October 4, 2005

Guideline on Risk Management Systems for Medicinal Products for Human Use– DRAFT – London, 6 September 2005. This guideline will be included as chapter i.3 of volume 9

Comments Submitted to the European Medicines Agency by the International Society for Pharmacoepidemiology (ISPE)

www.pharmacoepi.org

Comments compiled by S. Perez-Gutthann, MD, PhD, FISPE on behalf of the ISPE Public Policy Committee and Board of Directors

The International Society for Pharmacoepidemiology (ISPE) is very pleased to have the opportunity to offer our perspectives and suggestions, and submits for your consideration the following comments on the *Guideline on Risk Management Systems for Medicinal Products for Human Use.*

About ISPE

ISPE is an international, nonprofit, professional membership organization dedicated to promoting the health of the public by advancing pharmacoepidemiology, the science that applies epidemiological approaches to studying the use, effectiveness, values and safety of pharmaceuticals. ISPE is firmly committed to providing an unbiased scientific forum to the views of all parties with interests in drug, biologics, and devices development, delivery, use, costs and value, adverse and beneficial effects, and therapeutic risk management. Moreover, the Society provides an international forum for the open exchange of scientific information among academia, government, and industry and for the development of policy; a provider of education; and an advocate for the fields of pharmacoepidemiology and therapeutic risk management.

The Society's more than 800 members represent 45 countries. ISPE members work in academic institutions, the pharmaceutical industry, government agencies, and non-profit and for-profit private organizations. ISPE members are researchers with background and training in epidemiology, biostatistics, medicine, public health, nursing, pharmacology, pharmacy, law, and health economics.

Our comments are based on a careful review of the draft guidance by the Society's membership at-large as well as by ISPE Fellows, Past Presidents, members of the Board of Directors and Executive Committee and Public Policy Committee.

General Comments

We commend the European Medicines Agency (EMEA) for taking the initiative to move forward the current state of knowledge on risk management by drafting this guideline and soliciting public comment. We thank the Agency for requesting comments from ISPE. We encourage EMEA to move forward and foster further collaboration among all interested stakeholders at the Agency, MAHs and MAAs, and other institutions. As specific applications are initiated, we strongly recommend the Agency promote discussion and collaboration among stakeholders as early as possible in the process. Finally, as an international society, we encourage international harmonization of this guidance and other EMEA guidelines. We also have the following general comments:

- This is a very valuable guideline document, which reflects much work and thought, and represents an instrumental move towards increasing the

benefit-harm balance of treatments for patients while protecting access to these treatments.

- It is useful to have one integrated guidance for both Pharmacovigilance and Risk Minimization plans. The careful details in the guidance should result in facilitating the development of these documents as applied to specific treatments.
- The document integrates well ICH E2E pharmacovigilance guidances and concepts as well as other available guidances on pharmacovigilance and risk management such as the ones by the US Food and Drug Administration. (FDA). An important area of clarification is that the proposed definition of risk management seems to include also risk communication through the label as part of a risk management plan.
    - The contrast in approach with the existing guidance from the US FDA may lead to confusion and potential inefficiencies as risk management plans are implemented in different regulatory regions.
    - Within the EU, this could lead to perceptions that new treatments with similar labeling within a therapeutic indication are riskier than older available treatments that do not have a formal risk management plan.
- Pre-approval aspects of risk management, are not discussed in detail in the present guidance, other than a brief mention of its initiation at any stage of its life cycle.
- When planning actions and milestones, it is important to take into account how many people will be using the treatment and how. These assumptions should be explicit when potential timelines are discussed.
- Helpful detailed advice was provided in several sections. However, we recommend adding emphasis on the need to maintain flexibility and to plan discussion with appropriate stakeholders to tailor the plans for specific treatments and populations.
- Overall, epidemiological considerations are carefully addressed and described across numerous sections. They will guide implementation, including methodological aspects.
    - Some relevant examples of the epidemiological considerations that are carefully addressed are: The use of appropriate denominators, patients or person-time, including the impact of constant hazard rates; Rates estimated from spontaneous reports versus rates estimated from events in clinical trials or epidemiological studies; Differentiation of the concepts of relative and excess risks; Use of electronic databases reflecting medical care, prescriptions and tests to monitor adherence to prescribing and monitoring guidances for risk minimization (4.11.1); Detailed epidemiology methods, including references to Good Pharmacoepidemiology Practices and textbooks.
    - Care should be used in the definitions of risks in Section 6. Statistical significance aspects receive much emphasis, while other more relevant aspects such as the biological plausibility or magnitude of the association are not addressed.
    - Electronic or automated health databases are key for many risk and risk minimization action evaluations. While the specific steps to ensure that such data are available in each country/region/setting will vary, it is important to point out the key role of governments, data

