EDITORIAL

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Considerations for the upcoming FDA REMS proposal

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The abuse of prescription medications, particularly opioids, has increased over the last decade to a level that some have described as "epidemic."[1] According to researchers at the Centers for Disease Control, prescription drugs have replaced heroin and cocaine as the leading drugs involved in fatal drug overdoses in all urban-rural categories.[2] As these deaths have increased, so too has public outcry. This, in turn, has led to congressional hearings, increased regulatory actions, and remedial legislation.[3] At the same time, chronic pain has remained a serious public health concern whose treatment may be hampered by prescribers' fear of diversion and abuse of scheduled medications and the regulatory scrutiny that may follow.[4]

After more than a year of planning that included input from the public, expert panels and a special Industry Working Group (IWG), the Food and Drug Administration (FDA) in July 2010 proposed a Risk Evaluation and Mitigation Strategy (REMS) for long-acting and extended-release opioid drug products. The proposal was presented to a joint meeting of the FDA's Drug Safety and Risk Management Advisory Committee and the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC & DSRMAC).[5] At the conclusion of the meeting, 35 members of the joint advisory committees were asked to vote on the FDA's proposal. The vote was 25 to 10 against approval. When polled, those who voted against the plan and most who voted for the plan expressed doubt that the FDA's proposal would be sufficient to achieve the goal of reducing the nonmedical use of opioid medications.[5]

The concept of a "class-wide" REMS, specifically for long-acting and extended-release opioids, has generated significant debate and angst in the medical community.[6] There is concern that because the proposed opioid REMS was rejected as insufficient to achieve its purpose, the FDA may consider alternatives, including patient and prescriber registries, restricted distribution schemes, and other "elements to assure safe use," as the enabling legislation permits.[7]

The authors of this article represent several fields, including pain medicine, hospice and palliative medicine, behavioral medicine, and law enforcement. They have published, spoken and researched extensively on the issues of abuse and diversion of opioids, opioid pharmacology, tamper resistant opioid formulations, pain medicine and treatment, and other topics related to this paper's focus. In addition, all have been involved in community and professional efforts to reduce the abuse of opioid medications. Two of the authors have been very involved in the treatment of patients with chronic pain, and have prescribed or supported the prescribing of opioids for properly selected patients. It is from this platform that we make the following recommendations relative to the subject matter of this paper. This paper provides background on the REMS process and makes recommendations for achieving the goals of the REMS program as stated by the FDA: "Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of long-acting and extended-release opioids while maintaining patient access to these medications. Adverse outcomes of concern include addiction, unintentional overdose, and death."[8]

The FDA's opioid REMS proposal that was rejected in July 2010 focused on two main themes: prescriber training and patient education. In an earlier iteration, the FDA had considered registries for certified prescribers and patients, restricted distribution schemes, and communications plans to disseminate risk-related information to health care providers. Several of the 170 already approved REMS (mostly non-opioid medications) contain these and other requirements. Although the 2007 amendment to the Food, Drug, and Cosmetic Act provided the FDA

with broad authority to require, as a condition of NDA approval or continuation, these and other elements to insure that the benefits of a drug outweigh its risks, the statute does not require doing so on a class-wide basis.[9]

In its unsuccessful bid to create a class-wide opioid REMS, the FDA attempted to meet the statutory goals of the 2007 Amendment by making sure that the benefits of any new or existing drug outweigh its risks, including, in the case of opioids, the risk of accidental or intentional overdose and/or abuse.[9] It is important to bear in mind that the rejection of the FDA's opioid REMS proposal by two separate advisory committees was not because of differences over stated goals but, instead, because a majority (71 percent) of the FDA's consultants believed that the proposed plan was insufficient for achieving those goals.

RECOMMENDATIONS

1. Definition of terms: Guidance materials pertaining to the FDA's opioid REMS use various terms to describe drug abuse, drug misuse, drug addiction, intentional and accidental overdose, withdrawal, etc. Although clinical definitions for each of these terms exist in other contexts, to avoid misinterpretation and uncertainty they need to be specifically defined within a regulatory context when used in the REMS program.

2. Metrics: Current government-managed systems that measure drug abuse signals are ineffective and unreliable. Most in use were developed in the 1970s when the problem of prescription drug abuse was inconsequential by today's measure. Although data management has been enhanced by computer-assisted technology, basic data collection criteria and methodology have remained largely unchanged. For example, the most recent report of the National Survey on Drug Use and Health, described as the nation's premiere data source for tracking substance abuse, uses pill cards that depict photographs of various drugs that respondents can view as they identify drugs that they have used for nonmedical purposes. Of approximately 16 branded prescription stimulants mentioned or displayed on Pill Card C used in the last several surveys, 12 no longer are marketed in the US. Some, including Eskatrol, have been off the market for decades.[10,11] Paradoxically, some respondents report recent use of drugs removed from the market before they were born.[12] At the same time, newly approved and popular drugs of abuse are either not included in the surveys or relegated to non-core follow up questions. Contrary to how they are presented, none of these drug abuse data collection programs is actually conducted by federal employees but contracted to private organizations. New systems, capable of measuring current trends in prescription drug abuse and utilizing the latest in information technology to make these data publicly available online in a timely fashion are needed.

