

# **April 9-11 Public Workshop on Risk Management, Washington DC**

**REF: Docket Number 02N-0528**

## **Risk Management Public Workshop – Day 2 *Good Risk Management***

### **Final comments submitted on behalf of the International Society of Pharmacoepidemiology (ISPE)**

– [www.pharmacoepi.org](http://www.pharmacoepi.org)

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It is a pleasure and an honor to provide comments to the concept paper on RISK MANAGEMENT PROGRAMS on behalf of the International Society for Pharmacoepidemiology, ISPE. ISPE is a non-profit international professional membership organization dedicated to promoting the science of applying epidemiologic approaches to studying the use, effectiveness, value and safety of therapeutics. The Society provides an international forum for sharing knowledge and scientific approaches to foster the science of pharmacoepidemiology. ISPE has over 700 members representing 45 countries. Our members work in academic institutions, pharmaceutical industry, and government agencies, non-profit and for-profit private organizations. Specific backgrounds of the membership are: epidemiology, biostatistics, medicine, nursing, pharmacology, pharmacy, law, health economics, and journalism.

The following comments are based on the feedback provided by senior members of the Society, including Executive Committee, and Board of Director members and Past-Presidents, as well as the full membership.

We have identified a number of suggestions and clarifications. First, overall comments and proposals are provided. Then, comments targeting specific sections and statements on the concept paper follow.

#### ***General***

This concept paper is useful in the overview of the Agency's views on the considerations for initiating and designing a program, in particular the level of programs, the selection and development of tools, the evaluation of programs and the recommended elements of a program. As such it will be helpful in planning such programs.

On the other side, overall, the 3 concept papers suggest a very fragmented view of Risk Management. There is a danger of consolidating institutional divisions between those working in safety pre and post approval. Integration of specialists in both areas from early development through post market is needed.

### **Gaps in current approach**

- Risk management planning prior to launch
- Activities, timelines, interactions with Agency, relation to other development planning documents and meetings
- Determination of background risks based on epidemiological analysis of the patient population anticipated to be exposed to the therapeutic agent
- Formal document to provide overall overview of risks and decisions about moving or not beyond risk communication in IB/PI
- Guidance for therapeutic agents other than medications

### **Proposal**

A dynamic Risk Management Plan

- Initiated at the moment of entry into humans, based on data from toxicology, etc.
- Moving with the drug along in parallel with development milestones and regulatory meetings and deliverables
- With a specific Pharmacovigilance Plan section designed prior to approval
- Moving with the drug in the post approval periodic safety review process
- A specific Risk Management Program or Risk Minimization Program, would be then initiated when moving beyond IB/PI for a specific issue (s).

### **Outline of a RM Plan / Pharmacovigilance Plan**

- see end of document

### ***Specific Comments***

#### **Section I**

#### **C & D: What is Risk Management Planning, What is a Risk Management Program and what are its goals and objectives**

- Definitions of PVP and RMP as they overlap and partially contradict each other in the two concept papers.
  - RMP definition in Concept Paper III, line 65: a risk management program (RMP) would be a submission to FDA that comprehensively analyzes a product's risk profile and proposes active interventions to minimize them.
  - RMP definition in Concept Paper II, line 62: FDA is defining 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.
  - PVP definition in Concept Paper II, line 55. We envision a pharmacovigilance plan as being a plan proposed by a sponsor for the ongoing evaluation of identified safety signals through enhanced pharmacovigilance practices.

- This document largely seems to focus on tools for reducing risk in patients utilizing a pharmaceutical therapy.
- Clarification
  - "FDA is defining a risk management program as a strategic safety program designed to decrease product risk by using one or more interventions or tools beyond the package insert." (p. 3, lines 62-63; p. 4 lines 99-100)  
Should a risk management program be defined as lying outside the PI, or should the PI be considered part of the risk management program?

### **Section III: When would an RMP beyond the package insert be appropriate**

- Risk management planning should not be limited to exceptional cases. In some cases, the plan would include appropriate labeling, spontaneous report evaluation, and drug utilization studies to be certain there are no unexpected problems. However, risk management plans should become a routine part of every drug approval.
- "Ideally, an RMP would be broached 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." (p. 4, lines 113-115) This statement proposes a standard that it is desirable to implement a risk management plan (i.e., to minimize risks) if a product is so dangerous for some patients that it should not be used. In proposing this important standard for risk management plans, it is reasonable to ask whether it is not also desirable to reduce risks and further optimize risk benefits for products that are successful but which nevertheless might have serious adverse effects that could be further reduced?
- Lines 123-124, the wording suggests that the package insert is not part of a risk management plan. However, conceptually, it is a central part of every risk management plan.

