



A Review of the FDA's Approach to Implementing a Class-Wide REMS for Long-Acting and Extended-Release Opioids

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I. Background

In 2007, Congress passed The Food and Drug Administration Amendments Act (FDAAA). This legislation authorized the Food and Drug Administration (FDA) to impose new requirements to mitigate the risks of certain prescription medications.¹ These measures, termed Risk Evaluation and Mitigation Strategies (REMS), require the makers of certain prescription drugs to develop comprehensive plans to strengthen patient and prescriber knowledge and ensure the benefits of a drug outweigh its associated risks.² In exercising this new authority to require REMS, the FDA has ordered 16 producers of different long-acting and extended-release opioids to propose a class-wide, one-size-fits-all REMS.³

By law, REMS must address the risks of each individual drug and its generic equivalents. Although FDA efforts to curtail adverse events stemming from the use of prescription medications are commendable, the FDA lacks the authority to mandate a single REMS to cover all long-acting and extended-release opioids. A single, class-wide REMS threatens to limit patient access to the drugs that are vital to the health and well-being of so many Americans, and contravenes the FDAAA's express provisions.

II. The FDA has not met its scientific burden to impose REMS

Some of the long-acting and extended-release opioids included under the FDA's class-wide REMS may not be statutorily subject to REMS at all. Section 505-1(a)(2)(A) of the FDAAA allows the Secretary of the Department of Health and Human Services (HHS) to require that a drug that was approved before 2007 implement a REMS only if the Secretary "becomes aware of new safety information"⁴ for that drug. The statute goes on to define "new safety information" as information gained from clinical trials, peer-reviewed biomedical literature, or "other scientific data deemed appropriate by the Secretary."⁵ In its Federal Register notice requiring a class-wide set of REMS for all long-acting and extended-release opioids, the FDA failed to cite any empirical data, and instead attempted to satisfy this statutory requirement regarding new safety information by highlighting the growing abuse of these opioids as reported in the 2008 National Survey on Drug Use and Health (NSDUH).⁶ Although the NSDUH provides a valuable glimpse at drug use patterns in the United States,⁷ this type of survey does not yield "scientific data" within the context of the statute. Rather than deriving the required "scientific data" about specific medications and risks from a controlled study capable of repetition, the FDA has relied on an unspecific, interview-based survey to impose a burdensome, and possibly unnecessary, set of restrictions on patients, providers, and drug manufacturers.

Even if the evidence cited by the FDA to justify the imposition of REMS on already-approved medications satisfied the statutory requirements of the FDAAA, it is not at all clear that the FDA's data justify a REMS for all of the long-acting and extended-release products that the FDA has targeted. The worrying trend of long-acting and extended-release opioid abuse has not affected all products equally. For example, a 2006 study of opioid abusers found that 79% of participants had abused oxycodone in the previous thirty days, while 9% had abused fentanyl, another opioid subject to the FDA's class-wide

¹ Public Law 110-85.

² 21 USC 355-1(a)(1).

³ 74 FR 17967.

⁴ 21 USC 355-1 (a)(2)(A).

⁵ 21 USC 355-1 (b)(3).

⁶ 74 FR 17967.

⁷ See National Survey on Drug Use and Health. Available at <http://www.oas.samhsa.gov/NSDUH.HTM>.

REMS.⁸ As evidenced in this example, the FDA's blanket, class-wide REMS order does not take relative risks into account, and nevertheless places identical burdens on some long-acting and extended-release products that have not contributed equally to opioid abuse in the United States.⁹ From an even broader perspective, it is useful to recall that despite the undoubted need to address opioid abuse, the number of fatalities associated with common, over-the-counter drugs like non-steroidal anti-inflammatory (NSAID) analgesics such as aspirin and ibuprofen far outstrips deaths associated with all opioids. Experts conservatively estimate that complications stemming from relatively less-regulated NSAIDs take the lives of approximately 20,000 Americans every year,¹⁰ compared with deaths from opioid poisoning which numbered fewer than 14,000 in 2006.¹¹

III. The FDA's reading of the FDAAA conflates the distinct processes Congress has established for initially proposing and developing REMS and for modifying those REMS after their implementation

A. Initial REMS proposal

Congress has created a detailed roadmap that the FDA must follow for the initial proposal and development of REMS. According to Congress's statutory instructions, the Secretary of HHS, in consultation with the FDA's Center for Drug Research and Evaluation (CDER), may impose certain well-defined restrictions on an individual drug that has met the FDAAA's requirements for REMS eligibility discussed above.¹² These elements include a medication guide, a patient package insert, and a communication plan to health providers.¹³ Although the FDAAA does contemplate limited coordination of REMS elements between different drugs,¹⁴ the statute does not allow for such coordination at this first stage in developing a REMS. The statute sensibly requires the FDA at this preliminary phase to analyze each medication independently, taking into account the special makeup and unique effects of each.