owners and related institutions to ensure that such data are available for public health research.

Specific Comments & Clarifications

Section 1: Introduction

Page 4. First paragraph. Limitations of clinical trials
In addition to short duration of exposure, another problem is short duration of follow-up, critical for long latency effects, e.g. cancer. Note that duration of exposure is different from period at risk. Another limitation relates to trials that are non-inferiority or use a placebo comparator, and the use of surrogate endpoints as opposed to clinical endpoints.

Page 4: Lines 31-35 “This guidance aims…” could be moved after paragraph lines 36-40 defining risk management “Risk management is a continuum…”

Section 4

4.3 Page 7, line 27. Biosimilar: this term requires clarification

4.3 Page 7, line 28: although "safety concern" is defined in the glossary, it may be desirable to define it in the text the first time it is used or refer to the glossary.

- The definition provided for "safety concern" is "An important defined risk, important potential risk or important missing information. "It would be helpful if this could be further detailed, or alternatively if examples could be provided.
- Presumably, importance includes consideration of severity of the adverse outcome, frequency of the adverse outcome, therapeutic alternatives, and risks of the disease being treated. It would be helpful to provide additional detail on what is considered important.

4.3. Page 7 Line 34. Preapproval aspects are not described, other than the mention that RMP can be requested pre o post approval.

4.5 Safety specifications. It would be helpful to learn more about potential timelines.

4.5.2.1. Post-marketing (non-study) exposure

Estimation of exposure using kilograms of drug sold. Please note that few drugs are used only at one dose level and for a fixed period of time. Further clarification is needed to address this situation.

It is useful to monitor patterns of use at various points in time following launch, since use immediately after launch may be very different from use once market

has stabilized or when a newer product is introduced. Also, the presence of channeling should be assessed, i.e.: patients with risk factors for the adverse events may be channeled to the newer product.

See also applicable comments to 4.5.2.3

4.5.2.2. Populations not studied in pre-authorization phase
Methods for describing the characteristics of the “target population” of all patients who are likely to be prescribed the drug after licensure should be defined in the document. The document should note that the characteristics of the clinical trial population were directly observed, but the characteristics of the target population are basically a “best guess” at the time of licensure. The document implicitly defines the “population potentially at risk” as the subset of the “target population” who were not studied, or only studied to a limited degree, in the clinical investigations of the product (p. 18). However, the draft document does not provide a definition of the “target population”, which is key to define the “population potentially at risk”.

4.5.2.3 AEs/Adverse Reactions. Identified risks that require further evaluation
Since all serious or frequent side effects will have an effect on the benefit-harm balance of the product, it may be useful to discuss how the balance will be affected by the side effects.

4.5.2.3 AEs/Adverse Reactions. Presentation of risk data
Paragraph 1. We agree that there should be a clear difference in the presentation of rates estimated from spontaneous reports and from studies. It is important however to acknowledge the resources that are currently dedicated to produce the drug exposure estimates, and the challenge of estimating event rates when formal studies are not available. We suggest clarification and further guidance to address this situation. Ultimately all global estimations will be based to some degree on extrapolations, including from population-based studies.

Page 11, lines 6-7: Number needed to treat (or harm) could be added to the description of important identified risks.

Hazard rates: Please note than they may not be clear for some time after a new treatment becomes available.

