

## Attachment II

### Development and Use of Risk Minimization Action Plans Proposed Guidance

#### General Comments:

We were pleased to see that the FDA makes it very clear in the proposed guidance that for most products, routine risk minimization measures are sufficient to minimize risk and preserve benefits and that for only a small number of products should a RiskMAP be considered. J&J agrees that an appropriate PI along with good post marketing surveillance should be, in essence, the risk minimization measures for the majority of drugs. Since this is a primary tenet of the proposed guidances, we believe this should be reinforced at the Office level by measuring the number of products that require RiskMAPs and providing statistics on a yearly basis to industry.

Details should be provided about how the FDA plans to ensure that products in the same/similar class with similar safety profiles meet risk minimization expectations in a uniform matter. While it is very helpful to see that generics have been addressed as likely needing a RiskMAP if the innovator product has one (although it is difficult to understand why this requirement would not be an absolute if the product is actually a generic version of the same drug), how similar drugs for the same disease state would be handled still needs to be clarified.

Previously, it was suggested that the FDA include a complete review of all current and past RMPs so as to demonstrate the value of these overall programs as well as the individual tools used to achieve the objectives. We appreciate that the FDA is proposing to maintain a RiskMAP Web site, but it appears that the information will be primarily those data that it receives from sponsors and others. J&J would like to see an analysis by the FDA of previous plans and the tools used, including overall feasibility assessments. We understand there could be confidentiality issues, but believe that such an analysis could be done and still retain appropriate confidentiality since a number of programs have been publicly discussed. In addition, information on tool effectiveness and evaluation data would be available, and in isolation/out of context from the analyses and primary data, potentially misleading.

There is more information in this proposed guidance regarding when a RiskMAP should be considered or would be required. However, there is the statement that the FDA may recommend that a sponsor consider a RiskMAP based on the "Agency's own interpretation of risk information." This approach is certainly in the FDA's purview, but is of concern in that consistent standards must be used across all review divisions so that individual reviewers don't use different criteria in requesting such plans. We believe this is important in order to provide an evidence-based rationale for RiskMAPs for every drug for which they will be required.

In previous comments it was expressed that care must be taken not to overburden the healthcare system by using too many resource-intensive tools in RMPs. It was welcome to see that the FDA is acknowledging the need to use RiskMAPs judiciously so that drug availability is not encumbered and that access to patient benefit is not interfered with.

Also in previous comments, the collaboration needed between industry and FDA was called for. It is gratifying to see the attention paid to the various ways in which industry and FDA will have the opportunity to discuss safety issues early on in the drug development process, specifically at End of Phase II meetings or at specific meetings to discuss potential RiskMAP issues.

As stated earlier, J&J is very supportive of FDA's efforts to conform to harmonized international definitions and standards as much as possible. We think this is an opportunity for FDA to harmonize these proposed guidances with the ICH E2E draft Pharmacovigilance Planning document. Can there be some discussion of how these FDA documents relate to the ICH document, and special attention be paid to harmonizing definitions and terminology where possible?

Will these RiskMAPs be negotiated during NDA review and included in approval documentation? Would they be considered Phase IV commitments? It is imperative that the guidance outlines a process prior to approval (during NDA review) or prior to NDA submission to properly discuss and obtain consensus with the FDA on the RiskMAP so as not to impact the review and approval timelines or launch of a product.

## Attachment II

FDA's general encouragement of early and open discussion of safety concerns may not be enough if there is not enough definition attached to the potential discussion opportunities.

### Specific Comments:

*Lines 171-177*

Though it is laudable to set ideal goals, it is not realistic to achieve them absolutely. It is more appropriate to set high, but realistic and achievable, goals. To achieve absolute goals will probably require draconian risk minimization action plans that limit access of patients to medicines that they need, and may deter physicians from prescribing or recommending them if they perceive the burden on them or their patients as being excessive. Risk *Minimization* Plan, as indicated by the name, should be a realistic plan to minimize risk rather than to eliminate all risks. We agree with the FDA that the goals are translated into *pragmatic*, specific and measurable program objectives.

*Lines 208-217*

It is suggested "nature and rate of known risks versus benefits" be considered when trying to determine if development of a RiskMAP is desirable. The need to compare benefits to risks is obvious, although we agree with the FDA that such an assessment is a very complicated process. To avoid bias in how the risks are weighted in light of benefits, it might be useful for the FDA to consider models as they make such assessments in the future. Currently, this benefit-risk assessment is basically a judgment call, and that is partially due to the fact that most models are not sophisticated enough to be useful or have not been validated. While that is still the case, more work is being done with respect to evaluating such models as the Multi-Criteria Decision Analysis technique. Exploring and using such models as these might be considered as a way to help bring consistent thinking into the FDA review process concerning the balance of risks and benefits for drug products throughout the life cycle. A more rigorous approach may help to ensure that the assessment is not influenced, for example, by an inordinate emphasis placed on a very rare risk or on merely theoretical risks and that the assessment is actually more balanced.

