

American Medical Association

Physicians dedicated to the health of America



Michael D. Maves, MD, MBA 515 North State Street 312 464-5000
Executive Vice President, CEO Chicago, Illinois 60610 312 464-4184 Fax

July 6, 2004

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

RE: Draft Guidance for Industry on “Development and Use of Risk Minimization Action Plans” [Docket No. 2004D-0188]

The American Medical Association (AMA) is pleased to offer its comments on the Food and Drug Administration’s (FDA) May 2004 Draft Guidance for Industry on “Development and Use of Risk Minimization Action Plans” [*Fed Reg.* 2004;69:25130-25132]. The AMA’s comments focus principally on Sections II-V of the Draft Guidance, and generally are consistent with AMA’s previous comments of April 29, 2003 on the FDA’s Concept Paper, “Risk Management Programs” [Docket No. 02N-0528], and of May 22, 2002 in testimony at FDA’s Public Meeting on the Risk Management of Prescription Drugs.

General Comments about the Draft Guidance, “Development and Use of Risk Minimization Action Plans”

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. However, the AMA remains concerned about the number of Risk Minimization Action Plan (RiskMAP) *tools* described in the Draft Guidance that would directly manage or restrict physician prescribing. If these tools are expanded to more pharmaceutical products, the potential for unintended consequences such as reduced patient access to necessary drugs or reduced manufacturer investments in innovative therapies is significant. Thus, the AMA continues to recommend that higher level risk minimization tools, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

On the other hand, the AMA commends the FDA for incorporating changes into the Draft Guidance that respond to some of our criticisms of the Agency’s 2003 Concept Paper on

this subject. In particular, the AMA is pleased that the FDA is encouraging drug sponsors to:

- Develop RiskMAPs only for products that pose an unusual type or level of risk;
- Use RiskMAPs judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients;
- Seek the input of other stakeholders, including physicians, when planning risk minimization activities and when selecting specific RiskMAP tools;
- Apply objective criteria when determining whether a RiskMAP is necessary for a particular product;
- Select the minimum number of RiskMAP tools necessary to minimize the risk, select tools based on available evidence of effectiveness, and objectively evaluate the effectiveness of RiskMAPs and their tools using evidence-based performance measures;
- Adopt tools that facilitate the central role of the health care practitioner in controlling the risks of medical product use; and
- Consider unintended consequences of a RiskMAP, such as reduced access, as part of the sponsor's Evaluation Plan.

The AMA offers the following comments on individual Sections II-V of the Draft Guidance.

Section II: Background

The AMA agrees with the FDA that “when planning risk assessment and risk minimization activities, sponsors should consider stakeholder input (e.g., from consumers, pharmacists, physicians, third-party payers).” However, the AMA believes the FDA needs to put greater emphasis on this important point in a Final Guidance.

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 heavy-handed regulations that interfere with medical practice. Furthermore, collaboration among the FDA, a product sponsor, and relevant physician organizations also is recommended for individual product RiskMAPs, as described in the Draft Guidance, to ensure that the RiskMAP is effective, feasible and acceptable in usual health care practices.

Furthermore, the FDA also may wish to consider establishing a permanent advisory council of practicing physicians, representing a large number of national medical specialty societies, that could advise the Agency on issues like RiskMAPs on an ongoing basis.

Section III: The Role of Risk Minimization and RiskMAPs in Risk Management

Determining an Appropriate Risk Minimization Approach. The AMA strongly agrees with the FDA that the FDA-approved professional labeling (Package Insert [PI]), updated

from time-to-time to incorporate information from routine postmarketing surveillance, is sufficient to be the routine risk minimization plan for the vast majority of drug and biological products. The information provided in the PI, along with other information about a product (e.g., published clinical trials), should remain the standard method of providing benefit and risk information to physicians about the use of a drug or biological product.

However, as previously communicated to FDA, the AMA believes that the current PI for prescription drugs is a barrier to effective risk communication because it has become a legal document rather than a resource of useful information for busy practicing physicians. In December 2000, the FDA issued a Proposed Rule to modify the format and content of the PI with the goal of making the information more useful and user-friendly to physicians. The AMA has supported this effort, especially the proposed “Highlights of Prescribing Information.” The AMA urges the FDA to issue a Final Rule implementing these changes to the PI as soon as possible.

Furthermore, the FDA should promptly develop and make readily available (e.g., via the Internet) a computerized database of the most up-to-date prescription drug labeling for all products. Such a database could have prominently placed safety alerts for new risk information on selected drugs. Physicians need to be trained to use this database for their professional labeling needs in lieu of the hard-copy *Physicians Desk Reference (PDR)* that is both cumbersome and dated for certain products.

