

**Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852**

**Comments to: Docket No. 2004D-0188,
Development and Use of Risk Minimization Action
Plans;
69 Federal Register: Pgs 25130-25132**

From: Eli Lilly and Company

Eli Lilly and Company (Lilly) appreciates the opportunity to offer the following comments to FDA Docket No. 2004D-0188, Draft Guidance on Development and Use of Risk Minimization Action Plans. Lilly agrees with and supports the comments submitted by the Pharmaceutical Research and Manufacturers of America. The few comments of ours that duplicate ones included in their comments are intended to reinforce their importance. Our comments consist of general comments on the guidance papers, followed by general and specific comments on the individual guidance paper.

Lilly compliments the FDA on:

1. Separating risk assessment and risk management
2. Recognizing that risk assessment is iterative throughout a product's life cycle
3. Focusing risk minimization efforts on known safety risks
4. Eliminating references to different "levels" of risk management interventions
5. Recognizing that for most products FDA-approved professional labeling will be sufficient for risk minimization. We suggest that Patient Package Information be explicitly included as a tool whose use would not be considered to constitute a RiskMAP.

Lilly would like to express the following general concerns and suggestions:

1. Please provide clearer guidance and criteria (a unifying concept) to help companies determine when a RiskMAP should be prepared and submitted. For example, a unifying concept could be expressed as "Consider using more than routine labeling and pharmacovigilance when the number or severity of a product's risks appears to undermine the magnitude of its benefits in an important segment of potential or actual users".
3. The guidances should explicitly state that the information concerning RiskMAP tools that is made publicly available will not divulge any company's proprietary information.
4. Although the target number or rate of occurrence of the risk that is attempting to be minimized, can, as an ideal, be set at the theoretical "zero", such an approach is neither

practical nor informative with regard to setting a threshold for subsequent action. The guidances should explicitly acknowledge this point and direct sponsors and regulators to engage in open dialogue to establish a realistic target value for the risks being minimized.

5. FDA authority to impose requirements in this area needs to be understood, particularly when imposing requirements (other than labeling) on products that otherwise meet the statutory standard of "safe" (for instance, a manufacturer is required to *verify* that patients obtain lab tests prior to using product).
6. The guidances should be explicit in stating that sponsors of generic products will be held to the same risk-management standards as sponsors of the innovator product. This should be applied to both risk management elements that are contained in the label (and thus generic should be required to copy) as well as risk management elements (including RiskMAPs) that go beyond labeling.

General comments for Docket No. 2004D-0188, Development and Use of Risk Minimization Action Plans

1. We compliment FDA for providing clear guidance on the format of the RiskMAP submission document.
2. We compliment FDA on their plans for making information about RiskMAP tools publicly available, and recommend that this information include known advantages, disadvantages and limitations associated with a given tool.
3. Many of the items listed as tools for targeted education and outreach have other uses besides risk minimization, but even when deployed for other uses may contain information on the safety of a product. We suggest that you clarify that sponsors are allowed to include a PPI with their product submission without all of the "trappings" associated with a RiskMAP. Requiring sponsors who have a PPI to develop all of the components of a RiskMAP, including formal evaluation plan, could have the effect of discouraging the provision of a PPI when one may be helpful. Similarly, please clarify that the use of Dear HCP letters and other "tools" may be useful outside the context of a RiskMAP, and that their use does not constitute a RiskMAP if the intent is not to minimize a known risk.
4. We recognize that it is not straightforward to assess a product's risk and benefits and evaluate the benefit-risk balance. It would be helpful for the FDA to provide some additional guidance (including examples) on their understanding of how sponsors can perform this activity. We recognize that this is an evolving area and the guidance document may prefer to direct readers to another site or forum where such information can be more readily updated.
5. Please comment on the circumstances in which it would be appropriate for a sponsor to scale back or discontinue an element of a RiskMAP (e.g., goal achieved, prescribing habits established, etc.), or the entire RiskMAP if appropriate. For example, we believe that a RiskMAP intervention aimed at educating physicians about a new product could scaled back and refocused after documenting that appropriate prescribing habits have been established.

Line specific comments for Docket No. 2004D-0188, Development and Use of Risk Minimization Action Plans

1. Line 310 What distinguishes a certification program for practitioners (as a reminder system) from training programs for health care practitioners (as targeted education and outreach)? Is it that a certification program is more tightly focused on the risk to be minimized and provides documentation of competency to the physician and/or the sponsor?
2. Line 313 What distinguishes special educational programs that reinforce appropriate product use (as a reminder system) from training programs for health care practitioners and patients or continuing education for health care practitioners (as targeted education and outreach)? Is it that a special education program is more tightly focused on the risk to be minimized (but does not provide documentation of competency to the physician and/or the sponsor, as compared to a certification program above)?
3. Line 590 For what tools would sponsors be expected to perform pre-testing in a clinical trial setting such as a large simple safety study? Including testing of tools in clinical trials would add a layer of complexity to both the performance and analysis of the trials and could possibly lead to an increase in sample size to assure adequate population of analytical cells. We believe that, in most circumstances, the testing of these tools can be performed more efficiently in settings, and with sample sizes, more specifically designed for the purpose of testing tools rather than in large safety studies not designed for such purposes.

Regards,

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