



American Pharmacists Association
Improving medication use. Advancing patient care.

July 6, 2004

Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Docket No. 2004D-0188 Development & Use of Risk Minimization Action Plans

Dear Sir/Madam:

Thank you for the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance to industry on risk management activities for drug products. The American Pharmacists Association (APhA), founded in 1852 as the American Pharmaceutical Association, represents more than 50,000 practicing pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in advancing the profession. APhA, dedicated to helping all pharmacists improve medication use and advance patient care, is the first-established and largest association of pharmacists in the United States.

Risk management activities for prescription drugs are obviously of vital interest to pharmacists as we are committed to helping patients use their medications safely and effectively. As the number of drug products subject to formal risk management programs has grown significantly over the past several years, pharmacists' focus on, and participation in, these programs has increased. Risk management programs can be an effective method of minimizing a drug product's risks, but can also disrupt the health care system in which pharmacists play a crucial role.

APhA supports the Agency's efforts to examine risk management programs and identify measures that can be employed to minimize a product's risks while preserving access to the product's benefits. As part of the Agency's efforts, the FDA released three draft guidances for industry on risk assessment and risk minimization as published in the May 5, 2004 *Federal Register*. The guidance documents, which are based on FDA Concept Papers originally released in March 2003, are an important step in improving the development, implementation, and workability of risk management programs.

Each guidance document addresses a different area of risk management. The guidance document on "Premarketing Risk Assessment" focuses on measures pharmaceutical manufacturers can take during the later stages of clinical drug development to identify potential risks. "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" focuses on methods to obtain and evaluate data on adverse events or other signs that may signal a safety concern with a product after it has been approved

and made available to the general patient population. Risk assessment is a critical activity that must occur throughout a product's lifecycle. Premarketing and postmarketing risk assessment help product sponsors identify potential risks and make adjustments to minimize those risks. APhA strongly supports continuous risk assessment and appreciates the FDA's development of two guidances to direct the pharmaceutical industry in this area. However, APhA's comments will focus on the third guidance "Development and Use of Risk Minimization Action Plans" which focuses on the development, implementation, and evaluation of risk management plans – areas that have a direct impact on the practice of pharmacy.

What Prompts the Creation of a Risk Minimization Action Plan

Pharmacists, other health care providers, and patients rely on the FDA to regulate the safety of medications. But, we recognize that while medications are required to be safe, that does not equate with zero risk. A safe product has reasonable risks when balanced with the expected benefits and available alternatives. The goal of risk minimization is to minimize the risks while preserving the benefits. According to the draft guidance, the risks associated with most drug products can be minimized through traditional means such as professional product labeling and postmarketing surveillance; however, a small number of products should be considered for additional risk minimization efforts.

In the guidance document, the FDA recommends that manufacturers of products that may require additional risk minimization efforts consider developing a Risk Minimization Action Plan (RiskMAP); or the Agency may recommend that a sponsor consider a RiskMAP based on the FDA's interpretation of risk information. In either case, the decision to develop and implement a RiskMAP will be made on a case-by-case basis. APhA agrees that drug manufacturers, in conjunction with the Agency, with access to clinical development data, postmarketing surveillance reports, and phase IV study results, are in the best position to determine which products require a RiskMAP to manage potential risks. However, the standards for determining when products should be placed into various risk management programs are not clear.

The guidance document recommends that product sponsors examine and evaluate certain types of data to determine if additional risk minimization efforts should be considered. The FDA recommends that product sponsors consider the nature and rate of known risks versus benefits including the types, magnitude, and frequency of risks and benefits, the population at greatest risk and/or those likely to derive the most benefit, the existence of treatment alternatives, and the reversibility of adverse events observed; the preventability of the event including serious adverse events that can be minimized or avoided by preventive measures; and the probability of the benefit relative to known risks. APhA appreciates the Agency's inclusion of these recommendations in the draft guidance. By directing product sponsors to consider these areas, the guidance provides product sponsors with a starting point from which to evaluate a product's need for additional risk minimization efforts. While the inclusion of this information is an improvement over the March 2003 concept paper, APhA recommends that the FDA develop more specific criteria to guide the determination of when drugs will be placed in a risk management program.

