American Medical Association

Physicians dedicated to the health of America

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RE: Risk Management [Docket No. 02N-0528]

The American Medical Association (AMA) is pleased to offer its comments on the Food and Drug Administration's (FDA) Notice on risk management activities for drug and biological products that was issued in the March 7, 2003 Federal Register. The AMA's comments focus principally on Sections II-V of the FDA Concept Paper, "Risk Management Programs," and generally are consistent with the AMA's testimony at the FDA's Public Meeting on the Risk Management of Prescription Drugs on May 22, 2002. We further address the FDA's question about improving the quality of spontaneously reported case reports [of adverse events], which was part of the FDA Concept Paper, " Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment."

General Comments about the Concept Paper, "Risk Management Programs"

The AMA has had a longstanding commitment both to improving the quality of medical care delivered by physicians to patients and to promoting efforts to improve patient safety. In furtherance of this goal, the AMA established the National Patient Safety Foundation in 1997 and has participated in a number of initiatives on clinical quality improvement. The AMA also has been a partner and strong supporter of MedWatch, the FDA's adverse event reporting program. As such, 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, a number of the risk management tools described in the FDA's Concept Paper would directly manage or restrict physician prescribing. The AMA has serious concerns about the potential unintended consequences if these tools were expanded to more pharmaceutical products. We are particularly concerned that the use of these risk management tools could prevent some patients who would benefit from higher-risk drugs from having access to them, or that potential restrictions on prescribing could serve as a deterrent to manufacturer investments in innovative therapies. As expressed in our testimony last year, the AMA is also concerned that the FDA, and drug sponsors, may be

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attempting to regulate the practice of medicine through some of these risk management tools in ways that exceed the FDA's statutory authority.

Other than the AMA's testimony at the FDA Public Meeting in May 2002, we are unaware of any input from national medical specialty societies on the FDA's risk management initiatives. The AMA believes it is essential that there be open communication and collaboration among the FDA, the pharmaceutical industry, and national physician organizations on this subject. 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 when a risk management program, as described in the Concept Paper, is being contemplated for a specific drug or biological product.

Section II: Important Risk Management Concepts

The AMA strongly agrees with the FDA that the Package Insert (PI), as defined in this section of the Concept Paper, combined with routine postmarketing surveillance should constitute the risk management 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, 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.

Section III: When Would an RMP Beyond the Package Insert be Appropriate?

The AMA accepts the FDA's definition of a risk management program (RMP) as "a strategic safety program designed to decrease product risk by using one or more interventions or tools beyond the package insert" (see Section II of the Concept Paper).

Thus, the remainder of the AMA's comments will assume a drug or biological product requires a Level 2, 3, or 4 RMP, as defined in Section IV of the Concept Paper.

The AMA agrees with the FDA that the decision to develop an RMP for a particular product, and the level of the RMP, needs to be determined on a case-by-case basis. This will depend on the severity of the risks when compared to the magnitude of the benefits for a drug or biological product, and the likelihood that an RMP would lower the risks without adversely affecting the benefits. As discussed above, the input of relevant physician organizations in this decision-making should help the FDA and the product's sponsor select the most appropriate RMP for the product.

To help determine whether any drug or biological product needs an RMP, as well as the level of the RMP, the AMA believes it would be useful for the FDA, the pharmaceutical industry, and physician organizations to collaborate on the development of objective criteria for making this determination. Severity of risk, frequency of risk, reversibility of risk by an effective RMP, importance of product benefit to patient outcome, and availability and relative benefit/risk of alternative therapies are among the factors that should be considered in developing criteria for determining whether an RMP is needed. This collaborative development of objective criteria to determine the need for an RMP would give some assurance to all stakeholders that the process is equitable and driven by good science.

Section IV: What Interventions or Tools are Available for Use in Achieving RMP Goals and Objectives?

The AMA has a number of comments on this section of the Concept Paper. In making our comments, we have assumed the Level 1 – 4 categorization scheme, as proposed by the FDA under Section IV(D), is applicable.

Physician education (Level 2) should be the risk management tool used for most drug and biological products that need an RMP.

