

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

REF: Docket Number 02N-0528

**Risk Management Public Workshop – Day 3
*Risk Assessment of Observational Data: Good
Pharmacovigilance Practices and
Pharmacoepidemiologic Assessment.***

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

– www.pharmacoepi.org

Submitted: May 29, 2003

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behalf of the ISPE Membership and Board of Directors.*

The following are comments to the concept paper on RISK ASSESSMENT OF OBSERVATIONAL DATA: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT (referred to as Concept Paper #3) 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 pharmaceutical and biotechnology products. 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, and in 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 a careful review of Concept Paper # 3 by the ISPE Membership at large and the ISPE Board of Directors. These written comments are an elaboration of the comments provided orally during the April 11th Public Workshop.

There are several areas of the Concept Paper where, as epidemiologists, we suggest some clarification.

Comments on General Concepts:

Quantitative definition of risk

From an epidemiologic standpoint, we recommend providing a quantitative definition of risk. Risk is a measure of frequency based on a numerator AND denominator. The numerator consists of the number of people who develop an event and the denominator that represents the amount of exposure in the population. If the denominator may consist of number of people exposed then the measure of frequency is referred to as risk. Time is another important factor in the quantitative definition of risk.

Expansion of Types of Studies to be Considered as Risk Assessment Strategies

We would suggest that epidemiologic assessments of safety endpoints is important, and should be further emphasized in this document. Also very important are studies of the natural history of disease, as well as evaluations of drug use patterns and patient characterization studies. The latter serve to inform both our understanding of safety endpoints and spontaneous reports. Natural history of disease and safety studies among users of available therapeutics should be initiated early during product development. Drug use and patient characterization studies should be initiated during the development phase of a new drug, based on the therapeutic class, and should continue after launch to further understand drug use in diverse populations and across various countries. Similarly, evaluations of endpoints among products in the therapeutic class, and within diverse populations are important. Targeted safety studies should be initiated shortly post-launch based on the specifications of the development program and the pharmacovigilance plan.

We suggest adding a section to the final guidance document that outlines the many types of observational data (e.g., SRS, claims database, medical record data, registry data, and survey data) that are commonly used for conducting pharmacovigilance or pharmacoepidemiologic research, discussing the pros and cons for different research needs.

Importance of Capturing Benefit

There is little information in the Concept Papers on benefit and how to capture benefit in light of risk. As this is ultimately the context against which we weigh the risk, we recommend consideration of some discussion of the type of benefit data (beyond clinical trial efficacy) that may be pertinent. *NB: This suggests that the rules for labeling of risk and benefit should be more equivalent than they are currently.*

Information Sharing re: Risk Assessment Projects

Collaboration between the FDA's epidemiologists and corporate epidemiologists in planning and executing studies would be welcomed particularly when FDA is initiating a study with an external data source. At a minimum, there should be a process established for alerting a company that a database study has been initiated.

Similarly, another aspect of information sharing is establishing a formal mechanism to communicate the findings or methods used by FDA and sponsors in addressing issues that may be applicable to other products. Often this type of communication is embargoed by publication or covered in the confidentiality between company and Agency, yet it is of great benefit in advancing the science or Risk Management and in expanding the Risk Management tool box.

Analytic Methods

ISPE believes there is still a great deal of work to be done in the development and refinement of analytic methods for evaluating safety signals as well as methods for risk assessment and risk management evaluation. ISPE is committed to working with the FDA and others such as the CERTS to further knowledge of the methodological and statistical techniques required.

Use of Epidemiologic Studies in Labeling

Will consideration be given to the impact of well-conducted observational studies (retrospective) entering the labeling in more formal fashion (i.e., leading to new indications, dosing regimens, adjunctives that may prevent an AE, e.g., adding an antihistamine to the pre-treatment regimen to reduce the likelihood of a hypersensitivity reaction)?

