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July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0189: Draft Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (69 Federal Register 25130; May 5, 2004)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invested over \$32 billion during 2003 in the discovery and development of new medicines.

Members of PhRMA share a mutual interest with FDA in bringing safer and more effective products to the market as rapidly as possible, and we embrace the importance of minimizing the occurrence of avoidable adverse events. Bringing a new drug to the market requires considerable commitment of time and resources. In order for industry to appropriately design and execute efficient drug development programs, it is important that the Agency ensure that its policies and expectations are transparent to all stakeholders, and that the standards are consistently applied. The three draft guidance documents on pre-marketing risk assessment, development and use of Risk Minimization Action Plans (RiskMAPs), and good pharmacovigilance practices represent significant progress towards these goals. When finalized, the three guidance documents will provide a good framework for the Agency and industry in their risk management efforts. PhRMA appreciates the opportunity to provide comments on the draft guidance documents.

PhRMA member companies are pleased to see that the Agency has significantly revised the guidance documents to incorporate the public input on the risk management concept papers that were published last year (68 Federal Register 11120; March 7, 2003). We strongly support the development of concept papers and recommend that this approach be utilized routinely for development of major guidance documents that may precipitate extensive comments from interested parties. PhRMA agrees with and supports most of the concepts outlined in the draft guidance documents, particularly the over-arching philosophy that the ultimate goal of risk management is to ensure that risk management efforts are directed to effective processes that achieve a positive benefit/risk balance for patients. PhRMA is pleased to see increased reference to the balance between benefits and risks throughout the documents, as well as acknowledgment that RiskMAPs should be used judiciously, so as not to interfere with the delivery of benefit to the patient. This concept should also apply to pre-marketing risk assessment and post-marketing pharmacovigilance activities. Any activity beyond current

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regulatory requirements should be carefully assessed to ensure that it will provide meaningful benefit relevant to the patient population at risk, and not delay or hinder patient access to new effective therapy.

PhRMA is also encouraged to see that FDA has incorporated into all three draft guidance documents the concept that a number of different stakeholders must collaborate with industry and the Agency in risk management activities if significant improvement in the overall benefit/risk balance is to be achieved.

Since many of PhRMA's members are multinational companies, we also applaud the Agency's efforts to conform with internationally harmonized definitions and standards as much as possible. FDA guidance documents should be aligned with the approach developed by ICH and CIOMS to ensure that risk management can be a global process, as is appropriate for global products. The basic structure of risk management documents should be similar globally to allow use of the same document for all countries whenever possible. This increases the transparency and consistency of implementation of agreed post-marketing commitments. It would be useful for FDA to highlight in the guidance documents the important differences from ICH and EU guidance documents, the rationale for these differences, and the steps being taken to harmonize the differences. We believe that a global approach to pharmacovigilance and risk management is extremely important, and we strongly encourage FDA to harmonize with international consensus initiatives.

During public presentations regarding the risk management concept papers, FDA representatives have noted a diversity of information about post-marketing risk management activities that sponsors have included in marketing applications in response to new expectations derived from the FDA PDUFA 3 performance goals. We agree with the Agency's emphasis on those few instances when, due to a serious issue, a RiskMAP is warranted. However, we believe that the Agency's expectations pertinent to the majority of marketing applications, which do not require a proposed RiskMAP, should also be addressed.

While PhRMA supports most of the concepts outlined in the draft guidance documents, we are concerned that there could be a negative impact on the development of new and innovative medicines as an unintended consequence if certain concepts are applied in an inappropriate manner. Examples of such unintended consequences include requirements for pre-approval large simple safety studies that delay availability of new drug products, and RiskMAP programs that unintentionally prevent patient access to beneficial products. Indeed, burdensome RiskMAP requirements could steer patients to older products with a less favorable benefit/risk profile than one with a RiskMAP. It is critical that the FDA establishes clear transparency and consistency in the selection of products and circumstances for which additional risk assessment and risk minimization activities are requested, to ensure that patient access to new effective therapy is not jeopardized. We note that FDA's recently issued position paper "Innovation or Stagnation - Challenge and Opportunity on the Critical Path to New Medical Products" (March 2004) highlights the increase in complexity and inefficiency of the clinical development process as a major challenge for making new medicinal products available to the public. Industry and the Agency need to work together to ensure that these risk management initiatives do not add to that complexity and inefficiency.