The AMA believes that the FDA should promote physician education through improved risk communication as the tool that should be used for most drug and biological products that need an RMP. Level 3 and Level 4 RMPs should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

Based on our experience at the May 2002 Public Hearing, the AMA is concerned that the FDA has a predetermined view that risk communication to physicians is ineffective in modifying prescribing behavior to minimize risk. For example, the FDA considers the effectiveness of traditional "Dear Doctor" letters that are mailed to physicians when new and important risks are discovered to be questionable. While this may be true, it is an indication that more innovative and effective approaches to physician education about risk need to be developed, not an indication that Level 3 and 4 RMPs should be more frequently employed. The AMA urges the FDA to work with all stakeholders to make

physician education through improved risk communication an effective – and the preferred – RMP for most products.

The AMA believes that the FDA, the pharmaceutical industry, and physician organizations must collaborate and identify innovative ways to communicate new risk information about a drug or biological product to physicians so they will be aware of it, remember it, accept it, and act on it when prescribing a drug. At the May 2002 Public Meeting, the AMA presented a number of potential ways to accomplish this goal. Most of these options could be implemented immediately, including:

- The FDA, the pharmaceutical industry, and physician organizations should undertake a major CME initiative on risk communication. Physicians need to be aware of labeling changes that identify serious adverse events and that, in some cases, these serious adverse events can be minimized by modifications in prescribing. The AMA's recommendations that the FDA publish its final rule on the PI and create a computerized database of up-to-date PIs, as discussed above, should be implemented as part of this education initiative.

- The FDA, in collaboration with physician organizations, should work with major medical journals and medical society web site editors to identify standard places for the dissemination of important new risk information about drugs and biological products.

- "Dear Doctor" letters should be disseminated by mechanisms other than hard-copy mail. Alternative mechanisms should include publication in medical journals (possibly as paid advertisements), placement on medical society web sites, and transmission to individual physicians by blast fax, blast email, and direct daily downloads to personal digital assistants (PDAs). Unlike letters, electronic transmission is inexpensive, timely, and repeatable. Thus, important risk information can be reinforced by more than one transmission.

- The content and format of "Dear Doctor" letters should be changed to emphasize the need for action by the prescribing physician. For example, a "Dear Doctor" letter should contain a bold-faced opening paragraph that emphasizes the possible severe outcome (e.g., permanent harm or death) to patients from the new adverse event, that the adverse event is probably preventable if the drug is used appropriately, and what necessary steps the physician must take to prescribe the drug appropriately.

- Pharmaceutical companies should be obliged to train and send their sales forces to physicians to educate them on important new risk information about company products. The company should provide incentives to sales representatives to do this because the highest priority of any company should be to prevent harm to patients who use their products. The effectiveness of the 80,000 pharmaceutical sales representatives in the United States in promoting the benefits of their companies' products is well documented, and they could have similar success in educating physicians about important product risks.

- New information technologies, such as computerized physician order entry (CPOE), offer enormous opportunities to communicate important risk information about drug and biological products. CPOE systems with well-designed decision support programs potentially could communicate important new risk information to physicians at the point of prescribing, i.e., at a time when the information is most needed. As these new information technologies become integrated into physician practice, the FDA, the pharmaceutical industry, and physician organizations should work with database providers and software vendors to incorporate the appropriate risk information into these electronic systems.

The AMA encourages the FDA and the pharmaceutical industry to work with physician organizations to optimize physician education about the risks of drug and biological products through identification and implementation of effective methods of risk communication. The AMA also recommends that the Centers for Education and Research on Therapeutics (CERTs) program be charged with developing a research agenda in risk communication to help identify new and effective educational strategies.

Level 3 and Level 4 RMPs should be used only as a last resort to keep high-risk products with unique and important benefits on the market.

The AMA has concerns about many of the tools that the FDA has proposed under Level 3 and Level 4 RMPs including:

- prescribing only by registered physicians (restricted distribution);
- certification programs for physicians;
- enrollment of physicians in a safety program;
- specialized systems or records that attest to safety measures having been satisfied (e.g., stickers, physician attestation of capabilities);
- dispensing only to patients with evidence or other documentation of safe use conditions (e.g., lab test results) (restricted distribution); and
- patient agreements/informed consent.