Comments on Specific Sections of the Concept Paper #3

II. C. Pharmacovigilance Plans

The definition of a pharmacovigilance plan proposed on page 3 is very narrow (i.e., gaining further information on safety signals). We urge review of a recent publication in *Pharmacoepidemiology and Drug Safety* (PDS 2003; 12: 17 – 29, A Model for the future conduct of pharmacovigilance, by Patrick C. Waller and Stephan J. W. Evans from the MCA) which outlines a pharmacovigilance plan which would extend safety knowledge in a much broader way, i.e., not only in relation to what is known or possible but what is not known (e.g., safety with particular population sub-groups) and proposing milestones at which safety knowledge could be considered to have been extended. Such a pharmacovigilance plan would be linked to (and behind) a "safety specification" - a document summarizing the extent of safety knowledge at authorization and being updated thereafter when the milestones are reached.

IV. B. Definition of a registry

The definition of a registry is still open to much debate among epidemiologists. Some consider a registry as an observational cohort study while others believe it is much less structured. Establishing a clear definition as well as criteria or standards for registries or registry studies will be important, and is an area where ISPE is interested in working with the FDA. For example, as with all observational epidemiologic studies, a protocol is an essential element – this is somewhat ambiguous in the FDA concept paper.

Section IV.A. Definition of pharmacoepidemiologic studies

We recommend that in section IV.A. pharmacoepidemiologic SAFETY studies are differentiated. For clarification purposes, please be aware that pharmacoepidemiologic studies are not limited to safety studies, but include all observational studies that describe the use and effects of pharmaceuticals in the real world setting. We also recommend that in section IV.A. the definition of pharmacoepidemiologic studies be expanded to include prospective data collection in addition to the already mentioned existing automated claims databases. In several sections of the concept paper, pharmacoepidemiologic studies seem to refer only to those studies conducted in databases. Further, the large simple study (LSS) outlined in Concept Paper #1, is directly applicable (and perhaps better suited) to postmarketing risk assessment. The LSS concept should be incorporated into the strategies outlined for pharmacovigilance.

IV. C. Surveys

We would also like to comment on the inclusion of surveys as risk assessment or risk management evaluation tools. Although many of the examples provided are cross-sectional designs, surveys can also be conducted as longitudinal cohort studies to evaluate changes in risk over time. In addition to epidemiologic expertise, it will be important to include members of other academic disciplines as well, such as social scientists who bring expertise in areas such as knowledge, attitude and behaviors surveys.

Section V. Safety Signals

The list of 5 examples of safety signals (lines 254 – 258) is very useful and probably covers most safety signals. However, we recommend that the general category of “other risk factors” (factors associated with the development of the adverse event of interest) be mentioned. Safety signals regarding specific subgroups of people (e.g., racial, genetic, specific co-morbidities) or ways in which the drug is used (e.g., dose escalation) may also be very important.

We would like to ask for clarification of Line 319. Point #8 regarding analyses of safety signals. (Analyses of the potential for an excess of adverse events given the disease being treated, such as might be observed in advanced cancer or immunocompromised patients) Is it intended to address analyses to identify the background risk of adverse events in the disease being treated ?

Line 352. Point #2 mentions the relative risk or odds ratios from pharmacoepidemiologic studies to be used to evaluate causality. Although risk ratios or odds ratios are the very frequently reported as measures of outcome frequency in pharmacoepidemiologic studies, please be aware that risk DIFFERENCES, not ratios, are best for evaluating the frequency in which a drug causes or contributes to an event. In the end the frequency with which an event occurs because of a drug, along with other characteristics of the event, must be weighed against the benefit of the drug. In addition Risk Management should consider the risk associate with any intervention designed to reduce the risk of a particular event, e.g., the potential reduction of benefit associated with the use of the therapeutic product.

V. D. Reporting of Safety Signals

Line 374. Paragraph D. appears to combine elements of 1) hypothesis generation signal detection, 2) providing for hypothesis testing, 3) placing the signal in perspective of the benefit of the drug and finally 4) risk management. The implication is that the sponsor would initiate all actions simultaneously. It would appear that the steps should be addressed in logical temporal fashion, and that all may not be necessary, depending on the results of the earlier steps.

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. The combined 1st International Conference on Therapeutic Risk Management and the 19th International Conference on Pharmacoepidemiology will be held August 21-24 in Philadelphia, PA.