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Risk Management Public Workshop – Day 1 *Risk Management in Drug & Biologic Development*

**Final comments submitted on behalf of the
International Society of Pharmacoepidemiology (ISPE)
– www.pharmacoepi.org**

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It is a pleasure and an honor to provide comments to the concept paper on PREMARKETING RISK ASSESSMENT 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 epidemiological approaches to studying the use, effectiveness, value and safety of therapeutic agents. 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, the pharmaceutical industry, and government agencies, non-profit and for-profit private organizations. Specific backgrounds of the membership include 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.

General Comments

This concept paper is a useful summary of the Agency's views on many possible approaches to pre-marketing risk assessment, and it will be helpful for guiding the overall clinical development plan.

Although briefly mentioned, it is somewhat surprising that this concept paper on premarketing risk assessment does not link more closely with (1) the premarketing and clinical pharmacology activities, and (2) the companion concept papers on Risk Management and Risk Assessment of Observational Data. The activities in the premarketing period, including some key preclinical studies and certainly clinical

pharmacology studies, play a major role in identifying and characterizing the priorities in planning for risk management of a product. All of these activities should be integrated into a Risk Management Plan, interpreted in the broader sense – not as the RM Program described in concept paper II -over the life of a product, beginning prior to entry in man in clinical trials. Such lack of linkage poses the danger of consolidating institutional divisions between those working in safety pre- and post-approval. There should be integration of specialists in several areas from early development through post marketing.

Section II. Risk Assessment Concepts

Lines 23-27 in the Concept Paper note that this entails a program that “comprehensively describes its safety (as required by the Food, Drug and Cosmetic Act, which calls for conduct of all tests reasonably applicable to evaluate a drugs’ safety).

The *safety* of a product is a judgement made at a specific point in time based upon available information. It is well appreciated that even the most rigorous pre-marketing program cannot identify all risks that may occur when a product enters the market. Nonetheless, the concept paper outlines the possibility of expecting very extensive explorations of known or possible risks to support this judgement. It may be useful for the agency to evaluate the basis for its judgements made thus far on the data at hand to begin to determine just how “comprehensive” a risk assessment must be.

Section III. Important Considerations in Generating Risk Information

Size of the Database

It will be important to develop concepts of the ideal size of a database to support a judgement of safety. Even for chronic use, depending on the drug, ICH guidelines may not always be applicable for some risks due simply to lack of power. Thus, using the “rule of three”, the sample size of 1500 can detect an event occurring at 1/500. With 600 patients followed for 6 months, an event occurring at 1/100 person-yrs can be detected, and with 100 followed for 12 months an event occurring at 1/33 person-yrs can be detected. This may or may not be adequate, depending on the risk.

With respect to risks with acute use, other than supervised use within a hospital, the size of a database might be best informed by understanding the likely modes of use after marketing by prototypic indication populations. Even labeling and packaging for acute or short-term use may be ignored by prescribers and/or patients, as is the case for analgesics for acute, self-limited pain. As for several other recommended risk assessment activities in this concept paper, including medication errors, it would be useful to develop a *spectrum of scenarios* of how a drug will be utilized in the real world, including likelihood of using larger or smaller doses by the indication population, drawing upon a growing set of epidemiological resources that can do this.

Line 134. The paper indicates that a larger database would be useful if safer alternatives to the investigational product are available. It will be necessary to define not only a fair definition of alternative, but also the criteria for “safer,” since many

established products may not have had the scrutiny or risk assessment that may result in premarketing risk assessments going forward that address the concepts in this paper.

Characteristics to the Database

Re Long-term controlled safety studies. The need for more controlled data to evaluate premarketing safety is an important concept. The preferred comparisons would ideally be from randomized, even blinded studies. Further, such studies would benefit from the additional review by Data Safety Monitoring Boards since in such studies, rare events continue to be difficult to evaluate.

Dose Ranging

Better understanding of exposure-response relationships is clearly helpful in assessing benefit, but it would be important to further define how useful broadening of the range of doses will be to understand all but clearly common, dose-related risks. In some cases this could be informed by more intensive pharmacokinetic modeling early in development. Further, understanding may be further enhanced by concomitant use of pharmacokinetic measures in the trials, as recommended elsewhere in this concept document.