As discussed above, the AMA has general concerns about the FDA and product sponsors managing or restricting physician prescribing. There also are a number of other reasons why the AMA believes that Level 3 and Level 4 RMPs should be used only as a last resort to ensure that high-risk products with unique and important benefits remain on the market. These reasons include:

- While Level 3 and Level 4 RMPs may reduce risk, such programs most likely will also reduce access. Some patients who would benefit from a product subject to a high-level RMP may not be prescribed that product because of the added burdens on the prescriber.

- A less effective, less studied, and even less safe alternative drug or biological product not subject to a high-level RMP may be prescribed instead of a product with a Level 3 or Level 4 RMP. There is some anecdotal information to suggest that this may be

happening with drugs used to treat cardiac arrhythmias. Sotalol and quinidine, neither subject to an RMP, may be prescribed instead of dofetilide, which is subject to a high-level RMP, when dofetilide is actually the preferred drug.

- Level 3 and Level 4 RMPs that employ multiple tools are complex and may be confusing to both the physician and patient. This could result in unintended medication errors unrelated to adherence to the RMP. This could be magnified in patients with multiple diseases who are on multiple drug products with multiple high-level RMPs, all of which could be different.

- Many of the tools for Level 3 and Level 4 RMPs are administrative burdens for physicians. Therefore, unless the product provides a truly innovative therapy for a particular disease or for a specific subset of patients with a disease, it is unlikely that physicians will take the necessary time to prescribe the product.

- It is unclear what the impact of Level 3 and Level 4 RMPs will have on pharmaceutical company research and development plans. It is possible that a company could cease development of a promising drug because of the likelihood of a high-level RMP. High-level RMPs could have an adverse effect on pharmaceutical innovation, which would ultimately limit new drug discoveries.

- For certain drugs subject to Level 3 and Level 4 RMPs, patients may seek these products from alternative sources, such as illegal foreign Internet sites. For example, if a patient knows about the product but cannot find it easy to obtain in the United States, then the patient may take direct action and purchase the drug illegally. Also, a patient may be concerned about his or her privacy and want to avoid a high-level RMP that mandates patient registration with a pharmaceutical company.

For all of these reasons, the AMA believes the FDA must be highly discriminating in requiring a drug or biological product to have a Level 3 or Level 4 RMP. The serious nature of the risk must clearly be validated. As discussed earlier, objective criteria, agreed to by all stakeholders, should be developed to determine the need for such a high-level RMP. In addition, the FDA and the company must take great care in selecting the tools that will be employed in the RMP. Only the minimum number of tools needed to effectively reduce the risk should be employed in the RMP. Only those tools that have been shown to be effective in reducing the risk should be used, and the tools should be acceptable to other stakeholders (e.g., physicians).

An Integrated, Systems-Based Approach to Risk Management of Drug and Biological Products is Preferred to Product-Specific RMPs.

As discussed above, the decision to develop a RMP for a particular product, and the level of the RMP, needs to be determined on a case-by-case basis using objective criteria. On the other hand, the RMPs for any given level of risk should be as uniform as possible across products. This is especially the case for Level 3 and Level 4 RMPs.

Currently, the FDA uses a product-by-product approach in developing an RMP. Thus, every product has its unique RMP. For high-level RMPs, which often employ multiple tools, this results in a number of complex, administratively burdensome, and, in some cases, conflicting RMPs. As discussed above, this can be confusing to both physicians and patients and potentially could result in unintended medication errors.

Furthermore, it is unclear to the AMA whether any of the different Level 3 or Level 4 RMPs for currently marketed drug products, or the tools used in these high-level RMPs, have been thoroughly evaluated for effectiveness. The AMA requests the FDA to be forthcoming with any information about the effectiveness of current RMPs. The AMA also questions the impact on patient care of certain tools, such as requiring stickers to be placed on handwritten prescriptions, when physicians or hospitals no longer use paper prescriptions.

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 risk management programs. 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 risk management tools. When a product meets the criteria for a RMP at a certain level, to the extent possible, a standard set of tools should be employed in that product's RMP. At a minimum, any given tool should be consistent across products.

The AMA also believes that the FDA, the CERTs program, the pharmaceutical industry, physician organizations, and other stakeholders need to consider the incorporation of risk management for drug and biological products into more global quality assurance programs. As electronic medical records (EMRs) and CPOE 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 drug risk management, 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 EMRs to incorporate the performance measures into their systems so that satisfying the performance criteria becomes a routine part of medical practice.

