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

**RE: Risk Assessment and Mitigation Strategies; Public Meeting  
[Docket No. FDA-2010-N-0284]**

The American Medical Association (AMA) is pleased to offer its comments on the development and implementation of risk evaluation and mitigation strategies (REMS) for drugs and biological products. The AMA's comments address our general concerns regarding REMS process and four specific topical areas: (1) design, implementation and assessment of REMS; (2) the requirements for REMS; (3) establishing the goals of a REMS; and (4) issues regarding elements to assure safe use (ETASU).

General Comments About Risk Evaluation and Mitigation Strategies

The AMA shares a common goal with the FDA to optimize the benefit/risk balance of drug therapy and to minimize the risks of drug and biological products. The AMA firmly believes that the FDA-approved professional labeling, or Package Insert, should be the routine risk mitigation plan for the vast majority of drug and biological products. Changes enacted by the FDA affecting the format and content of the Package Insert, particularly the addition of a "Highlights" section, have made this document more user-friendly to physicians.

Secondly, the AMA supports improved risk communication to physicians as the preferred risk mitigation plan for most drugs that require risk management beyond the Package Insert. However, a need clearly exists to identify and implement more effective strategies for the FDA and sponsors to communicate drug safety problems to physicians in a collaborative manner. The AMA continues to urge open communication and collaboration among the FDA, the pharmaceutical industry, and national physician organizations on the subject of risk management. Such communication and collaboration is needed at the macro level so that the FDA's overall risk management initiative achieves an appropriate balance between the need to protect patients from harm and the need to avoid unwarranted interference with medical practice.

Thirdly, reliance on Medication Guides is the most common REMS approach. A general consensus exists that Medication Guides as currently constructed are inadequate in conveying appropriate and useful written information on prescription drugs to patients. The AMA urges the

FDA to take the necessary steps to develop a single document solution for written patient information in a format, and with content, that balances benefit and risk information. Additionally, REMS-related documents intended for patients must be tested for comprehension and provided at the appropriate patient literacy level in a culturally competent manner.

Finally, the AMA remains concerned about the increased use of ETASU as part of REMS and the process used to develop, approve, and monitor such elements, especially the routine exclusion of practicing physicians from this process. When considering those products that have been deemed (in effect) to have REMS, the number of drugs with REMS that rely on ETASU has nearly doubled since the Food and Drug Administration Amendments Act (FDAAA) of 2007 was implemented. The AMA continues to recommend that higher level risk mitigation tools, including ETASU, be used only as a last resort to keep high-risk products with unique and important benefits on the market.

#### Design, Implementation and Assessment of REMS

Physicians are the most important managers of product risks once a drug is marketed. Yet, the FDA has not established a process for the agency to obtain feedback from physicians on planned REMS, despite the fact that in previous *Guidance (2005) for Industry on Risk Management of Prescription Drugs*, the agency advised that when selecting and developing the best tools to manage risks, industry should “identify and seek input from key stakeholders.”

Therefore, the FDA and sponsors should identify key stakeholders, including national medical specialty societies whose physician members have the capacity to minimize the product’s risks, and seek their input when planning REMS and selecting specific REMS tools. Sponsors should be required to conduct this consultation early in the process when developing REMS, especially those with ETASU, and should establish a transparent process to allow for physician feedback on emerging issues with REMS requirements. Advisory Committee review of any proposed REMS that rely on ETASU also should be required.

In particular, input should be sought from physicians on the feasibility of implementing and accepting a particular element in usual health care practices. This may require pilot testing to assess comprehension, acceptance, feasibility, and other factors to determine how readily elements will fit into everyday physician practices. When additional training or certification of prescribers is contemplated, the REMS educational component should be developed with the assistance of appropriate physician organizations and the program should be offered in multiple formats.

Ultimately, elements or tools with the least burdensome effect on the patient-physician relationship should be selected and these tools should facilitate the central role of physicians in controlling the risks of medical product use. To the extent possible, such tools should be based on available evidence of effectiveness in achieving the specified objective. A process whereby the FDA and sponsors work toward standardized procedures and elements for REMS programs would assist in achieving these goals.

Additionally, because REMS assessments are required, relevant baseline measures on prescribing patterns and behaviors must be available in order to adequately assess their effectiveness. This is especially important for REMS that are being implemented, based on new safety information, for drugs that are already marketed. For new chemical entities or biologics, baseline information should be derived from comparable products if available. The AMA also recommends that long-term assessments of the prescribing patterns of drugs with REMS requirements should be conducted.