Section III C. Unanticipated Drug Interactions

The possible types of drug interactions listed underline the fact that for any therapeutic agent, there are myriad possibilities for interactions, and it is unlikely that all of these possibilities could be explored in a reasonable clinical program. That said, certain steps could help to focus this effort:

1. Conduct of studies of the natural history of the indication population, using epidemiological databases, to determine the most common possible interactions, combined with a reasonable pharmacological /pharmacokinetic assessment of the likelihood of those interactions.
2. Design of the trial and adverse reaction collection protocols (and training of investigators) to assure assiduous collection of data that might reveal an interaction in the event of an adverse event.

Section III. D. Comparative Safety Data

The need for comparative data is well recognized, but the Agency will need to develop clear concepts on *how* comparisons will be made. That is, how will two agents with comparable benefits be compared when risks differ. For example, how does one compare equally beneficial drugs where one can cause irreversible renal failure, the other, irreversible hepatic failure at roughly the same rate, measured in comparable databases?

Section III. E. Special Considerations

The recommendations in this section are broad and if required for all products would be prohibitive. Therefore it would be hoped that the needs for these special studies would be directed to clear areas of public health concern and where it can reasonably be assured that the additional clinical data will provide a clear basis for better decisions.

For example, the large, simple safety study (LSSS) is very useful for understanding the risk in diverse populations, but it is very hard to maintain simplicity if questions over risk measures are not well-defined and the results lead to continued uncertainties. If LSSS are conducted, it should be with the *mutual agreement* on these possible uncertainties and resulting actions before launching such trials.

Section III. F. Medication Errors

Since a large part of clinical development in the premarketing period is conducted under conditions not analogous to usual use, much of the experience derived in clinical studies is not useful to inform the sponsor of possible errors. To predict medication errors, it is necessary to develop detailed time-motion scenarios of how a product is selected, prescribed/ ordered and used by the patient, although some clues might be derived from studies in the indication population and their use of comparable drugs to determine the potential for medication errors

IV. E. Data Analysis: Appropriate methods for data pooling.

The concept paper provides a useful outline for these analyses. However, as noted above, an overall risk management plan that starts at the outset of clinical management can facilitate data pooling by assuring that all collections of safety data are standardized and analyzed utilizing similar terminology and term groupings throughout the development.

Line 481, re on pooling and use of person-time. This recommendation is generally, but not always, a good one. This would depend on the event of interest and would not apply to idiosyncratic reactions. For idiosyncratic events which occur uniquely during early exposure the frequency estimate should use number of people exposed as the denominator. Perhaps it should also be clarified that person-yrs are the units for the denominator when estimating the frequency of an event in a pooled analysis.

Conclusions

In conclusion, this paper provides an array of possible ways in which the risk of a product in development may be assessed. However, it is not really clear how to balance the recommendations in this document versus the recommendations in the other two. In other words, how much safety assessment must be done in development and how much can be done postmarketing. For example, what are the trade-offs for a large simple safety study during development versus a more extensive safety program during the postmarketing phase? There are no easy answers to this question and it may even require a separate guidance document. However, this document describes all possible safety assessments which might be done during development and provides little guidance on which circumstance FDA recommend for applying many of the pieces described in this document.

In part this can be remedied by better integration of risk assessment and risk management from the outset of development. In the best of possible worlds, product development with a risk management perspective is an iterative and informative process that, with greater experience in overall “therapeutic” development and regulation, should improve with time.

ISPE is firmly committed to providing an unbiased scientific forum to the views of all parties with interests in the safety of therapeutics, and as such is deeply committed to the advancement of Risk Management Sciences.

We welcome the opportunity to work together with the Agency in this area, and will engage our full membership in the feedback process of this concept paper.

Our next annual conference will be focused on Risk Management. Several workshops and sessions are being planned jointly with FDA staff. I take this opportunity to invite you to join us at the combined 1st International Conference on Therapeutic Risk Management and the 19th International Conference on Pharmacoepidemiology. This meeting will be held August 21-24 in Philadelphia.

Thank you!