Section V: How and When Can Risk Management Programs be Evaluated?

The AMA strongly supports the evaluation of RMPs for effectiveness. In particular, we support the FDA's intent to require risk management tools to be pretested prior to their implementation in an RMP. As part of this pretesting, the FDA and the sponsor should seek the input of physicians and other affected stakeholders to see if the particular tool is acceptable. The AMA strongly concurs with the FDA that any RMP also must be evaluated after implementation to determine whether the program has met its desired objectives. As an important first step and as discussed above, the AMA believes that the

FDA and the relevant sponsors of drug products with high-level RMPs currently should evaluate those RMPs, and the tools used in the RMPs, for effectiveness.

The AMA concurs with the FDA's view that metrics which capture actual health outcome data are preferred to those that measure a surrogate event or a process. Metrics, preferably quantitative, should be well-defined and validated. The AMA agrees with the FDA that two different and complementary evaluation methods should be used for key RMP goals or objectives. The AMA shares the FDA's view that spontaneous adverse event data should not be used as an outcome measure for RMP evaluation. The AMA also agrees with the FDA about the limitations of administrative claims data for evaluation of RMPs.

Summary Comments on Concept Paper, "Risk Management Programs"

In summary, 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 concurs with the FDA that the PI, combined with postmarketing surveillance, should constitute the risk management plan for the vast majority of drug and biological products. The AMA urges the FDA to publish its final rule on the PI and to develop a computerized database of PIs that is publicly available.

The need for a RMP, and the level of the RMP, should be made on a case-by-case basis using objective criteria that need to be developed by the FDA, in collaboration with the pharmaceutical industry and physician organizations. The AMA believes that the vast majority of drug or biological products that require an RMP should fall into Level 2. Again, the AMA supports a collaborative effort among the FDA, the pharmaceutical industry, and physician organizations to optimize physician education about the risks of drug and biological products through identification and implementation of effective methods of risk communication.

The AMA has a number of concerns about Level 3 and Level 4 RMPs and recommends that these high-level RMPs be used only as a last resort to keep high-risk products with unique and important benefits on the market. There needs to be a clear documented need for a high-level RMP that is based on objective criteria. Furthermore, the FDA is encouraged to use an integrated, systems-based approach to these high-level risk management programs to make them more uniform and less intrusive to physicians. While evaluation of the effectiveness of RMPs, and of their risk management tools, is recommended for all levels of RMPs, this is especially important for Level 3 and Level 4 RMPs.

The AMA also is concerned that the FDA and drug sponsors may be attempting to regulate the practice of medicine through some of the tools proposed for these high-level risk management programs. It has been long established that the FDA is not authorized to control the practice of medicine (American Pharmaceutical Association vs. Weinberger 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), aff'd sub nom. APhA v. Mathews 530 F.2d 1054 (D.C. Cir 1976)

How Can the Quality of Spontaneously Reported Case Reports be Improved? (From FDA Concept Paper, "Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment"

Spontaneous adverse event reports serve an important purpose in generating signals about serious adverse events that may be caused by drug and biological products. Because physicians are the group best able to observe and communicate information about adverse events, the AMA has had longstanding policy that physicians have an obligation to inform the FDA or product sponsors about potential serious adverse events associated with drug and biological products.

For the above reasons, the AMA has been a proactive MedWatch partner since the program's inception. For example, the AMA was a co-sponsor of one of the first public meetings on MedWatch. Over the years, the AMA has also worked with the FDA to educate physicians about the importance of voluntary reporting, on what to report, about how to make a meaningful report, and how to cooperate fully with follow-up calls from sponsors or the FDA. The AMA reaffirms its commitment to the MedWatch program and stands ready to work with the FDA and the pharmaceutical industry to continue to educate physicians about the importance of spontaneous reporting.

Conclusion

In conclusion, the AMA appreciates the opportunity to comment on the FDA's risk management activities. We hope that our insight into the issues discussed in the Concept Papers proves helpful for the FDA, and we look forward to working with the Agency as it moves forward in this area.

Sincerely,

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