Definition of Risk Minimization Action Plan (RiskMAP). The AMA accepts the FDA’s definition of a RiskMAP as “a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits.” Moreover, the AMA agrees with the FDA that *tools* used to meet RiskMAP goals and objectives do not apply to routine risk minimization plans, i.e., FDA-approved professional labeling.

Determining When a RiskMAP Should be Considered. The AMA agrees with the FDA that the decision to develop a RiskMAP needs to be determined on a case-by-case basis. Moreover, the AMA supports the FDA’s recommendation to use objective criteria, such as type of risk, magnitude of risk, frequency of risk, populations at greatest risk and/or those likely to derive the most benefit, existence of alternative treatments, reversibility of adverse events observed, preventability of the adverse event, and probability of benefit, when considering whether a RiskMAP is necessary. As previously discussed, the AMA encourages the FDA and the product sponsor to seek the input of relevant physician organizations in determining whether a RiskMAP is needed. This will give further assurance to physicians that the process is equitable and driven by good science.

Section IV: Tools for Achieving RiskMAP Goals and Objectives

Relationship of RiskMAP Tools to Objectives and Goals. The AMA has no specific comments on this section.

Categories of RiskMAP Tools. The AMA accepts the FDA's three categories of RiskMAP tools, i.e., targeted education and outreach, reminder systems, and performance-linked access systems.

Description of RiskMAP Tools. The AMA supports the establishment of a RiskMAP Web site by FDA. At a minimum, this Web site should contain a description of RiskMAP tools that have been used and all available evidence on the effectiveness of each tool in achieving a risk minimization objective and/or goal. The AMA believes this is necessary to convince health care practitioners that a potentially burdensome RiskMAP tool can effectively improve the benefit/risk balance for a drug product.

Selecting and Developing the Best Tools. This is an especially important section of the Draft Guidance, and the AMA commends the FDA for its recommendations to product sponsors, that when selecting RiskMAP tools, to:

- Maintain the widest possible access to the product with the least burden to the health care system that is compatible with adequate risk minimization;
- Identify the key stakeholders (e.g., physicians) who have the capacity to minimize the product's risks and to define their roles;
- Seek input from these stakeholders, including physicians, on the feasibility of implementing and accepting a particular RiskMAP tool in usual health care practices;
- Use RiskMAP tools with the least burdensome effect on physician-patient relationships;
- Select tools based on available evidence of effectiveness in achieving the specified objective; and
- Consider, and seek to avoid, unintended consequences of tool implementation that obstruct risk minimization and product benefit.

The AMA also appreciates the FDA's recognition that physicians are the most important managers of product risks once a drug is marketed and, furthermore, that the FDA does not have the authority to control prescribing decisions made by physicians for their patients. The AMA strongly agrees with the FDA's view that product sponsors should recognize this central role played by physicians in controlling the risks of medical product use and should adopt tools that facilitate this role.

Only time and experience will answer the question as to whether drug product sponsors are implementing RiskMAPs that are consistent with the recommendations put forth by the FDA in this section of the Draft Guidance. The AMA is hopeful that this will be the case. When RiskMAPs are considered necessary, the AMA encourages the FDA and the product sponsor to work with relevant physician organizations to assure that the minimum number and least intrusive RiskMAP tools are selected to achieve the risk minimization objective. Whenever possible, targeted education and outreach should be the RiskMAP tools selected, and the AMA refers the FDA to our letter of April 29, 2003 to Docket No. 02N-0528 for detailed comments on how risk communication to physicians can be improved.

As stated earlier in this letter, the AMA continues to believe that higher level risk minimization tools, such as performance-linked access systems and some reminder systems, should be used only as a last resort to keep high-risk products with unique and important benefits on the market. As discussed in detail in our earlier letter of April 29, 2003, a number of potential unintended consequences, including reduced access to necessary therapies, substitution of less effective therapies that are not subject to RiskMAPs, multiple burdensome and confusing RiskMAPs that can lead to errors, and adverse effects on pharmaceutical innovation, may result if RiskMAPs with high level risk minimization tools are more commonly employed.

Mechanisms Available to the FDA to Minimize Risks. The AMA has no specific comments on this section.

Section V: RiskMAP Evaluation: Assessing the Effectiveness of Tools and the Plan

Rationale for RiskMAP Evaluation. The AMA is in strong agreement with the FDA regarding the need for well-designed studies to periodically evaluate the effectiveness of a RiskMAP. The AMA concurs that the most important evaluation is of the overall performance of a RiskMAP in achieving its targeted health outcomes and goals. However, the AMA also agrees that separate assessments should be done for individual tool performance and for acceptability of RiskMAP tools by physicians.

