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Practice Tip

Navigating the FDA's Recent RiskMAP Guidance

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As part of the Food and Drug Administration's ("FDA") ongoing and comprehensive efforts to minimize risks while preserving the benefits of medical products, the FDA recently released three industry guidance documents on risk management strategies. These final guidance documents, applicable to various stages of drug and biological product development, will assist manufacturers in developing and improving methods to assess and monitor the risks associated with drugs and biologics. The risk minimization action plan is one of these initiatives that promises to further tip the balance of the risk-benefit profile of drugs and devices.

While FDA Guidance documents do not technically create legal obligations for manufacturers, as one writer noted, they still carry "the same weight as a 'recommendation' from the Godfather." Barlas, S., *Drug Safety Drama: FDA Opens Curtain on a New Era and New Guidance Documents*, 29 Pharmacy & Therapeutics J. 752, 752 (Dec. 2004). The recently released guidance documents concern: 1) Premarketing Risk Assessment (focusing on risk assessment during the later stages of clinical development); 2) Development and Use of Risk Minimization Action Plans (focusing on specialized risk management systems); and 3) Pharmacovigilance Assessment (focusing on post-market risk assessment strategies). *See Guidance for Industry: Premarketing Assessment*, U.S. Dep't of Health and Human Services Food & Drug Administration (FDA), *available at www.fda.gov/cder/guidance/6357fnl.htm* (last modified March 24, 2005) at 1; *Guidance for Industry: Development and Use of Risk Minimization Action Plans*, FDA, *available at www.fda.gov/cder/guidance/6358fnl.pdf* (last modified March 24, 2005) at 1 [hereinafter *FDA RiskMAP Guidance*]; *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, FDA, *available at www.fda.gov/cder/guidance/6359OCC.htm* (last modified March 24, 2005) at 1. These guidances were produced in part to fulfill the FDA's commitment to certain risk management performance goals agreed to in relation to the Prescription Drug User Fee Act ("PDUFA") upon its reauthorization in June 2002. Under PDUFA III, drug companies agree to pay fees that boost FDA resources, and the FDA agrees to time goals for its review of new drug applications. As the FDA works to increase its efficiency in shepherding drugs through the approval process, improvements in the way drug safety is assessed and monitored can lead to earlier identification of safety problems and enable a more proactive approach to minimizing these risks.

Role of Risk Minimization and RiskMAPs in Risk Management

A risk minimization action plan, known as a "RiskMAP" is a "strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits." *Id.* at 5. The FDA recommends the use of a RiskMAP for a small number of products, but cautions sponsors to tailor a RiskMAP carefully to "minimize risks without encumbering drug availability." *Id.* Together, risk assessment and risk minimization form what the FDA calls "risk management." *Id.* at 2. The FDA views risk management as an iterative process encompassing the assessment of a product's risks and benefits, the implementation of tools to minimize such risks, coupled with a maximization of the product's benefits. *Id.* Accordingly, the premarket guidance and the pharmacovigilance guidance discuss how sponsors should engage in evidence-based risk assessment for all products in development and on the market to define the nature and extent of a product's risks in relation to its

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benefits. *Id.* at 3. The goal of risk minimization is to minimize a product's risks while preserving its benefits. *Id.* However, while, routine risk minimization measures are sufficient to minimize risks for a majority of products, few products are likely to merit consideration for additional risk minimization efforts. *Id.* at 4. There appears to be no ready formula for comparing risks and benefits; thus decisions are made on a case-by-case basis. *Id.*

Risk Minimization Tools and Goals

A RiskMAP targets one or more safety-related health outcomes and applies one or more *tools* to achieve the desired goals. *Id.* at 5. The term *tool* in this context means a risk minimization action in addition to a routine risk minimization measure. *Id.* For example, some tools may be incorporated into a product's FDA-approved labeling, such as medication guides or patient package inserts. *Id.* The FDA recommends that RiskMAP *goals* target the achievement of particular health outcomes related to known safety risks and that sponsors state goals in a way that aims to achieve maximum risk reduction. *Id.* An example of a RiskMAP goal is "patients on drug X should not also be prescribed Drug Y." In essence, the *goal* should be a statement of the ideal outcome of a RiskMAP.