Identifying what would trigger the need for a formal risk management system should yield more consistency in the marketplace, and help health professionals and consumers deal with those products appropriately. Criteria for product involvement will also help ensure that the proper products are placed into a formal risk management program. Evaluating each product against the criteria will help

identify those medicines or devices that demand special attention to minimize risk to the patient; and separate out those that can be managed through more traditional means. Not only is it important to place high-risk products into a formal system, it is equally important that products are not unnecessarily placed into a risk management system. If every drug is placed into a program, pharmacists, other health care providers, and patients will become desensitized to the potential risks.

APhA encourages the Agency and product sponsors to solicit input from pharmacists when planning risk assessment and risk minimization activities, and we appreciate the Agency's suggestion in the draft guidance that product sponsors solicit stakeholder input. However, the gathering of stakeholder input should not be ad hoc. Experience to date suggests that some manufacturers conduct very elaborate, well planned and broadly based stakeholder input initiatives, while others question only three or four pharmacists in an informal manner. Input from pharmacists, prescribers, and other health care professionals must be obtained in well-defined process, from providers in all practice environments.

Risk Minimization Action Plan Design

There are a variety of tools that are currently used to communicate and manage risk – product labeling, *Dear Health Professional* letters, patient package inserts and Medication Guides, computer generated alerts, as well as “sticker programs” for products like isotretinoin, and mandatory prescriber and patient education for products such as alosetron hydrochloride. Each of these tools was designed to help educate health care providers and patients of the potential risks and how proper medication use can mitigate the risks.

The guidance document identifies three types of interventions or tools that can be used in risk minimization plans: 1) targeted education and outreach, 2) reminder systems, and 3) performance-linked access systems. These three interventions include a myriad of tools such as health care professional letters, training programs for health care practitioners and patients, patient package inserts and medication guides, patient agreements, certification programs for practitioners, prescribing or dispensing only by specially certified practitioners, and dispensing only to patients with evidence of safe use conditions. That is a long and impressive list. But having so many tools to select from has an inherent problem – it can lead to an equally vast number of risk management programs each with different and sometimes conflicting requirements.

APhA was encouraged by the Agency's proposal in the March 2003 concept paper to create levels of risk management programs and their appropriate tools according to the severity, frequency, or duration of the product's risks. The concept paper proposed establishing four levels for risk management programs, ranging from level one in which the package insert is the sole tool used to mitigate risk, to level four in which access to the drug product would require adherence to specific program elements. We are pleased that the new draft guidance retains the concept behind the risk management “levels.” According to the guidance, a product sponsor should select tools from the appropriate risk management category based on the program's risk minimization goals. For the majority of drug products, risk would be minimized through the routine measures of product labeling and postmarketing surveillance (Level 1 in the concept paper). In cases where routine measures are insufficient, product sponsors should select tools from the targeted education and outreach category (Level 2). When a product's risks cannot be minimized through routine measures and targeted education and outreach, a sponsor should incorporate reminder systems tools (Level 3). Tools from the performance-linked

access systems category should be used when products have significant risks that cannot be managed by targeted education and outreach or reminder systems (Level 4).

While the Agency's recommendation that sponsors select tools for a RiskMAP from the appropriate category based on the characteristics of the particular risk is helpful, APhA is concerned that the guidance provides product sponsors too much latitude when selecting tools. In the guidance, the Agency suggests that tools be selected on a case-by-case, or product-by-product, basis. The guidance also encourages product sponsors to develop tools that "may be optimal for their particular products." The product-by-product approach to risk management presents a significant challenge. Current risk management programs are developed on a product-by-product basis and each program uses a different tool or combination of tools to manage the product's risk. Unfortunately, this creates a situation where products with a similar risk are subject to very different risk management programs. Risk management tools should be selected based on the risk the program is intended to address. Instead, product sponsors are inclined to develop a risk management program specific to their particular product – in effect branding the risk management program to their particular product.

