INTERNATIONAL SOCIETY FOR PHARMACOEPIDEMIOLOGY

Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

By the
International Society for Pharmacoepidemiology (ISPE)
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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to offer our perspectives and suggestions, and submits for your consideration the following comments on the *Draft Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment.* We commend the Food and Drug Administration (FDA) for taking the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

ISPE acknowledges that this draft guidance is improved over the previous concept paper, particularly in providing definitions and processes. We are also pleased with the encouragement for collaboration between the FDA and the sponsor in planning and following pharmacovigilance and pharmacoepidemiology activities. However, in

addition, collaboration between the FDA's epidemiologists and corporate epidemiologists in planning and executing studies would be welcomed when FDA is initiating a study with an external data source. At 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 toolbox.

One area that requires further attention in this draft guidance is 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.*

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

Specific Comments

Section: III. The Role of Pharmacovigilance in Risk Management

Line(s)	Comment
115–123 (115-117) (121-123)	Two definitions of pharmacovigilance are offered, and have some inconsistencies: "Pharmacovigilance [is] all observational (nonrandomized) postapproval scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic safety studies." And "Pharmacovigilance principally involves the identification and evaluation of safety signals in reports suggesting an excess, compared to what would be expected, of adverse events associated with a product's use." The 1st definition is broad and includes pharmacoepidemiology studies while the 2nd definition is narrower and implies that pharmacovigilance involves review of (spontaneous?) reports. The 2nd is the more traditional definition. This is also consistent with the FDA comment in line 136 that "good

	pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports…" Another perspective is provided by the WHO definition of pharmacovigilance, which is being incorporated into the CIOMS VI document on clinical trial safety. This definition is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" – with drug-related problems being further defined as "issues that affect the safety and safe use of medicines." Further, pharmacovigilance activities may confirm the safety profile observed during development, or be used to characterize a better safety profile than a comparator product. That is, it should not be restricted to only signal detection. We suggest that the term pharmacovigilance be used consistently throughout the three documents. We believe that pharmacovigilance is not restricted to the marketed use of a product or to spontaneous reports. The term "signal" must also be defined. Otherwise, some may misinterpret the intention of a signal as establishing or even necessarily reflecting an association. There is an operational definition provided in the context of data mining (lines 327-328) but a general "all-purpose" definition is needed.
125-126	While we agree that a single case can in some circumstances be viewed as a signal, the term "occasionally" does not confer the rarity of this occurrence. We suggest a modification to "rarely".

Section: IV.A. Good Reporting Practice

Line(s)	Comment
148	FDA comments that queries to initial reporters focus on "clinically relevant" information associated with the product and the adverse event." We suggest that the emphasis be simply on clinical information as it can be very difficult to ascertain what is relevant early in the assessment process. Better to have too much information and sort through it as additional data come in. Having too little because something did not seem relevant at the time may prove a problem as assessment of the potential adverse event progresses. It must be acknowledged however that in some circumstances, such as receiving the initial AE report from a consumer/patient, it may be difficult to obtain any medical confirmation of the event from a health care provider.

Section: IV.B. Characteristics of a Good Case Report

Line(s)	Comment
168	It is important to note that concomitant products include OTC products, dietary supplements, and herbals. These are very important potential confounders that a high proportion of the US population considers "safe" despite their great potential for toxicity and interactions.

Section: IV.C. Developing a Case Series and Assessing Causality of Individual Reports

Line(s)	Comment
216	Add the word "potential" to ...case definitions be used to assess <u>potential</u> cases"
247	What is a "confounded case?" While it is true that "apparent lack of confounding could be due to incomplete data acquisition", it could also be true that an apparent lack of confounding is in fact a lack of confounding.

Section: IV.E. Use of Data Mining to Identify Product-event Combinations

Line(s)	Comment
316	As noted earlier, a definition of a signal is needed. As indicated later (in line 337) data mining is referred to as "exploratory" and (in lines 348-349) as hypothesis-generating. Data mining should NOT (as suggested in line 316) be used to make causal attributions. At best, data mining identifies <u>potential</u> reporting associations between drugs and events that <u>may</u> be worth further investigation.
319	We suggest avoiding the term rates in the context of spontaneous reports. If used, always specify as "reporting rates".