Additionally, the FDA recommends that RiskMAP goals be translated into pragmatic, specific and measurable program *objectives* that result in process or behaviors leading to achievement of the RiskMAP goals. *Id.* Thus the *objectives* should be thought of as intermediate steps to achievement of the RiskMAP goals. *Id.* For example, a RiskMAP goal could be the elimination of dangerous concomitant prescribing for which the objectives could include lowering physician co-prescribing rates and/or pharmacist co–dispensing rates. *Id.* 5-6.

While the FDA suggests that the best tools be selected on a case-by-case basis, it recommends that sponsors: 1) maintain the widest possible access to the product; 2) identify key stakeholders (such as prescribing physicians, pharmacists) who have the capacity to minimize the product's risks and define the role; and/or 3) seek input from key stakeholders on the feasibility of implementing and accepting the tool in usual healthcare practices or lifestyles. *Id.* at 11. Additionally, RiskMAPs should be designed to be in line with current technology; applicable to both outpatient and inpatient use; accessible to a broad spectrum of patients; and consistent with pre-existing effective tools and programs. *Id.*

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There are many processes or systems to minimize known safety risks available for use in RiskMAPs. *Id.* at 7. These systems include: targeted education and outreach to communicate risks; reminder systems, processes, or forms to foster reduced-risk prescribing and use, and performance-linked access systems that guide prescribing, dispensing and use of the product to target the population. *Id.* A RiskMAP might include tools from one or more categories, depending on its risk minimization goals. *Id.* at 8.

The primary purpose of targeted education and outreach is to inform; sponsors must consider when risks cannot be minimized with routine measures alone (such as with the package insert). *Id.* The FDA suggests sponsors consider tools in the targeted education and outreach category when routine risk minimization is known or likely to be insufficient to minimize product risks. *Id.* The targeted education is meant to increase the knowledge of key stakeholders who have the capacity to prevent or mitigate product risks. *Id.* This can be achieved by various means, including healthcare practitioner ("HCP") letters, professional or public notifications, training programs for HCPs or patients and/or patient labeling. *Id.* at 9. Overall, the educational tools can be used to explain how to use products in ways that maximize benefits and minimize risks. *Id.* at 9.

The primary purpose of the Reminder Systems is to nudge. The FDA suggests that tools in the reminder systems category be used in addition to tools in the targeted education and outreach category when such educational tools are known or likely to be insufficient to minimize identified risks. *Id.* These tools include systems that "prompt, double-check or otherwise guide healthcare practitioners and/or patients in prescribing, dispensing, receiving, or using a product in ways that minimize risk." *Id.* Some examples are: patient acknowledgment of having read educational material on the product (consent forms); HCP training programs that include testing; enrollment of physicians, pharmacies and/or patients in special data collection systems; limited number of doses in any single prescription; specialized product packaging to enhance safe use of the product; and specialized systems or records that are used to attest that safety measures have been satisfied (*eg*, prescription stickers). *Id.*

The primary purpose of the Performance-Linked Access Systems is to block unsafe use of a product. Performance-linked access systems link product access to laboratory testing results or other documentation. *Id.* at 10. Examples of tools in this category are: the sponsor's use of compulsory reminder systems; prescription only by specially certified HCPs; product

dispensing limited to pharmacies that elect to be specially certified; product dispensing only to patients with evidence or other documentation of safe-use conditions (*eg,* lab test results). *Id.* Performance-linked access systems should seek to avoid unnecessary or unintended restrictions or fragmentation of healthcare services that may limit access by physicians, pharmacists, or patients. *Id.*