For example, under the risk management program for isotretinoin, pharmacists may only dispense the drug after receiving a prescription that was written within the past seven days with a yellow qualification sticker. The pharmacist may only dispense a one month supply per prescription, and must provide the patient with a Medication Guide. In contrast, under the thalidomide risk management program, pharmacists may only dispense the product after registering with the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program, verifying that the prescriber is a registered S.T.E.P.S. participant and that the patient has signed an informed consent. The pharmacist must only provide a four-week supply at one time and must record each prescription. Although both programs were created with the same goal in mind – to minimize the risk of fetal exposure – the requirements of each program are very different, utilize different risk management tools, and utilize different access points for pharmacists attempting to access those tools. At best, this creates administrative burdens for patients, pharmacists and other health care providers. At worst, it creates clinical confusion that actually compromises patient care.

Because of the patient populations pharmacists serve, many pharmacists must deal with several of the risk management programs. Imagine the administrative difficulties and confusion that is generated by trying to keep track of each program's differing requirements. The sheer number and complexity of current risk management programs may keep some providers from choosing to participate. The product-by-product approach to risk management programs is challenging, and compromises the pharmacist's role in improving medication use. We must take a more consistent and reliable approach to risk management programs.

APhA strongly supports a utility approach to risk management, an approach that could be built into the structure proposed in the Guidance. A utility or systems-based approach uses standard tools with common access points (single risk management Internet portal, single toll free telephone number for help desks and standard voice response systems), targeted education, consistently written/presented participation agreements, patient screening and training, enhanced drug interaction screening, compliance documentation, and program evaluation, to meet known risk management issues. As products are identified that require special attention, the risk management program would be built with the appropriate tools from the standard system. The tools would be selected based on the product's risk level, the risk to be mitigated, and the workability of the tool for the particular product.

A utility approach would provide consistency to risk management programs. For example, if lab test verification is required before dispensing a product or, for a different product, within 30 days after dispensing, the access points and the system the pharmacist enters to determine or document the testing would operate in the same manner in both situations. Utilizing risk management tools that operate in the same or a similar manner would allow pharmacists and other providers to become increasingly familiar with the tools over time. Pharmacists would no longer be forced to learn and implement new risk management tools each time the need for a risk management program is identified – forcing providers to juggle the requirements for several different risk management programs at once.

A utility based approach would also limit the administrative burden generated by multiple programs. Identifying similar risks and managing them with similar programs would free pharmacists, prescribers, other health care professionals, and patients from the confusion of trying to navigate differing program requirements. This would increase the efficiency and effectiveness of risk management programs and would allow health care providers to place greater focus on effective clinical use of medications and patient care.

A standardized approach would also increase the number of pharmacists and other health care professionals who choose to work with drug products that involve a RiskMAP. APhA strongly believes that pharmacists and other providers should be allowed to choose to participate in a risk management program. We caution the Agency against the establishment of any RiskMAP that arbitrarily excludes pharmacists or prescribers. We are concerned that one of the tools included in the performance-linked access systems category – “product dispensing only by specially certified pharmacies or practitioners” – appears to rely on restricted distribution. APhA has significant concerns with arbitrary restricted distribution programs. Restricted distribution creates problems for both health care professionals and patients: posing substantial risks, including problems with drug interaction checking, product availability, and communication with their prescriber and pharmacist of choice. An appropriate alternative is an opt-in program which maintains the patient-pharmacist relationship without requiring every pharmacist in the nation to participate unless they so choose. While it is understandable that program participation may require that health care providers meet certain requirements such as completion of an educational program or willingness to submit data to a patient registry, providers who meet these requirements should be allowed to opt-in to the program, not be automatically excluded.

We are also concerned that this tool makes reference to “certification.” “Certification” is not the correct term to indicate that providers are qualified to participate in a risk management program. Certification, a process to grant formal recognition that an individual has met certain predetermined qualifications and attained the requisite level of knowledge, skill, or experience in a well-defined, often specialized, area of the total discipline, is a level of specialization much broader than risk management programs. Risk management programs are product-specific and far narrower than a specialty certification program. Instead, APhA recommends that programs designed to allow a provider to participate in the prescribing or dispensing of a product as part of a RiskMAP be referred to as “qualification” programs.