319-321	The explanation of deriving the reporting rates is unclear, and should read: ...comparison of the fraction of all events reported for particular products, which are for a specific event (e.g., liver failure), the "observed reporting rate", with the fraction of reports for all drugs that are for that same event... While the above description clarifies the calculation of a reporting rate, the text should also more strongly emphasize the limitations of this calculation. For instance, calculating a reporting rate using the entire safety database to derive an expected rate – a more appropriate expected rate is the AE profile of comparable chemical entities with similar indications, or at least all drugs with comparable indications to reduce the number of false positive signals due to the disease being treated or its known and expected complications.
325-331	Since we do not know the "truth" nor do we have a "gold standard" to use when performing data mining, use of terms such as sensitivity and specificity (as well as false positive, false negative, predictive value) are inappropriate in this situation. These terms have well accepted definitions in medical screening and the diagnostic world where "gold standards" exist. We cannot "optimize sensitivity and specificity" when we do not have a gold standard against which to compare the test (data mining) results. We must find different terminology to use in the context of data mining.
339-342	Differences in adverse event rates could be due to may other biases in addition to the ones mentioned here. These spontaneous report databases should not be used to make treatment comparisons, especially in publications.

Section: IV.F. Safety Signals that May Warrant Further Investigation

Line(s)	Comment
377-378	Although we realize that the examples provided in parentheses are not an exhaustive list, it would be informative to add "unapproved use" to the list.
380 -382	Re: item # 8 – it should be noted, however, that an increase in AE reports after implementation of a risk management plan will likely result from the increased health care practitioner and patient awareness, and this alone is not necessarily a signal that the plan is not working.

Section: IV.G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

Line(s)	Comment
394	"Time of exposure" is not accurate; one should state "time at risk", which may be completely different due to minimum time of exposure needed to become at risk, residual risk after interruption of treatment, and depletion of susceptibles effect (if an event did not occur within a given time period after treatment initiation, it will likely not occur; therefore to include all treatment period in the denominator will likely under-estimate the rate).

395-396 (396)	Since both over and under reporting are problems that hinder quantification of the numerator, we suggest re-wording to: ...it is not possible to quantify the total number of cases from spontaneous adverse event reports because of under-reporting and over-reporting (duplicate reports from separate sources) ... The term "exposed population" should be replaced with "population at risk"
395-414	This section indicates that both the estimate of the number of cases of AEs for a drug and the total number of patients exposed to the drug are unreliable. If so, then it is hard to understand why FDA recommends (lines 408-409) calculating crude event reporting rates. Given the deficiencies of the numerator and the denominator, it is hard to understand the value of the calculation. It is entirely possible that this calculation could become regarded, entirely incorrectly, as a number with meaning, and that actions could be taken as a result without any foundation. If a reporting rate is large enough to warrant further investigation, then it is worth undertaking a serious investigation using other data sources (and other methodologies) to provide a credible estimate of the incidence or absolute risk of the AE.
397	With regard to the reasons for limitations in denominator estimates, limitations in these estimates also depend on the data source and assumptions. For instance, the limitations using the IMS sales database are different from those using the National Disease Therapeutic Index (NDTI).
406	Suggest adding the word "specific" and modifying the sentence so it ends "...may not be available for the specific population of interest".
408-423	Reporting rates differ dramatically during the product lifecycle (e.g., Weber effect, temporal trends in reporting). We request that FDA clarify how these crude reporting rates will be used in the understanding of the risk benefit and how the variation in reporting rates over the product's life-cycle should be taken into account.
412	Selecting the unit for the reporting rates should be determined on a situation-by-situation basis. For chronic diseases, person-years are commonly used to describe exposures. For infectious diseases, number of prescriptions may be more appropriate. The DDD is a suggested standard unit by the WHO for assessing market penetration of a drug and for making comparisons between countries. In non-U.S. countries, the patient-level estimates are seldom available. We suggest that FDA not endorse a specific methodology and should ask the sponsor to provide the rationale for the use of a particular denominator estimate and how it was derived.
417-423	In addition to uncertainties in numerator and denominator, this section should also state that it is the differential under-reporting rate that greatly limits the comparisons across products.
431-434	Attention should be given in harmonization of diagnostic criteria since those used in spontaneous reports may be very different from those used to derive the background rate.
436-439	The statements regarding higher reporting rates indicating a high incidence rate could be misleading. A higher reporting rate compared to background rate could mean anything because of the low quality of spontaneous reports and the unreliability of the exposure estimates. The number of cases may be over-reported. Similarly, the estimate of the exposed population may be underestimated.