### **Section IV: Intervention or tools available**

- In this guidance it is not really clear that use of such tools is based on the assumption that risk factors for one or more adverse events have been identified and that there is some understanding of how the medication should be used to minimize risk. This point could be made clearer at the front of the document, perhaps even as a separate section.
- Role of PI as risk communication tool: Does the PI serve its purpose of informing patients and providers about important risks? The content should be revised in view of its use as risk management communication tool. Does expressing risks as crude percentages without specifying the exposure duration for which the percentages obtain reward pharmaceutical companies for conducting shorter studies that necessarily have lower percentages than longer studies? Is it desirable for the PI to emphasize common adverse events instead of serious adverse events? Are patients aware of the PI and its contents? Should there be an obligation to quantify in the PI certain serious adverse events? Should the PI be distributed directly to patients?
- On page 8, line 275, states that risk management interventions have been variably effective. Clearly, this is true. In addition to the references showing they do not

work, however, one might want to include references showing they do work, to some degree. For example, there's a cisapride paper published in Pharmacoepidemiology and Drug Safety indicating that such interventions did work, but only against the drugs that were specifically named in the label, as opposed to all of the drugs that were contraindicated, by name or by class. Internationally, the experience is that educational / academic detailing programs have a wide range of success, and require extensive efforts and resources. In selected countries, the use of flag warning systems in pharmacy computers have shown success.

#### **D: Choice of tools – Broad characterization**

- What are the views on guiding criteria to - Preventable, frequency of event... - to move from level 1 to level 2, etc.

#### **Section V: How and when can risk management programs be evaluated**

- It is important to evaluate risk management programs. Furthermore, it is desirable that such evaluations be as scientifically rigorous as possible.
- On page 9 (lines 304 and 320), it is mentioned that evaluation of an RMP might involve a metric of reducing the occurrence of an adverse event. This is certainly the goal of any program, but may be very difficult to measure. Perhaps it should be mentioned that for most drugs, the frequency of serious adverse events, which are usually the focus of RMPs, the evaluation of such events might be problematic because of sample size considerations. For an event, which occurs at 1/1000, for example, it would take tens of thousands of patients to detect a halving of this frequency.
- Additional complication is the fact that "No ready formula currently exists to determine when risks exceed benefits." (p.4, lines 119-120).
- Given the limitations of spontaneous reporting (e.g., p.10, lines 368-372), should there be a more prominent role of formal pharmacoepidemiologic studies in assessing risk and evaluating risk? If so, what role should pharmacoepidemiologic studies play?

#### **Section VI: Desired elements of RMP submission**

- Line 463 – Like a protocol, any evaluation plan for an RMP should include the objective of each evaluation effort, as well as the methods of data collection and analysis plan.

#### **Caution**

- Impact on health delivery systems: the mushrooming of RM programs can overwhelm prescribers and pharmacists if Level 2 or 3 RM programs are initiated on a routine basis
- RM program only for 1 drug in a therapeutic class with similar effects, usually the “new kid on the block”, while the rest of drugs are not focus on RMP.

## **Special considerations**

- International coordination: EMEA released in January the EU strategy on RM. Some content and definitions would benefit from international coordination.
- The guidelines should emphasize the important role of close collaboration between the Agency, Sponsor and Experts in the decision to move beyond PI, choice of tools, evaluations, etc.

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# **OUTLINE OF RMP - PVP**

## **Executive Summary**

## **Objectives**

## **Product (Project) Description**

## **Product Summary**

*Non-clinical safety assessment*

*Clinical safety assessment*

*Disease Epidemiology*

## **Unmet medical needs & Therapy benefits**

## **Preventable risks**

*General actions*

*Risk A)*

**Assessment**

**Identification**

**Quantification**

**Prioritization**

**Response Development**

**Risk Identification & Quantification**

**Risk Communication & Minimization  
(intervention)**

**Risk Minimization & Intervention**

**Response Control: Risk Management Evaluation**

*Risk B)*

Same as Risk A)

**Interactions**

**Medication errors**

**Product defects**

**Overview tables & Action Plan**