligate practitioners to document each patient's need for an opioid according to specific criteria of dosing, frequency, and opioid tolerance. This appears to be regulation of healthcare practice, for which the federal government has no authority?

(3) The FDA should consider the possible unintended effects of a REMS. It is incumbent on the FDA to anticipate the potential, although perhaps unintended, effects of a REMS requiring certification for all practitioners who prescribe, dispense, or administer the class of long-acting opioids. Perhaps we can learn from the controversial history with state prescription monitoring programs (PMPs) requiring the use of a government-issued prescription form for Schedule II medications only. PMPs largely have been states' principal drug control mechanism designed to reduce prescription medication abuse and diversion. The scant available research suggests that states implementing such a program witnessed a substantial decrease in the prescribing of Schedule II medications, along with a concomitant increase in the use of medications not covered by the PMP.[9-14] This phenomenon has come to be known as the "substitution effect" and has been used as evidence that a government drug control program designed to address a

critical public health issue (i.e., medication abuse and diversion) can have a detrimental, albeit unintentional, impact on a separate public health issue (i.e., treatment of severe and debilitating pain).[12] One can assume that avoidance of past PMPs' additional, seemingly onerous, prescription requirements would predict clinicians' reactions to a federal REMS solely for long-acting opioids. Many clinicians will avoid the certification requirement of the REMS, and inevitable monitoring by the federal government, and will be unable to prescribe long-acting opioids. Given this expectation, it is also highly probable that the medical use of short-acting opioids will increase even further, despite the fact that many of the medications are not indicated for treating severe pain and are associated with other significant adverse effects like liver toxicity and GI bleeding. As a result, it is likely that more patients will suffer from a lack of available effective pain treatments.

(4) The FDA should consider how to determine "success" of the REMS. Ultimately, the FDA's *Federal Register* query, "How restrictive a [REMS] should be designed?" (p. 17969), is an inapt question. Appropriately addressing the societal problem of prescription opioid abuse and mortality requires a more thorough understanding of the issues, and can come about only when there is better evidence about the sources of diversion. We know that opioid-related non-medical use and mortality are increasing, but unfortunately at this time we know very little beyond that, especially as it relates to developing an effective abuse and diversion minimization system. Likewise, a "restrictive" REMS may in fact reduce abuse and diversion of long-acting opioids, but we will not know whether this benefit derives from drastically limiting the availability of medically-necessary drugs or rather from successfully addressing a substantial source of opioids used non-medically. Currently-available federal databases, like the NSDUH, cannot provide clarity on this issue.

This reality makes it difficult to define an appropriate context in which to assess "success" of the REMS. Reductions in the number of people reporting non-medical use of prescription opioids to the NSDUH certainly could be deemed a "success." However, what would be the implications of this finding in light of the FDA's stated objective of developing "a REMS, to adequately manage the risks of these products without unduly burdening the health care system or reducing patient access to these medications" (p. 17968)? Fortunately, it is relatively simple to measure impact on medication availability by determining how REMS implementation changes the frequency of prescribing long-acting opioids, or the proportion of practitioners who become certified within the REMS since this can be compared against the number of practitioners registered by the DEA to prescribe controlled substances. These seem like essential outcomes to measure and the metrics are available. But how will documented impact on both abuse and patient care be measured against one-another?

(5) The FDA should consider ways to better utilize already-existing drug control programs. Again, the long history of state PMPs suggests the difficulty of developing a program to simultaneously protect public safety and support public health by enhancing patient care. However, recent PMPs, in the form of electronic data transfer (EDT) programs for multiple medication schedules, are better able to accomplish these dual societal goals. EDT systems generally have eschewed the prevalent barriers characterizing past PMPs and are not considered detrimental to medication availability or patient care.[15] Although there has been little evaluation of the effectiveness and safety of EDT systems, nascent empirical research is beginning to document their value for identifying and addressing the phenomenon of doctor-shopping and other abuse- and diversion-related activities. Moreover, recent legislation establishing EDT systems occasionally requires the development of an educational program for practitioners using the system. The educational program often relates to prescribers' transmission, access, and use of the prescription data, and can include content specific to treatment referrals for patients who

abuse the prescribed medication or have an addictive disease, medication pharmacology, and even pain management practices.