Section: V.A. Pharmacoepidemiologic Safety Studies

Line(s)	Comment
465	We strongly support the use of pharmacoepidemiologic "nonrandomized observational studies of patients in the real world" to characterize, clarify or validate safety signals for pre and/or post-marketed drug products. Pharmacoepidemiologic studies, however, may be either randomized (e.g., LSS) or non-randomized.
469-470	Pharmacoepidemiologic studies may be designed to study the natural history of disease or pattern of product use as indicated on line 477-478. They are not always designed to test hypotheses, and do not necessarily require a control group. Line 469 could be clarified as: "Unlike a case series, a pharmacoepidemiologic safety study designed to assess the risk attributed to an exposure has a protocol ..."
471	Insert the word "can" as indicated "Pharmacoepidemiologic studies can allow for estimation ..."
472	"Incidence" should be "incidence rate"
476	The Guidance states that there may be "rare" occasions when a pharmacoepidemiology study is launched prior to approval. However, studies on disease natural history and those for estimating the background rate of an adverse event could ideally be launched during the clinical development program, and therefore, we suggest that the word "rare" be deleted from this sentence.
489-491	This paragraph states that observational studies are more prone to confounding and effect modification and other bias and potentially more difficult to interpret than clinical trials. This is not always true as long as observational studies are designed, performed, and analyzed appropriately. Inappropriate randomization or long term duration in clinical trials will result in serious bias. In addition, there are methods to adjust for confounders, effect modifiers and other biases in observational studies. As noted above, it is important to be aware of the strengths and limitations of clinical trials as well as those of observational studies.
492-493	It is not correct that a study large enough to detect small differences in risk surmounts issues of bias. In fact, these issues are most prominent with large studies and small effects, because such effects, while statistically stable, can be entirely accounted for by bias. This is a frequent misconception that should be clarified.
504	A further clarification can be added that these studies can be etiological (when compared to unexposed) or comparative (compared to another product or class prescribed for the same indication)
509	"Because of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results." Clinical trials, in particular long-term studies, are also subject to an array of biases that can lead to difficult to interpret results. Our proposal is to delete the statement or, as noted earlier, include a statement about the limitations of clinical trials.
530	Note that not all automated databases are based on claims. FDA should provide guidance on the use of non-US automated databases, which are increasingly available.
537-551 537	Another factor that might affect the choice of a database is access to patients (e.g., to obtain retrospective or prospective data not available in the electronic database). Point # 1 can be further clarified as "versus target population of the study"

548-549	Add to # 6 "or availability of procedures codes or prescriptions that could be used as markers for occurrence of the adverse event".
553	We support the statement on the high desirability of validation in automated database studies. Special circumstances, such as medical data privacy legislation, can however prevent these efforts.

Section:IV.B. Registries

Line(s)	Comment
562-599	This section should include statements re: the possible biases of voluntary registries, as opposed to registries that attempt to include all relevant subjects (or a scientifically selected sample). While voluntary registries may often be the only feasible approach, it is particularly important to refer to this limitation since it is tempting to cut costs by not having a rigorous recruitment mechanism.
580	A third point should be added: that a registry is especially useful when there is a lot of switching between health care providers ("doctor hopping") because ascertainment and data collection are done through the patients.

Section: VI. Interpreting Safety Signals: from Signal to Potential Safety Risk

Line(s)	Comment
654-663	Clarify # 1 with "Spontaneously reported and published case reports, ideally with denominator information to aid interpretation" Add as # 6: "Background rates in general and specific patient population, if available"
674	The example of temporal association is not a measure of strength, and should be listed as a separate factor.

Section: VII. Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan

Line(s)	Comment
699-	In addition to the list, FDA should provide guidance regarding ICH proposed situations to prepare a PVP. The title and the text under the section "Beyond routine pharmacovigilance: Developing a pharmacovigilance plan" indicate that a PVP should be developed if "routine pharmacovigilance" is not sufficient. Specifically, the PVP will only be developed when unusual safety signals have been identified, either before or after approval. This does not seem to be in line with draft ICH E2E. On section 1.3 (Scope) the ICH document states: "For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan". ICH E2E requires sponsors to summarize the identified risks of any drug, the potential for important unidentified risks, the populations potentially at risk and "situations" that have not been adequately studied in a section titled: PV specification". The PVP (section 3 of ICH E2E) is then based on the PV specification and describes the risk minimization steps to be taken based on the findings described in the specification. According to currently available draft

	documents, the scope, goal, process and document structure and content strongly differ between ICH and FDA recommendations. The scope in this guidance seems restricted versus ICH, and could be interpreted in the extreme as the "background" section of a RiskMAP. We propose to harmonize this section of the guidance with the ICH proposal to avoid conflicting requests across regulatory regions. By harmonizing this section with ICH, further detail, e.g., an outline or structure, for a Pharmacovigilance Plan could be included, such as that seen for the RiskMAP.
756-761	It is unclear what is meant by "Adverse event collection mechanisms include electronic health information systems ..." Is the intent that these electronic systems are useful for generating spontaneous reports, or that they may be useful for conducting pharmacoepidemiologic studies?
763-764	As noted in other sections of the document, pharmacoepidemiologic safety studies can be conducted in many ways. Therefore, there is no need to highlight the specific example of database studies.

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.