



Michael D. Maves, MD, MBA, Executive Vice President, CEO

May 17, 2010

Margaret A. Hamburg, MD  
Commissioner  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dear Commissioner Hamburg:

On behalf of the physician and medical student members of the American Medical Association (AMA), I am writing to provide recommendations related to the agency's implementation of the Risk Evaluation and Mitigation Strategies (REMS) provisions in the Food and Drug Administration Amendments Act of 2007 (FDAAA). We are concerned about the increased use of "elements to assure safe use" (EASUs) as part of REMS and the process used to develop, approve, and monitor such elements, especially the exclusion of practicing clinicians from that process. In addition, while required by FDAAA, it appears that methods and metrics to assess the impact of EASUs on clinical practice and on access, particularly to underserved communities, have not been required by FDA or developed by manufacturers. Below we have outlined recommendations that we believe will ensure that REMS support physician decision-making and help promote safe prescribing without erecting additional barriers that prevent the delivery of appropriate quality care.

The number of drugs covered by EASUs has expanded since the passage of FDAAA. It appears that the current process utilized to develop EASUs, as well as the actual implementation, may not be consistent with congressional intent nor the express statutory language. During the legislative process, the AMA had extensive discussions with congressional staff concerning the EASU provision. Throughout the process the AMA was repeatedly assured that the intent was simply to codify then existing FDA regulations concerning "restricted distribution" that had been promulgated from a general grant of authority. We were concerned then that a significant increase in reliance on EASUs as part of REMS could present problems for patient access to appropriate care. The FDA's actions since FDAAA was enacted suggest these concerns were not unfounded.

To address potential adverse impacts from EASUs, statutory language was included that explicitly requires that the EASUs 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. Also, the statute provides that to “the extent practicable, [the element(s)] must conform with other elements for other drugs with similar serious risks and be designed to be compatible with established distribution procurement and dispensing systems for drugs.”

**To date, the FDA has not required manufacturers to engage practicing physicians to obtain input concerning proposed EASUs in order to assess the likely efficacy of the proposed elements or the impact of implementation on the statutorily identified categories of patients that could be adversely impacted by EASUs.** The FDA has not established a process for the agency to obtain such feedback from physicians who are indispensable stakeholders, 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 “maintain the widest access while minimizing burden,” and “identify and seek input from key stakeholders.” After all, physicians prescribe the medication and would be required to implement or comply with the EASUs. In addition, there does not appear to be any guidance or draft guidance that requires manufacturers to specify the metrics to assess the ongoing impact on access and clinical practice. Most recently, 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 the FDAAA provision that EASUs cannot be unduly burdensome on patient access to the drug, patients with serious or life-threatening diseases, or patients who have difficulty accessing health care.

In light of the foregoing, we are concerned that EASUs will be adopted that will have unintended consequences such as: discouraging prescriptions for the optimal drug to treat the patient’s condition; encouraging the prescribing of alternatives that may be less effective (but are not subject to EASUs); reducing access for some patients to medically necessary drugs; and creating confusion and possible errors by physicians for whom a new EASU is one new regulatory burden too many. 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 EASUs, this concern will grow. For example, the number of drugs subject to an EASU that primary care physicians might prescribe is currently limited. Nonetheless, the impact of poorly chosen EASU on primary care physicians in underserved areas could have unintended consequences where such physicians, already confronting shrinking resources, could be less likely to prescribe the drug. This changes clinical practice and limits access to patients in underserved areas. Another example on the other end of the continuum would be oncologists who may have more resources, but who must implement a growing number of EASUs. Keeping abreast and complying with varied EASU requirements that lack uniformity creates confusion and can lead to suboptimal prescribing. EASUs also consume time to implement because these are paper driven tasks and divert valuable time and attention away from discussions with patients.

**All of these potential unintended consequences could be significantly mitigated by an FDA requirement that the process for developing REMS include consultation with specialties and/or practicing physicians who prescribe the drugs subject to EASUs.**

Currently, the FDA consults with manufacturers (but not physicians). Manufacturers develop proposed REMS, but are not required to consult with physicians. The foregoing is deeply perplexing. Although EASUs impact how physicians practice medicine, the available prescribing options, how medications are provided and how physicians are required to interact with patients, at no point during the REMS process is physician input required or sought out with the exception of the still developing REMS for certain Schedule II opioid medications—which involved a wide number of manufacturers. Even more vexing: at no point in the process are the FDA, manufacturer(s), and physicians in the same room to discuss the proposed EASUs.

All of the foregoing may, in part, have contributed to a growing tendency of REMS skewing heavily toward identification and communication of 'risk' without balanced communication of benefits. Currently, the materials concerning benefits are delivered by pharmaceutical detailers (who physicians may heavily discount) or physicians receive no corresponding information on the benefits when they receive the REMS. This does not provide a proper clinical perspective.

It is not evident that the FDA has required that manufacturer(s) undertake an ongoing assessment—as well as an initial one—of the impact on access to care and performance of the EASUs as specified by FDAAA. Finally, the lack of uniformity among EASUs, the possible competing or conflicting nature of EASUs, are onerous administrative burdens physicians face when they must meet the requirements at the same time that they are obligated to meet other administrative and clinical requirements of private and public insurance companies such as prior authorization, step therapy, and obtaining off formulary drugs through an appeals process for their patients.

**In light of the array of issues that we have raised above, we recommend that the FDA:**

- **Issue final industry guidance with provisions that:**
  - **Require all manufacturers to consult with and incorporate recommendations of impacted physician groups when developing EASUs.**
  - **Provide that FDA will convene a meeting with impacted physicians and manufacturers prior to finalizing REMS.**
  - **Clearly specify that manufacturers must produce an assessment of the impact of EASUs on patient access, particularly in underserved areas or for patients with particular conditions.**
- **Where specialties or certain physicians are impacted by multiple REMS, identify strategies to reduce administrative burdens and compliance activities to standardize the process.**
- **Ensure manufacturers undertake an ongoing assessment of the impact of EASUs on access and clinical practice and publicly disclose the information when it is evident that the EASUs are hampering access to appropriate medical care.**

Margaret A. Hamburg, MD

May 17, 2010

Page 4

- **Ensure that FDA Advisory Committees review proposed REMS/EASUs before they are finalized in addition to reviewing the drugs prior to marketing.**

Recent outreach to the national medical specialty societies as part of the new Safe Use Initiative is certainly a step in the right direction to improve communications. We look forward to working with you on this matter. Please contact Sandy Marks in our Washington office at 202-789-4585 or [sandy.marks@ama-assn.org](mailto:sandy.marks@ama-assn.org) with any questions or if you wish to arrange a meeting to discuss this issue.

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