3. Education: We enthusiastically support prescriber, dispenser and patient education and training about the risks associated with the use of opioids and other prescription drugs. However, we believe that there needs to be a rational basis for such training. Too often training is used as a bureaucratic response to a problem for which no empirical evidence exists to indicate that a lack of training caused or contributed to the problem.

4. Needs assessment: Thus, an initial step before designing any REMS should be an assessment of the actual needs intended to be met by such a plan. The class wide opioid REMS does not appear to do this, according to the FDA's own panel of expert consultants.

5. Patient responsibility: In line with the above, it would appear that more emphasis should be placed on the responsibility of the patient who is prescribed controlled substances to safeguard the drug and to ensure that it is taken as directed. Federal survey data mentioned elsewhere in this paper show that friends and family members of respondents who used pain relievers for nonmedical purposes constitute an important source of diversion.[14] Unique, creative and multifaceted educational programs for prescribers and physicians should be

designed. They should be focused on specific needs that are identified and updated frequently to reflect changes in regional and national drug abuse patterns.

6. Complete REMS: All opioids should require some form of a REMS, including Schedule III combination products and Schedule V elixirs. One of the most frequently prescribed, abused and diverted opioid in the United States is hydrocodone (currently always in combination with acetaminophen and/or other non-narcotic analgesics). There are over 100 such products and none would have been covered by the recently proposed (and rejected) class wide opioid REMS. In addition there needs to be a separate REMS program for methadone. Methadone is a drug with a unique pharmacology and potential for harm. Included in the REMS requirements should be a special certification for practitioners who prescribe methadone for pain.

7. Expert opinion: The government's REMS program cannot succeed without the expertise and cooperation of the private sector. This should include professional pain organizations (as well as individual pain specialists), other federal and state agencies (eg, DEA), and other stakeholders, as needed. The FDA was shortsighted in not actively soliciting recommendations from these sources and asking, instead, only for the industry's perspective.

8. Governmental agency cooperation: Administrative rulemaking authority in executive branch agencies is narrowly confined to carrying out statutory responsibilities assigned to such agencies. Some of the recommendations offered by the members of the FDA advisory committees in July 2010, as well as some offered here, may exceed administrative law or rulemaking authority. Agencies such as FDA and DEA have channels for recommending legislative amendments, when needed, for achieving agency goals. As the advisory panels noted in July 2010, "voluntary requirements," besides being an oxymoron, do not work and must be enforceable by law. State medical boards, although they may provide important contributions to protect the nation's public health, do not have the necessary and consistent authority, nor the expertise to implement an effective and uniform drug risk management program.[13]

9. Prescription pads: We recommend continued development of tamper-resistant prescription pads and education efforts to improve security of prescription pads in prescriber's offices. Similarly, we recommend and support electronic prescribing and dispensing for all schedules of drugs, as authorized and described in DEA's Interim Final Rule, dated March 22, 2010.[14]

CONCLUSION

The continued fate of the FDA's class wide opioid REMS remains uncertain as a result of the above-described actions of its joint advisory committees. While the FDA is not required to accept the recommendations of its advisory committees, in this instance it would be most unusual if it did not respect the overwhelming vote of two expert committees. As of April 19, 2011 strategy was announced by Office of National Drug Control Policy (ONDPC) and the FDA concerning a class wide REMS program for long acting opioids.[15] This proposal is similar in some ways to the rejected proposal of July 2010. However, education is strongly endorsed as is the support of PMPs. Although funding of this proposal is not clear, ie, whether this comes from private or public funding. Further, there is still much work to clearly flush out what this proposal will look like in actuality. However, we feel our criticisms are applicable to this recent ONDPC/FDA proposal as well.

A REMS program for opioids, or for any controlled substance, must satisfy the needs of pain patients, as well as reduce the diversion abuse, misuse, overdose and deaths from pain medications. This, we understand, is easier said than done. We have offered some recommendations for how the REMS program might be improved to reduce or mitigate the risks of abuse, addiction, and overdose associated with opioid medications. We believe, however, that these risks are unique enough to warrant their own specialized risk management

program. Moreover, any such program must be individually tailored to address the individual abuse characteristics of each drug deemed to require a REMS program. The REMS legislation passed in 2007 may need to be changed or revised in order to carry out the recommended actions and this should be part of the deliberation. The FDA will be presenting a new REMS proposal later this year. It is unclear how a new REMS will be designed by the FDA in light of the rejection the previous proposal received, however we hope our recommendations will be taken seriously by the FDA.

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