Given the current prevalence of EDT systems across the nation, as well as the continued availability of federal funding making it likely that most if not all states will have a functioning PMP in the next few years, it is possible to enhance the infrastructure of existing and further future PMPs to accomplish the same objectives as the considered REMS. Of course, resources would be required to systematize and coordinate all PMPs to function similarly and to allow inter-programmatic communication of prescription data. Such a strategy is advantageous because it would integrate and fully utilize already-available data sources from programs created with the same goal as the REMS. Pilot studies will be necessary to determine how best to enhance the existing systems' efficiencies and capacities. It must be recognized, however, that focusing solely on PMPs only addresses prescriptions to patients and still does not deal with the myriad diversion sources that contribute to the non-medical use of prescription opioids.

Overall, reducing the non-medical use of prescription opioid medications is a critical objective, but is one that cannot be achieved in a vacuum. Implementing a REMS with the characteristics that have been proposed may have the effect of reducing abuse, but could do so at the expense of patients suffering from unremitting and severe pain. Is this an tolerable outcome? Such a public health policy response is unbalanced and unacceptable, and the FDA's appreciation of possible negative consequences of the considered REMS has not been forthcoming. Even a global REMS approach for the entire class of prescription opioids remains only an incomplete response to non-medical prescription opioid use because it does not address the unknown, but potentially significant, proportion of diversion and abuse that occurs outside of the prescriber-patient context. We, therefore, strongly urge the FDA to reject approaches that do not take into account the above issues when considering a REMS to minimize medication risks. The complexities and nuances of this issue demand a suitably thorough and considered response. The FDA's new statutory authority to require a REMS while "assuring access and minimizing burden"[16] (§505-1(f)(2)) seems to necessitate adherence to the principle of Balance. Given this legal obligation, the FDA must strive to clearly conceptualize a balanced public policy that has the most favorable consequences for the two public health concerns of abuse/diversion and patient pain care.

Respectfully,

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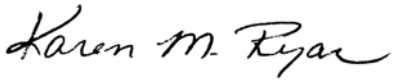