Considerations in Designing a RiskMAP Evaluation Plan. The AMA is in general agreement with the FDA on the details of this section. In particular, the AMA supports the following FDA recommendations:

- When possible, drug product sponsors should select well-defined, evidence-based, and objective performance measures tailored to the particular RiskMAP to determine whether the RiskMAP's goals or objectives are being achieved.
- Whenever feasible, drug product sponsors should design evaluation plans to include at least two different, quantitative, representative, and minimally biased evaluation methods for each critical RiskMAP goal to compensate for the limitations of the other.
- Drug product sponsors should periodically evaluate each RiskMAP tool to ensure it is materially contributing to the achievement of RiskMAP objectives and goals to eliminate ineffective tools and concentrate resources on useful tools.
- Drug product sponsors should evaluate RiskMAP tools prior to implementation; this should include pilot testing to assess comprehension, acceptance, feasibility, and other factors to determine how readily RiskMAP tools will fit into everyday physician practices.
- Formal evaluation plans are unnecessary for routine risk minimization plans, i.e., FDA-approved professional labeling.

FDA Assessment of RiskMAP Evaluation Results. The AMA generally supports this section on how the product sponsor reports a RiskMAP evaluation to the FDA, and that FDA will perform its own assessment of RiskMAP effectiveness.

Making Information from RiskMAP Evaluation Available to the Public. As stated earlier in this letter, the AMA supports the establishment of a RiskMAP Web site by FDA that would include descriptions of RiskMAP tools and all available evidence on the effectiveness of these tools. The AMA also believes that this Web site should contain results of evaluations of RiskMAPs that have been previously implemented to inform physicians and the public about the effectiveness of the program in meeting its risk minimization objectives and goals. While the AMA understands that some product sponsor information will remain proprietary, we believe it is in the sponsor's and FDA's best interests to be as transparent as possible about the effectiveness of a RiskMAP. Such transparency will provide credible evidence to physicians and the public that a particular RiskMAP either did or did not effectively improve the benefit/risk balance for a drug product.

Additional Comments

In our letter of April 29, 2003, the AMA offered two additional comments that have not been adequately addressed by the FDA in the Draft Guidance. First, concern has been expressed by physicians and pharmacists that it is difficult to remember the various risk management programs (now called RiskMAPs), and especially the multiple risk management (RiskMAP) tools, currently employed for various drug products. This is because each risk management program has been uniquely developed for a specific drug product and, therefore, all of the current programs are different in their requirements. However, in Section IV(D) of the Draft Guidance, FDA continues to suggest that the best RiskMAP tool or tools be selected on a *case-by-case* basis.

To address this concern, the AMA encourages the FDA, in collaboration with the pharmaceutical industry and other stakeholders (e.g., physician organizations), to take a more systems-based approach to RiskMAPs. Appropriate tools should be prospectively developed based on evidence of effectiveness, and a standard set of tools for each level of risk should be part of a standard "toolbox" of RiskMAP tools. When a product meets the criteria for a RiskMAP at a certain level, to the extent possible, a standard set of tools should be employed in that product's RiskMAP. At a minimum, any given tool should be consistent across products.

The AMA's other comment that was not addressed in the FDA's Draft Guidance regards the incorporation of RiskMAPs for drug products into more global quality assurance programs. The AMA believes that the FDA, the pharmaceutical industry, physician organizations, and other stakeholders need to consider the incorporation of risk management (RiskMAPs) for drug and biological products into more global quality assurance programs. As electronic health records (EHRs) and E-prescribing become more common and they are electronically linked to other aspects of care (e.g. lab test results), it should be possible to effectively incorporate RiskMAPs, as part of overall quality assurance, into the normal routine of physician practice. As an analogy, the Physician Consortium for Performance Measurement, convened by the AMA, is currently developing physician performance measures derived from evidence-based practice guidelines. The AMA is working with physician group practices that have EHRs to

incorporate the performance measures into their systems so that satisfying the performance criteria becomes a routine part of medical practice.

Conclusion

In conclusion, the AMA appreciates the opportunity to comment on the FDA's Draft Guidance for Industry on "Development and Use of Risk Minimization Action Plans." We hope that our insight into the issues discussed in the Draft Guidance proves helpful for the FDA as it moves to finalize this Guidance. 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 "M D Maves". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Michael D. Maves, MD, MBA