Comments that are specific to the Draft Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment are attached. Our comments on the other two draft guidance documents are submitted separately to the respective dockets.

We thank FDA for the opportunity to comment on this important topic. Please do not hesitate to contact me if any of the issues presented herein require clarification. PhRMA member companies look forward to continued dialog as the Agency proceeds with this significant initiative.

Sincerely,

A handwritten signature in black ink, appearing to read "Alan Feldman". The signature is fluid and cursive, with a long horizontal flourish extending to the right.

**PhRMA Comments on FDA Draft Guidance for Industry: Good Pharmacovigilance
Practices and Pharmacoepidemiologic Assessment
Docket No. 2004D-0189**

July 6, 2004

General Comments

PhRMA member companies commend FDA for the significant improvements in the draft guidance over the previous concept paper, particularly with regard to the clear descriptions of the components involved in identifying and describing potential safety signals.

PhRMA member companies agree with FDA that it is not possible to detect all safety concerns during clinical trials and that post-approval safety data collection and risk assessment is vital to ensure that patients are able to take our drugs safely. We are pleased to see that the FDA supports the concept that for most products routine pharmacovigilance and FDA-approved professional labeling are sufficient for post-marketing risk assessment and risk minimization. In addition, we strongly agree with the Agency that dialog and collaboration between the Agency and sponsor in the planning and follow-up of pharmacovigilance and pharmacoepidemiology activities is an essential component of understanding and managing the risks associated with medicines.

Although there are a number of aspects of the draft guidance that are improved over the concept paper, there are several broad topics of concern to industry that we feel are not adequately addressed in the draft guidance. These are described below, followed by our comments on specific sections of the draft document.

Definitions

Pharmacovigilance: While there is a fairly broad definition of pharmacovigilance in the draft guidance (line 115), PhRMA is concerned that it is not fully harmonized with the definition of pharmacovigilance contained in the ICH E2E draft guidance on Pharmacovigilance Planning. That document uses the WHO definition, "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem." A major difference between these two definitions is that the FDA definition is specific to post-approval activities, whereas the ICH/WHO definition does not include this limitation. In addition, although both the FDA definition and the ICH/WHO definition encompass pharmacoepidemiologic studies, the FDA definition limits this to pharmacoepidemiologic *safety* studies, while the ICH/WHO definition does not. As noted in our more detailed comments below, pharmacoepidemiologic studies can be used both pre- and post-approval to examine many aspects other than safety, including patient characteristics, patterns of drug use, and the natural history of disease. PhRMA strongly recommends that FDA adopt the internationally accepted definition of pharmacovigilance in this guidance document, and that the term be used consistently throughout the document.

Signal: PhRMA suggests that FDA include a definition of "signal" in the guidance document, as this term is used frequently throughout the draft document, with apparently different meanings. For example, in line 121, there is an implied definition that a signal is "an excess...of adverse events associated with a product's use", but there is also a wide-ranging list of "safety signals that warrant further investigation" (lines 361-384) which are potentially more substantial than just a simple excess of events. The Data Mining section defines a "signal" as "any product-event combination with a score exceeding the specified threshold" (line 327). To further add to the confusion, the FDA appears to envision a sequence of "signal to potential safety risk to safety risk". Since applicants will be asked to do quite a bit of investigation based on "signals" it is critical that the Agency and applicants have a clear definition of the term "signal" stated and that it

be used consistently throughout the final guidance. PhRMA member companies would be happy to work with FDA to develop an appropriate definition.

Data Mining and Signal Detection

Data mining techniques offer an important tool in the armamentarium for post-marketing product surveillance. However, the application of these techniques is evolving. Although data mining may increase the potential for earlier identification of rare events, the methodology must be used with care. Limitations of the underlying data and data mining techniques must be fully appreciated to avoid false positive causality conclusions. PhRMA recommends that the Agency take care with regard to describing data mining activities in the guidance document, so that it is clear that use of data mining techniques is not a mandatory or expected part of signal identification/evaluation.