Structured Form: Please provide further detail on how this form should be developed, including type of desired data.

4.5.2.8. Page 11. Depending on the indication of the treatment, specific EU epidemiological data may not be available. While it is worthwhile exploring the possibility of generating new data, this may represent a challenge.

4.5.3 Summary. Important missing information
Consider including missing information as a component of identified and potential risks. Also, consider including examples of information that is missing

such as whether the event is related to the dose or duration of the exposure, hazard rate, special subgroups at risk, etc.

4.6.2. Footnote reference n.1 in page 13: Good Pharmacoepidemiology Practice guidelines can also be referenced as: International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiology and Drug Safety 2005; 14 (8): 589-595

4.11. Ensuring the effectiveness of risk minimization tools: Page 16, line 11: Consider addressing "ineffective" and "insufficiently effective" strategies.

Section 6

The section regarding the definitions of type of risks has triggered much discussion due to different existing definitions and perspectives.

Safety concern Consider the alternative definition: An important risk needing better characterization and/or quantification.

The definition of an Identified risk in Section 6 page 17:"*an adverse drug reaction observed in well-designed clinical trials or epidemiological studies and for which a statistically significant difference has been found with the comparator group (placebo or active substance, or unexposed group) on a parameter of interest such as the rate ratio or the rate difference*" may lead to confusion, as it relies only on statistical significance and not on the magnitude of the association.

- In a large study a very small association with negligible clinical relevance may be statistically significant,
- In the opposite situation, unless sample size has been calculated in order to evaluate the specific event, most events will not reach statistical significance, while their clinical impact may be substantial

It is recommended that other aspects of the association such as the magnitude (relative risk or rate difference), biological plausibility, etc. are taken into account.

This also applies to the definition of Potential Risk (Section 6, page 17).

Annex A. Epidemiological Methods for Post-Authorisation Safety Studies

Section 1.1.3 Drug Event Monitoring:

Prescription Event Monitoring is the name by which this approach is known in the United Kingdom and selected countries. The following up-to-date references are available: Mann RD. Prescription-event monitoring: recent progress and future horizons. 1998. Brit Journl of Clin Pharmacol. 46(3):195-201.Shakir SAW. Prescription Event Monitoring. In Pharmacoepidemiology. 4th Ed. Ed. B Strom. Wiley 2005.

It is important to know this method requires active individual participation of physicians to provide questionnaires. This will affect response rates. Also, could the term “large number of physicians and /or patients” be specified, although this may depend on which indication will be evaluated.

Section 1.2 Comparative Studies:

Large simplified safety trials and randomised epidemiology studies should be added as an option to provide comparative safety information.

Registries – It could be clarified that exposure registries often involve follow-up whereas other outcomes registries, e.g. birth defects registries, frequently do not involve follow-up

Section 1.2.3 Inclusion of case series within this section seems to be inappropriate. In contrast to the case-crossover or case-time-control designs, case series are descriptive and are inadequate for formal hypothesis testing. However, a case series may serve as a source of cases for the more formal designs described within this section.

In planning timelines of studies, please note the impact of uptake of new treatment and lag time of data availability in large automated datasources.

Reference N.2 update: Strom BL. 4th. Edition, 2005 is the most recent version.

Annex B. Risk Minimization.

- 1.1.1 Additional Educational Material: Aim should also include early diagnosis and treatment of the adverse event.
- 1.6 Restricted Access and 1.7 Patient Registries: The differences between both approaches are not clear.
- It is important to acknowledge that the risk minimization evaluation component is one of the more challenging aspects of risk management.

Annex C RMP Template

While not available in current draft, this is a helpful document. We encourage its development.

Other

- Specific proposals regarding the timelines and triggers of updates and reporting of findings of activities in the risk management plan would be helpful. We suggest that the routine updates or reporting of findings should be aligned to existing safety regulatory documents, both approval and post-approval.
- We recommend adding emphasis on the important role of discussions and agreement between all stakeholders to move forward risk evaluation and risk minimization actions.
- We look forward to specific guidance for risk communication activities.