Draft Guidance for Industry
Premarketing Risk Assessment

[Docket Number 2004D-0187]

Submitted to the
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

By the
International Society for Pharmacoepidemiology (ISPE)
www.pharmacoepi.org

Comments prepared by
Judith K. Jones, MD, PhD, FISPE
on behalf of the ISPE Membership and Board of Directors

July 2, 2004

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to offer our perspectives and suggestions, and submits for your consideration the following comments on the *Draft Guidance for Industry on Premarketing Risk Assessment.* We commend the Food and Drug Administration (FDA) for taking the initiative to move forward the current state of knowledge on risk management by drafting industry guidance and soliciting public comment. We thank the Agency for including many of ISPE's comments and suggestions on the 2003 concept papers. We encourage the FDA to move forward and foster further collaboration among all interested stakeholders at the Agency, sponsor(s), 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 FDA guidance.

About ISPE

ISPE is an international, nonprofit (501-c-3), professional membership organization dedicated to promoting 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 provide 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 700 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, members of the Board of Directors and Executive Committee and past presidents.

General Comments

As was the case for the original concept paper, this augmented Draft Guidance represents a very useful outline of important considerations for pre-marketing risk assessment. If seriously considered in all drug and medical product (referred to as "drug") development programs, the Guidance can not only greatly facilitate product benefit-risk evaluation, but also lay the

framework for both Pharmacovigilance and Risk Minimization plans following product approval.

Although presented as a Proposed Guidance, this document can have far-reaching implications for shaping drug development programs worldwide. If implemented thoughtfully by sponsors in discussions with regulators, the resulting safety database can provide a very comprehensive, standardized risk profile for a product, and can allow this risk to be properly placed in context with analogous products by both the sponsor and FDA.

The Proposed Guidance also serves as a platform for a major need in understanding overall drug and medical products' benefits and risks. There is a woeful lack of standard tests and measures of most categories of drug risks. If both the sponsor and regulatory community view this guidance as reasonable, then the development of relatively *standardized terminology* and *data summarization conventions*, applied to all drug products, will allow for considerably improved comparisons of benefit and risk across products, as is described briefly in one of the following sections.

Given these strengths, concerns about this guidance from the ISPE constituency continue. There is still relatively little integration between the pre- and postmarketing guidances, despite the fact that the risk profile of a drug, and all the activities around those risks represent a continuum that is now operational in a large number of sponsor companies.

Thus, much of our original comment re this issue still applies and a copy of the original comments are appended to this document (Appendix A). The original text of the first part of our comments is cited below

> "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."

Specific Comments

A. Need for reference to greater use of epidemiology in the pre-marketing period

The current proposed guidances still do not provide very explicit guidance to the value of epidemiological data and studies to enhance the understanding of a products risk profile prior to marketing. There are many ways in which epidemiological data can enhance understanding of a product and its indication population to facilitate both regulatory decision making on benefit risk as well as refine plans for postmarketing risk assessment and minimization. Further, we are now in an era where (1) there is access to a very large number of different databases (medical claims, computerized medical records, hospital and pharmacy databases) that capture most activities in the healthcare arena and (2) there is a growing array of epidemiological and statistical methods that can be applied to these data to enhance understanding of disease, actual and potential drug risk and human behavior.

The ways in which epidemiological data can be use, which are in use in many instances, already include:

- *Natural history of disease studies of the indication population*. This type of study is often essential, especially in populations with multiple co-morbidities to provide a basis for expected rates of events prior to introduction of the new product.

- *Natural history of the treatment and healthcare utilization of the indication population*. Many assumptions may be made about the regularity or lack thereof of treatment and care by specialists or generalists of particular disorders and in which sites. Use of epidemiologic methods to detail health care and concomitant drug utilization can provide a detailed map of practice and patient behaviors and outcomes that in turn can:
    - Instruct the development of appropriate prescriber, pharmacy and/or patient communications, where risk minimization plans are needed.
    - Identify the probability of drug interactions that might occur more or less frequently
    - Create a “map of longitudinal health care utilization” that can be used to anticipate possible foci of medication errors.