While data mining methods are promising supplements to the pharmacovigilance “toolkit,” the systematic performance characteristics of these techniques have not been established and, in particular, the incremental utility they provide when used as one component of a rigorous and comprehensive pharmacovigilance program remains to be established. At this time, if an organization is contemplating the use of one or more of the available data mining algorithms, they should carefully consider the aforementioned limitations; a data mining algorithm should be considered only as a potential supplement to, and not a substitute for, traditional or standard methods of signal detection that utilize clinical and pharmacological judgment and/or decision trees. PhRMA also recommends that FDA clarify that data mining is not a technique that can be used to make causal attributions between products and adverse events.

The document could also be enhanced with the addition of guidance on the use of traditional methods of signal detection, such as the use of cumulative number of cases, increased frequency of reports over time (simple trend analysis) or a single report (or a few reports) of a pre-defined critical medical event.

Pharmacovigilance Plans versus Risk Minimization Action Plans (RiskMAPs) and International Harmonization

PhRMA believes that a global approach to pharmacovigilance and risk management is very important, and we strongly encourage FDA to harmonize with international consensus initiatives. This is especially important when the same term is used to refer to things that are actually different. For example, this document and the ICH E2E draft guidance on Pharmacovigilance Planning both describe a “Pharmacovigilance Plan” (PVP). However, the FDA document (line 699) indicates 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 the ICH E2E document, which states: “For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan.”

Since both the ICH E2E document and the FDA guidance document are in draft, PhRMA strongly urges FDA, as a member of ICH and the E2E Expert Working Group, to harmonize the terminology used in these documents. The final FDA guidance document should incorporate the terminology and definitions agreed to in the final ICH E2E guidance document.

It would also be useful if an explicit cross-reference to the ICH E2E Guidance on Pharmacovigilance Planning was included in Section VII, Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan. This would help clarify how the requirements of the ICH guidance document could be incorporated into a RiskMAP when a RiskMAP is needed, and how a Pharmacovigilance Plan could be developed and submitted in the absence of a RiskMAP.

Individual Benefit-Risk Decisions

The draft guidance addresses population risks; however, benefit-risk tradeoffs for individuals should also be addressed. Individual benefit-risk trade-offs are an important consideration in the management of risk. The issue is more than simply a minimization of risks for the fixed benefits of the population at risk; many sub-groups and individuals may be willing to accept more risk for benefit, depending on personal preferences, life-style choices, disease, stage of disease, or aggressiveness of the progression of the disease.

Specific Comments

Section: III. The Role of Pharmacovigilance in Risk Management

Line(s)	Comment
115-118	As stated in our introductory remarks, the definition of pharmacovigilance is not consistent with that proposed in ICH E2E document. While FDA may choose to focus this guidance document on the post-approval period of development, it is not necessary to introduce a new definition. Since FDA is a partner to ICH and a member of the E2E Expert Working Group, we recommend that FDA use definitions that have been agreed to internationally. PhRMA proposes the following revision to this paragraph: "Pharmacovigilance (provide reference to ICH E2E) is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem. This definition encompasses the use of pharmacoepidemiological studies. For the purposes of this guidance document, we will focus the discussion on the post-approval period of development."
119-120	The goal of pharmacovigilance activities is not to prevent adverse events, but rather to gain additional insight through the gathering of information, which may be helpful to the goal of safe drug use and risk minimization. PhRMA recommends modifying this sentence to read: "These activities are undertaken with the goal of identifying these events and understanding to the extent possible, their nature, frequency, and potential risk factors. This information is critical to the goal of minimization and/or prevention of adverse events."

Section: IV.A. Good Reporting Practice

Line(s)	Comment
145-147	FDA recommends that sponsors make every attempt to obtain complete information during initial contacts and subsequent follow-up, and encourages sponsors to use trained health care practitioners to query the initial reporters. PhRMA suggests that this sentence be clarified to indicate that it applies to serious cases only (as outlined in the March 2003 proposed safety reporting regulations). We also suggest that the word "reasonable" be inserted into line 146, so that this sentence reads: "...make every reasonable attempt...".