Elements of a RiskMAP Submission to the FDA

The FDA suggests that a RiskMAP submission to the FDA include: 1) Background; 2) Goals and Objectives; 3) Strategy and Tools; and 4) Evaluation Plan. *Id.* at 19. The FDA recommends the Background explain why the RiskMAP is being created and describe the risks to be minimized and benefits that would be preserved by implementation. *Id.* It also suggests the Goals and Objectives describe how the stated objectives will individually and collectively contribute to achieving the goals. *Id.* at 20. For the Strategy and Tools section, the FDA recommends that the sponsor provide a rationale for choosing the overall strategy and should describe how each tool fits into the overall RiskMAP. *Id.* at 20. Lastly, for the Evaluation Plan, the FDA suggests the section describe the evaluation measurements or measures that will be used to periodically assess the effectiveness of the RiskMAP's goals, objectives, and tools. *Id.* at 21. An excellent example of a comprehensive risk management program involves the prescription pharmaceutical Accutane (isotretinoin), indicated for the treatment of severe recalcitrant nodular acne.

Accutane is contraindicated for female patients who are or may become pregnant, as there is an extremely high risk that severe birth defects will result if the patient becomes pregnant while using the drug. Accutane Package Insert, Revised Aug. 2005. Because of Accutane's teratogenicity and to minimize fetal exposure, Accutane is approved for marketing only under a special restricted distribution program approved by the FDA, called iPLEDGE. A jointly supported risk management program developed for Roche Pharmaceuticals and generic manufacturers Genpharm, Mylan/Barr, and Ranbaxy, by a contractor, Covance, Inc., iPLEDGE meets the recommendation of a 2004 FDA Joint Advisory Committee for a single, mandatory, strengthened risk management plan for all marketed isotretinion products that links access to isotretinoin with pregnancy testing to lower the chances of drug exposure during pregnancy. *See FDA Public Health Advisory: Strengthened Risk Management Program for Isotretinoin*, FDA, *available at www.fda.gov/cder/drug/advisory/isotretinoin2005.htm*. An Aug. 12, 2005 FDA Public Health Advisory notified healthcare professionals and patients about iPLEDGE. Accutane already has clear warnings and there have been protocols in place to avoid its use in pregnant women for many years. The strengthened program requires registration of wholesalers, prescribers, pharmacies and patients who agree to accept specific responsibilities designed to minimize pregnancy exposures in order to distribute, prescribe, dispense and use Accutane. *Id.*

The following are key elements of iPLEDGE:

- Only wholesalers registered with iPLEDGE will be able to obtain isotretinoin from manufacturers.
- Only pharmacies registered with iPLEDGE will be able to receive isotretinoin from registered iPLEDGE wholesalers.
- iPLEDGE pharmacies must obtain authorization from the iPLEDGE system before filling any Accutane prescription. If the patient is registered, the pharmacist will receive an iPLEDGE authorization. For females of childbearing potential, this authorization is based on a current, valid negative pregnancy test result. Only prescriptions from prescribers registered in iPLEDGE will be accepted.
- iPLEDGE Prescribers must agree to assume the responsibility for pregnancy counseling of female patients of childbearing potential. Prescribers must obtain and enter into the iPLEDGE system negative pregnancy test results for those female patients of childbearing potential prior to prescribing isotretinoin.
- The sponsors will provide educational programs and materials for all parties in iPLEDGE regarding the risks of isotretinoin and program requirements.
- The sponsors will implement a reporting and collection system for serious adverse events associated with the use of isotretinoin through iPLEDGE. All pregnancy exposures to isotretinoin must be reported immediately to the FDA via MedWatch and the iPLEDGE pregnancy registry.
- The sponsors and the FDA will assess pregnancy rates and compliance with program requirements to monitor the success of the program. *Id.*

Conclusion

At the heart of a physician's decision to prescribe a medical product is a judgment about whether the product's benefits to the patient will outweigh its risks. *Reyes v. Wyeth Labs.,* 498 F.2d 1264, 1276 (5th Cir. 1974) *cert. denied* 419 U.S. 1096 (1974). Since no FDA-regulated product is totally risk-free, these judgments are important. A RiskMAP allows the prescribing physician, the manufacturer, the patient and the pharmacist to work together to minimize the risks, thereby increasing the potential benefit to the patient.