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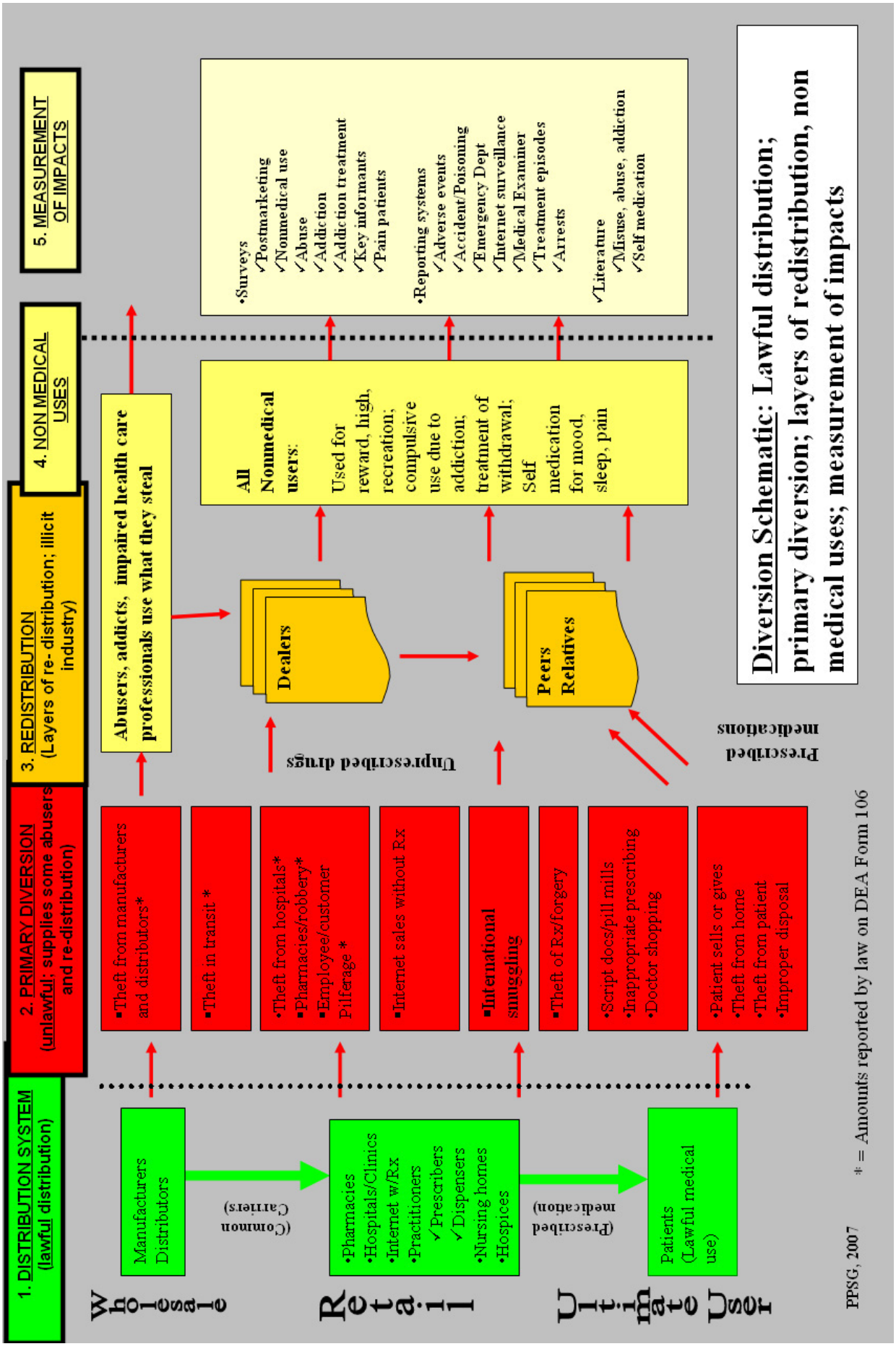
(16) Food, Drug and Cosmetic Act. Title 21 USCS §505-1(f)(2).

Appendix A


1. DISTRIBUTION SYSTEM (lawful distribution)
2. PRIMARY DIVERSION (unlawful; supplies some abusers and re-distribution)
3. REDISTRIBUTION (Layers of re-distribution; illicit industry)
4. NON MEDICAL USES
5. MEASUREMENT OF IMPACTS
Wholesale
Retail
Ultimate User
Manufacturers Distributors
(Common Carriers)
Pharmacies
Hospitals/Clinics
Internet w/Rx
Practitioners
✓Prescribers
✓Dispensers
Nursing homes
Hospices
(Prescribed medication)
Patients (Lawful medical use)
Theft from manufacturers and distributors*
Theft in transit *
Theft from hospitals*
Pharmacies/robbery*
Employee/customer Pilferage *
Internet sales without Rx
International smuggling
Theft of Rx/forgery
Script docs/pill mills
Inappropriate prescribing
Doctor shopping
Patient sells or gives
Theft from home
Theft from patient
Improper disposal
Unprescribed drugs
Prescribed medications
Abusers, addicts, impaired health care professionals use what they steal
Dealers
Peers
Relatives
All Nonmedical users:
Used for reward, high, recreation; compulsive use due to addiction; treatment of withdrawal; Self medication for mood, sleep, pain
•Surveys
✓Postmarketing
✓Nonmedical use
✓Abuse
✓Addiction
✓Addiction treatment
✓Key informants
✓Pain patients
•Reporting systems
✓Adverse events
✓Accident/Poisoning
✓Emergency Dept
✓Internet surveillance
✓Medical Examiner
✓Treatment episodes
✓Arrests
✓Literature
✓Misuse, abuse, addiction
✓Self medication
Diversion Schematic: Lawful distribution; primary diversion; layers of redistribution, non medical uses; measurement of impacts
PPSG, 2007
* = Amounts reported by law on DEA Form 106