- *Study of the nature of anticipated drug-associated diseases*. At present, there is still a paucity of data on many disorders that are repeatedly associated with diverse drugs. Examples include hepatic hematologic, pulmonary and skin disorders, to name a few. In some cases, these can be anticipated for a particular product and understanding of this disorder and its various etiologies can provide a clearer guide to anticipated risk minimization efforts.

- *Treatment of the clinical trial database as an epidemiological dataset for more detailed analysis*. Particularly if the clinical trial data has been collected under relatively standardized conditions (e.g., use of MedDRA terminology, standard SAE reporting forms, standard outcome data), combined analysis of these data using a variety of epidemiological methods can provide new insights into hypotheses raised during the development process.

At present in the guidance, mention is relegated primarily to a footnote. In Section V, Special Considerations for Risk Assessment, Line 404. Footnote 10:

> *"The Pharmacovigilance Guidance discusses additional risk assessment strategies that may be initiated either pre or postapproval. In particular, the Pharmacovigilance Guidance includes a detailed discussion of pharmacoepidemiologic safety studies. Although such studies should principally be initiated after marketing, the Pharmacovigilance Guidance discusses certain situations when they could be initiated pre-approval."*

As explained above, we contend that the applications of epidemiology deserve more detail, since they are not really that fleshed out in the Pharmacovigilance Guidance either. In fact, the PDUFA III legislation wording is considerably more specific in this regard.

Therefore, based upon the rationale laid out above, we would propose that this concept be given greater emphasis by moving it to the main text (rather than the footnote) and suggest the following wording:

> *"The Pharmacovigilance Guidance discusses additional risk assessment strategies that may be initiated either pre- or postapproval. In particular, the Pharmacovigilance Guidance includes a detailed discussion of pharmacoepidemiologic studies. While those studies focusing on the association of the target drug with specific safety endpoints are started post-approval, they benefit from advanced planning as soon as their need, feasibility and validity has been established. Often pilot studies can be conducted among the same target population prior to approval to streamline efforts post-approval. Also other safety goals can be addressed through epidemiological studies pre-approval: to study natural history of disease; drug use and patient characteristic patterns prior to the introduction of a new therapy; and to evaluate the potential population impact of pre-clinical or early findings. Finally, epidemiological sampling and analysis methods can be applied to clinical trial databases to evaluate cluster of safety events, as well as modeling and simulation techniques."*

B. Size of the Pre-Marketing Database

Line 226 re circumstances where a larger database may be appropriate because

"a safe and effective alternative to the investigational product is already available."

There is some concern that this basis implies a largely global judgment that is based on data that is not as rigorous as that expected for any new product. That is, a product that entered the market several years ago may be perceived to be "safe and effective" but in fact could have a similar or even more problematic profile (as for example, undesired drug interactions that are not necessarily detected or reported even in the postmarketing period) if the current guidances were applied.

Another issue related to database size is, as noted in the guidance, the usual trial database is insufficient to assess many of the toxicities that create concern in the postmarketing period. Although in some cases it may be desirable to increase the database size, it may never capture the populations at risk after marketing because of the nature of the studies. Thus, alternately, it may be useful to make the limitations of pre-marketing data explicit by including a notation in the label such as the size of the data or the size of the rate the existing data is capable of detecting.

Concluding Comments

ISPE is committed to providing an unbiased scientific forum to consider the views of all parties with interests in the safety of therapeuticals, and as such is deeply committed to the advancement of risk management science generally and this proposed industry guidance specifically.

The Society welcomes the opportunity for further collaboration with the FDA and its Centers on risk management and other related initiatives.

ATTACHMENT A

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

REF: Docket Number 02N-0528

Risk Management Public Workshop – Day 1

Risk Management in Drug & Biologic Development

Comments of behalf of the International Society of Pharmacoepidemiology (ISPE) –

www.pharmacoepi.org

ISPE speaker: Judith K. Jones, MD, PhD, VP Finance, ISPE

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 therapeuticals. 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 they are 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 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 judgment made at a specific point in time based upon information available. 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 risk to support this judgment. It may be useful for the agency to evaluate the basis for its judgments 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, ICE 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. However, 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 things could help to focus this effort:

1. Conduct of natural history of the indication population 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 <u>denominator</u> 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 clear how to balance the recommendations in this document versus the recommendations

in the other two. In other words, how much safety assessment is 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 therapeutical 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 therapeuticals, 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!