According to the proposed guidelines, one of the characteristics to be weighed when determining RiskMAP desirability is the "existence of treatment alternatives". We suggest that this consideration include "and the benefit-risk balance of the treatment alternative".

*Lines 226-228*

It is not clear why opiates are taken as an example of products requiring specific RiskMAPs as the special controls in their distribution are already intended to ensure that.

*Lines 258-343:*

The previous concept paper on this topic had called for categorizing RMPs into levels. We were not in favor of this for many reasons and so we were happy to see that the FDA has rethought this position. Instead there is a description of categories of RiskMAP tools, which seems to be a more appropriate approach. We were also pleased to see that the proposed guidance notes that a selection of specific tools should not be used in an assessment of comparative safety to another drug product. However, we do note that the sentence in lines 263-265 is poorly worded, and we may have misunderstood its meaning. We suggest this be reworded to be clearer as to its meaning.

*Lines 274-285*

We acknowledge the need for direct information dissemination to healthcare practitioners may be part of a RiskMAP. Please clarify if the use of such health care practitioner letters would always fall under 21 CFR 200.5, including unique envelope requirements and red box (Warning)? For example, would communication/education to health care professionals describing a unique packaging/dosepack usage to reduce medication errors require a "Dear Healthcare Professional letter" with accompanying bells and whistles? Will all such communications/tools (education/outreach) require pre-approval?

## Attachment II

*Lines 356-366*

Please elaborate on the mechanism for FDA's recommendation of class tools/labeling/text?

*Lines 406-407:*

The proposed guidance states that the design of the RiskMAP should seek to avoid unintended consequences of tool implementation that obstruct risk minimization and product benefit. J&J absolutely agrees with the point, but we would like to see more from the FDA on how they propose to make sure that this does not happen. One of the most obvious ways that this occurs is when an inappropriately onerous RiskMAP drives doctors and patients to use a riskier drug without a RiskMAP. As stated above, this scenario has not been adequately addressed in the proposed guidance.

*Lines 414-421*

Is the FDA implying that industry must consider off label use and devise a RiskMAP taking this into consideration to minimize its possible safety consequences?

*Lines 468-471*

We suggest that these lines be deleted. They imply that statistical considerations are irrelevant or only marginally relevant to decisions about the need for a RiskMAP and its evaluation. This is obviously not the case, unless the FDA is really trying to assert that counter-measures should be implemented to address random variations in the observed data.

*Lines 516-518:*

Spontaneous AE data are described as "potentially" biased outcome measures. We suggest that this be corrected to say that spontaneous report data are "inherently biased outcome measures".

*Lines 568-571*

The proposed guidance discusses the potential for an evaluation of a RiskMAP to allow the opportunity to discontinue a tool if the individual tool is performing poorly. While poorly performing tools should be discontinued, we would also like to see the acknowledgement that it might be appropriate to discontinue a tool if it proved to be successful and therefore was no longer needed or if there were another redundant tool, which superseded the need for the tool.

*Lines 581-588*

Please clarify what degree of pretesting risk minimization tools will be required and what the process will be for identifying this need. Also clarity is needed as to whether the evaluation and testing of the tools is required to be submitted at the time of NDA submission or whether a plan to perform these activities before implementation would suffice.

In general, we believe that pretesting of assessment tools will be difficult, especially for new concepts. This may not be a realistic expectation for gathering meaningful information.

The proposed guidance suggests that if risks are identified in Phase 1 or 2, that Phase 3 trials could provide an opportunity to pretest targeted education and outreach tools. It would be helpful to have an example here. As we are developing a drug, if a significant risk is seen in Phase 1, it is unlikely that this drug would be continued in further development. If it is seen at the end of Phase 2, after proof of concept, this may be a more likely candidate.

*Lines 632-637*

Developing a complete risk minimization plan at an early stage (IND/NDA) can be difficult or impossible prior to approval of a product or agreed upon indications/settings for the treatment, as these things will greatly influence the use of the product and therefore the boundaries of the risk minimization plan.

## Attachment II

*Lines 666-674*

Are RiskMAPs to be specific to a product or could they be unique to an indication? For example, if a product were under consideration for multiple indications, across divisions, but the risk were unique to one population under study, could the RiskMAP be assigned to this IND only?

*Lines 823-824*

Inclusion of raw data in the RiskMAP Progress Reports could be quite onerous without being worthwhile. It should be adequate for the sponsor to summarize the results and conclusions based on data collected.

*Lines 838-839*

And along similar lines, the proposed guidance states that a sponsor might choose to propose modifications to the RiskMAP "if the RiskMAP goals were not achieved". We would like to see some discussion about when it might be possible to modify a RiskMAP if the goals WERE achieved. In other words, will a RiskMAP be a never-ending activity or will there be the potential for modification or termination based on success?