Finally, the importance of assessing the impact of ETASU on clinical practice and patient access cannot be overstated. To address potential adverse impacts from ETASU, statutory language was included in FDAAA that explicitly requires that the ETASU must be commensurate with the specific serious risks listed in the labeling and cannot be “unduly burdensome on patient access to the drug, patients with serious or life-threatening diseases, or patients who have difficulty accessing healthcare.” The *2009 Draft Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* does not contain any language that specifies how manufacturers are to comply with these FDAAA provisions relating to ETASU. In issuing the final guidance, the FDA should clearly specify that sponsors must produce an assessment of the impact of ETASU on patient access, particularly in underserved areas or for patients with particular conditions.

#### Requirement for a REMS

The statutorily enumerated factors that the FDA must consider in determining whether to require REMS are reasonable. Furthermore, for REMS with ETASU, the AMA strongly supports the statutory requirement that such elements: (1) be commensurate with the specific serious risks listed in the labeling of the drug; (2) not be unduly burdensome on patient access to the drug; (3) conform with ETASU for other drugs with similar serious risks; and (4) be compatible with established drug distribution, procurement, and dispensing systems. However, the AMA believes that the threshold for requiring REMS with ETASU has been too low. REMS should comprise a strategic safety program designed to meet specific goals and objectives in mitigating known risks of a product while preserving its benefits. REMS with ETASU should be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients.

Additional criteria that might be worth considering include the availability (or lack of) alternative treatments with similar efficacy, and the reversibility and preventability of the adverse events in question. Additionally, the question of whether populations at greatest risk and/or those likely to derive benefit could be stratified using pharmacogenomic information should be considered. This approach would assist in selecting appropriate patients for therapy and lessen the need for REMS.

### Establishing the Goals of REMS

With respect to factors that should be considered in establishing the goals of REMS, the AMA urges the agency and sponsors to seek to maintain the widest possible access to products with the least burden to the health care system that is compatible with adequate risk mitigation. Furthermore, the FDA should ensure that benefit considerations remain an integral part of the decision-making process.

A primary factor in considering whether to modify existing REMS should be the FDA's statutory obligation to ensure that REMS are commensurate with the specific serious risks listed in the labeling of the drug, and are not unduly burdensome on patient access to the drug. This obligation extends in particular to patients with serious or life-threatening diseases or conditions, and those who have difficulty accessing health care, such as patients in rural or medically underserved areas.

### Issues Regarding Elements to Assure Safe Use

As previously noted, the AMA remains concerned about the number of REMS with restricted distribution features and their potential unintended consequences. Concerns include reduced patient access to necessary drugs, the prescribing of less effective therapeutic alternates, and reduced manufacturer investments in innovative therapies.

Stakeholders agree that ETASU impose significant burdens and high administrative costs, disrupt patient care, and contribute to physician opt out. Features that are most likely to adversely affect appropriate patient access to approved drugs include additional education or certification requirements for prescribers, the use of mandatory patient or physician registries, or any other features that are time-consuming and disrupt normal workflow.

Survey data from the National Comprehensive Cancer Network demonstrate the potential influences of such elements on physician's willingness to prescribe drugs with REMS. For example, approximately 50% of practitioners in their network believe that REMS interfere with the provision of patient care, will drive utilization towards drugs without REMS, and create or increase disparities in care. Of the six drugs with ETASU that commonly affect oncology practice, a significant minority of physicians had no plans to register because of perceived administrative burdens. Only 41% of physicians would prescribe a drug with REMS that required a combination of the following: (i) additional education/training; (ii) patient enrollment in a registry, and (iii) two to three additional data collection forms per patient.

The existence of complex REMS that are not standardized and are program-specific, as well as the lack of uniformity among ETASU create onerous administrative burdens for physicians. Physicians are already obligated to meet other administrative and clinical requirements of third party payers, such as prior authorization, step therapy, and obtaining off formulary drugs through an appeals process for their patients. In this environment, introducing new REMS that impose additional training or administrative requirements is likely to do more harm than good.

While the possibility of confusion and administrative burden may be minimal for some practices at this time, as the FDA increases the number of products subject to ETASU, this concern will grow. Therefore, the FDA and sponsors should identify strategies to reduce administrative burdens and compliance activities, particularly where medical specialties or certain physicians are impacted by multiple REMS with ETASU. Additionally, design features should be incorporated that reduce the negative impacts of ETASU on the health care delivery system. Required forms should be compatible with electronic systems and health records where possible. Generally, the FDA should ensure that features and requirements of REMS, including ETASU are “user friendly.”

The AMA appreciates the opportunity to comment on the FDA’s current approach to Risk Evaluation and Mitigation Strategies. We hope that our recommendations on this issue prove helpful for the FDA. We look forward to working with the agency as it continues its activities in this area.

Sincerely,

A handwritten signature in black ink, appearing to read "Mike Maves". The signature is written in a cursive, flowing style.

Michael D. Maves, MD, MBA