If the Secretary of HHS, in consultation with the CDER, determines that a medication "would be withdrawn"¹⁵ from the market unless additional REMS elements are imposed to "assure safe use of the drug because of its inherent toxicity or potential harmfulness," the FDAAA authorizes the Secretary to develop a second tier of REMS elements.¹⁶ In developing this second, more stringent set of requirements, known as elements to assure safe use (ETASU), Congress requires the FDA to take care not to impose REMS elements that would "be unduly burdensome on patient access to the drug" and to "minimize the burden on the health care delivery system."¹⁷ Among the possible elements that may be included are additional training and special certifications for health care providers, restrictions on the settings in which the individual drug may be dispensed, special laboratory monitoring of patients taking the drug, or patient registries.¹⁸

⁸ A. Rosenblum and others, "Prescription Opioid Abuse Among Enrollees into Methadone Maintenance Treatment," *Drug and Alcohol Dependence* 90 (2007).

⁹ The high rate of oxycodone abuse may be attributable in large part to the intentional misbranding of the medication. In 2007, several executives of Purdue Pharma pled guilty to the federal criminal charge of misbranding and misrepresenting the risks of their name-brand version of oxycodone, Oxycontin.

¹⁰ M. Wolfe and others, "Gastrointestinal Toxicity of Nonsteroidal Anti-inflammatory Drugs," *New England Journal of Medicine*, no. 24 (1998). The FDA continues to cite this study when quantifying NSAID deaths. In light of the time that has passed since the study's release, the number of NSAID deaths in the United States likely exceeds 20,000.

¹¹ "Increase in Fatal Poisonings Involving Opioid Analgesics in the United States 1999-2006." *NHCS Data Brief* (2009). Available at <http://www.cdc.gov/nchs/data/databriefs/db22.pdf>.

¹² 21 USC 355-1(a).

¹³ *Id.* at (c)-(e).

¹⁴ *See id.* at (f)(2)(D)(i).

¹⁵ The FDA does not appear to be in compliance with this section of the statute with regard to long-acting and extended-release opioids. The FDA has not demonstrated that the medications under discussion should be withdrawn from the market unless elements to assure safe use are imposed.

¹⁶ 21 USC 355-1(f)(1).

¹⁷ *Id.* at (f)(2)(C).

¹⁸ *Id.* at (f)(3).

At this second stage in the REMS guidance, Congress does require that the FDA attempt to create ETASU that generally conform, “to the extent practicable,”¹⁹ with the ETASU for other drugs with similar, serious risks.²⁰ Nevertheless, the FDAAA mandates that ETASU for each medication be developed on the foundation of the preliminary REMS that the FDA must develop for each individual drug.²¹ Any attempt to mandate a one-size-fits-all, class-wide REMS for multiple drugs from the start of the REMS development process would require the FDA to ignore the initial steps that Congress has so clearly detailed: 1) Identify the need for REMS with new, scientific data²²; 2) Determine whether a medication guide, communications plan, or packaging insert, pursuant to section 355-1(e), is sufficient to fulfill the requirements of the FDAAA without further safety measures; and 3) Establish whether the medication would be otherwise withdrawn without the inclusion of additional ETASU.²³ If such control were ultimately found to be necessary, there is little doubt that patients, providers, and drug manufacturers would be well served by a degree of consistency among the burdensome ETASU for similar drugs. This coordination, however, should not come at the cost of eliminating the FDA evaluation of the unique features and risks of individual medications. Such an approach threatens to reduce the effectiveness of the REMS by ignoring the important characteristics of different drugs in favor of a catch-all REMS program developed for the sake of expediency.

A uniform, class-wide REMS would also eliminate any market-based benefits that might accrue to the pharmaceutical industry and the public as a result of increased competition between manufacturers. A number of studies have demonstrated the benefits of competition in the field of healthcare risk management.²⁴ The individual, market-based approach practiced in many spheres of the healthcare industry has resulted in greater innovation and cost savings.²⁵

B. REMS assessment and modification

The process that the FDA is now employing to develop a class-wide REMS for extended release and long-acting opioids mistakenly follows the procedures Congress has established for assessments and modifications of existing REMS for discrete medications. It is only at this assessment stage in the REMS process that the FDAAA permits the FDA to address the effects of an entire drug class. Section 555-1(h)(7) states that “[w]hen a concern about a serious risk of a drug may be related to the pharmacological class of the drug,” the Secretary, in consultation with the CDER, “may defer assessments of the *approved* risk evaluation and mitigation strategies for such drugs until the Secretary has convened 1 or more public meetings to consider possible responses to such concern (emphasis added).”

Even this section of the FDAAA that allows dealing with the challenges of an entire class of medications does not contemplate a total merging of the REMS for all medications in the class. According to the assessment language in the REMS statute, if the FDA determines that regulatory action is necessary in response to a class-wide REMS evaluation, the FDA must publish an announcement of the planned action in the Federal Register “including a modification to *each* risk evaluation and mitigation strategy for the drugs in the pharmacological class (emphasis added).”²⁶ The text of the FDAAA expresses Congress’s intent that providing for conformity within an entire class of drugs for REMS purposes is not meant to eliminate the need for all such medications to have individual, carefully calibrated REMS that responds to the unique needs and challenges of each medication.