An area still unaddressed by the draft guidance is the issue of incentives. Patients and health care providers would be more likely to participate in RiskMAPs with the proper incentives. Working with a drug product that requires a risk management program will create additional work for patients, prescribers and pharmacists, and will require additional time. It will be necessary for someone – most

likely product sponsors – to compensate providers for performing interventions associated with RiskMAPs.

Evaluation of Risk Minimization Action Plans

In the draft guidance, the Agency states that it “considers evaluation of the effectiveness of a RiskMAP to be important and recommends that every RiskMAP contain a plan for periodically evaluating its effectiveness after implementation.” According to the guidance, the FDA recommends that product sponsors test and evaluate risk minimization tools prior to implementation, and evaluate the performance of both the individual risk minimization tools and the overall risk management program after the RiskMAP is implemented.

APhA is pleased that the draft guidance also recommends that sponsors’ risk management evaluations go beyond measures of the actual health outcomes and include evaluations of the acceptability of RiskMAP tools by health care practitioners and their patients, and compliance levels with RiskMAP processes and procedures. The Association supports this expanded evaluation of risk management programs and encourages the FDA to require product sponsors to regularly evaluate health care professionals’ and patients’ knowledge of risk management programs, identify barriers to compliance, and assess the impact of these programs on pharmacy and medical practice, as well as, patients’ ability to access the product.

It is important to evaluate how risk management programs are working on a practical level for the pharmacist, prescriber, and patient. Are health care providers receiving adequate information about each program? Are the program tools working as designed without creating an insurmountable barrier to care? Have the tools created a noticeable change in health care professional or patient behavior? Periodically reviewing the effects of risk management programs will assist product sponsors and the Agency in their efforts to ensure that risk management programs do not create inappropriate or unworkable programs for patients, pharmacists, or prescribers. Such evaluation is essential to the success of the programs.

Currently, sponsors are generally and naturally resistant to changes in risk management programs once implemented. However, better data analysis could lead to important and rapid system improvements if the appropriate incentives are in place, or if disincentives are removed. APhA suggests that focused stakeholder dialogue might lead to solutions to this issue.

In conclusion, APhA reiterates our support for the Agency’s efforts to examine the risk management process and provide the pharmaceutical industry with guidance to improve the development, implementation, and evaluation of risk management programs. The Association is encouraged that the draft guidances focus on minimizing a drug product’s risks throughout its lifecycle to optimize its benefit/risk balance. Recommendations in the draft guidance that product sponsors seek input from prescribers, pharmacists, and patients when designing a RiskMAP, and select tools that will have the least burdensome effect on the pharmacist-patient-prescriber relationship, are essential to ensure that risk management programs work within the broader health care system. In order for this to occur, risk management programs must be properly designed.

The draft guidance provides product sponsors with areas to consider when determining whether non-routine risk minimization efforts should be considered. APhA appreciates the direction that product sponsors examine and evaluate certain types of data when evaluating the need for a RiskMAP;

however, APhA recommends that the Agency provide more specific criteria to identify what would trigger the need for additional risk minimization efforts.

APhA also supports the grouping of risk management tools into four different categories. By providing risk management categories, product sponsors can more easily identify the appropriate type of risk minimization tools based on the type and severity of the product's risks. We urge the Agency to expand upon the "levels" concept and move towards developing a standardized-process to work with medicines demanding special attention. APhA strongly supports an integrated systems-based approach that allows pharmacists and other practitioners to help patients mitigate the risks of their medications and maximize the benefits, while eliminating administrative barriers that prevent pharmacists from doing what they were trained to do – help patients make the best use of their medications.

With the help and commitment of the FDA and the industry, pharmacists are prepared to, and want to, play an increasing role in risk management. It is a pharmacist's top priority to ensure that their patients have access to safe and effective medications – and that patients know how to use them properly.

Thank you for your consideration of the views of the nation's pharmacists. Please contact Susan C. Winckler, APhA's Vice President of Policy and Communications, at 202-429-7533 or SWinckler@APhAnet.org or Susan K. Bishop, APhA's Senior Manager of Regulatory Affairs and Political Action, at 202-429-7538 or SBishop@APhAnet.org with any questions.

Sincerely,



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