In light of the FDA’s May 27, 2009 public meeting to consider a class-wide REMS strategy for an entire pharmacological class, in this case long-acting and extended release opioids, it appears that the

¹⁹ *Id.* at (f)(2)(C)(i). In light of the enormous difficulties in coordinating a class-wide REMS between 16 pharmaceutical manufacturers, it seems unlikely that the FDA’s current demand for a class-wide REMS is compatible with a plain-meaning understanding of the word “practicable.”

²⁰ *Id.*

²¹ *Id.* at (c).

²² *Id.* at (a)(2)(A).

²³ *Id.* at (f)(1)(A).

²⁴ See, e.g., Ahn, S. “Competition, Innovation and Productivity Growth: A Review of Theory and Evidence.” OECD Economics Working Paper No. 317, (2002). Available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=318059.

²⁵ *Id.*

²⁶ 21 USC 355-1(h)(7)(D)(i).

FDA has erroneously invoked the provisions Congress intended to guide assessments of individual drugs' existing REMS and applied them to the initial REMS implementation process. In doing so, the FDA ignored the extremely thorough process Congress set forth for REMS proposal and development.

IV. A textual analysis of the FDAAA reveals Congress's insistence on product-specific REMS

A. Plain language

The precise REMS language of the FDAAA is consistent and clear. Virtually every reference to a REMS refers to single drugs, not to an entire group of drugs. In mandating class-wide REMS, the FDA is stretching the FDAAA beyond the plain meaning of its text.

The FDAAA provides a clear process to drug manufacturers and the FDA for developing REMS after the Secretary has determined that a drug should be subject to REMS. In each step of the process, the FDAAA directs the FDA to work with a single drug manufacturer, not a group of manufacturers.²⁷ As explained above, after a drug manufacturer proposes a REMS to the FDA, the Secretary and the FDA offices involved in the approval process must review the application. The FDAAA directs the Secretary to review promptly "each proposed risk evaluation and mitigation strategy for a drug."²⁸ This language makes no reference to a class-wide application, or standard requirements across a particular class of medications, and strongly suggests that Congress intended each manufacturer to submit an individual application for a single drug, and for the Secretary to review these applications individually as well. The drafters of the FDAAA understood that such an approach is more thorough and effective than a one-size-fits-all solution.

In only one instance does the FDAAA contemplate an integrated REMS system. The legislation directs generic drug manufacturers to develop a single, integrated REMS system with the pioneer manufacturer of the same drug.²⁹ Given that Congress went out of its way to permit specifically this one narrow exception, it is apparent that Congress intended not to grant the FDA authority to require a single, class-wide REMS. FDA's mandate of a single, class-wide REMS greatly exceeds the scope of the generic-pioneer exception. Where the FDAAA does call for a limited, integrated REMS with regard to innovator drugs and their generic counterparts, Congress recognized that even this limited exception might result in an undue burden on the health care system, on patient access, and on drug manufacturers. As a result, Congress granted the Secretary the discretion to waive this requirement.³⁰ Congress's sensitivity to the burden of shared REMS in even relatively limited circumstances should caution the FDA against imposing such a burden on the much expanded scale it seeks to mandate.

B. Legislative history

Shortly before passage of the FDAAA, the House of Representatives released an explanatory report of the bill's provisions. In its discussion on REMS, the House drafters made no reference to class-wide REMS. The Report explains that a section of the FDAAA allows the Secretary to convene advisory committees to review REMS. In particular, the Report interprets the FDAAA as charging the advisory committees with reviewing the REM "strategy" of "a drug" or "strategies" for a "group of drugs." The language of this note, therefore, does not support the imposition of a *single* strategy for a *group* of drugs, as the FDA is attempting to accomplish with its class-wide REMS.³¹

V. Recommendations

Lawmakers, regulators, prescribers, patients, and pharmaceutical companies all agree on the necessity of providing a degree of coherence to the balanced and effective regulation of opioid medications. Nevertheless, the single, class-wide REMS that the FDA seeks to impose on long-acting and extended-release opioid manufacturers lacks the flexibility to effectively address issues unique to

²⁷ See, e.g., 21 USC 355-1(a)(2)(B).

²⁸ *Id.* at (h)(1).

²⁹ *Id.* at (i)(1)(B).

³⁰ *Id.*

³¹ House Report 110-225. Title IX, Section 901(p).

specific medications. A more effective and less cumbersome strategy should allow patients, providers, and pharmaceutical manufacturers to determine how best to provide conformity among certain REMS elements for their long-acting and extended-release opioids, while pragmatically leaving individual manufacturers to propose those elements which do not lend themselves to a one-size-fits-all strategy. Proposals for voluntary coordination in opioid risk management include the preparation and distribution of a common opioid medication guide, as well as support for grants to enable states to implement and optimize prescription monitoring programs. The Center for Lawful Access and Abuse Deterrence will more thoroughly set forth its recommendations for voluntary coordination on REMS in its *2010 National Prescription Drug Abuse Prevention Strategy*, to be released in May 2010.