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

Line(s)	Comment
180	PhRMA suggests adding the word "relevant", so that this point reads: "Relevant therapeutic measures..."
188-205	The reporting of medication errors and the use of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy tool implies that there are specific regulatory reporting requirements for medication errors. To

	<p>date the most specific guidance from the Agency regarding medication error reporting was in the March 2003 proposed safety reporting regulations (the "Safety Tome"). Since it is highly unlikely that final regulations regarding medication error reporting will be issued before this guidance document is finalized, we suggest that this section be revised to conform with the current regulations, which require reporting of medication errors only when they also involve an adverse event. We also suggest that the information in lines 196-199 be deleted, as medication errors caused by work environment and personnel are outside of the control of the pharmaceutical industry.</p>
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Section: IV.C. Developing a Case Series and Assessing Causality of Individual Case Reports

Line(s)	Comment
243	The use of the term "confounding" in this context may lead to confusion with the epidemiological definition of confounding. We recommend revising the bullet to read: "Absence of an alternative explanation (e.g., no concomitant medications that could cause or contribute to the event; no co- or pre-morbid existing medical conditions)."
255-257	The draft guidance states that "rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with long-term follow-up, are usually needed to assess causality..." Although case-control studies could be employed to examine the association between a drug and an adverse event, or to identify risk factors for an adverse event, they cannot be used to determine causality. PhRMA recommends that the document be revised to clarify this statement.
252-271	The text affirms that for an individual case report, it is rarely possible to assess causality with a "high level of certainty" and that there are "no internationally agreed upon standards or criteria for assessing causality". Further it states that the FDA does not recommend any specific categorization of causality, and that "if a causality assessment is undertaken,...causal categories are specified". From these statements, it would appear that individual case causality assessments are not required, which is a concept we support. However, several places in the draft guidance appear to make individual case causality assessments mandatory, including line 283 ("After individual cases are assessed for causality...") and line 636 ("...FDA recommends...assess product relatedness at the case level..."). Individual spontaneous reports cannot truly be assessed for causality; overall trends should be evaluated in aggregate form and hypotheses formed and tested based on the aggregate data. PhRMA recommends that any expectation or requirement for individual case level assessment of causality be deleted from the guidance document.
273-279	PhRMA suggests that root cause analysis of medication errors by sponsors/applicants be limited to those causes over which the sponsor/applicant has control (e.g., brand name, labeling and packaging).

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

Line(s)	Comment
313	The statement that data mining methods can be used to provide information on the "characteristics" of a signal is imprecise and could be interpreted to mean that these methods can be used for signal evaluation in addition to signal detection. PhRMA suggests that FDA clarify this sentence.
316-317	Data mining is NOT a technique that can be used to make causal attributions between products and adverse events. As stated in the sentence preceding line 316, data mining may be able to identify unusual or unexpected product-event

	<p>combinations warranting further investigations. The purpose of data mining techniques is to analyze whether a drug-event combination occurs disproportionately more than expected based on statistical modeling. Data mining is a signal-generating tool, not a technique for attributing causality. Please delete the sentence in line 316-317, which appears to have evolved from a statement that data mining is but one method of signal detection. We suggest that the sentence in line 316-317 be replaced with the following: "Historically, identifying potential drug-event associations of interest has utilized a variety of judgments, rules, and/or decision trees based on sound clinical/pharmacological judgment. Data mining is an additional technique that may have value as a supplement to, but not as a substitute for, existing signal detection strategies."</p>
319-320	<p>PhRMA suggests that the term "rate" should be avoided in the context of spontaneous reports, since it may lead to confusion with the epidemiologic definition of rate (i.e., quantification of the frequency of an event in a population per unit of time). If used, it should be specified as "reporting rates" (e.g., "observed reporting rate", "expected reporting rate").</p> <p>In addition, there seems to be a lack of consistency in the use of the terms "events" and "reports". The document describes comparing "the fraction of all events reported for a particular product...with the fraction of reports for all drugs that are for the same event". In this context, it should be clearly defined whether the unit of analysis is events or reports (individual cases).</p>
321	PhRMA suggests that the word "corrected" be changed to "stratified".
325-353	<p>The statistical validity of the available data mining tools has not yet been established. The draft guidance document makes reference to thresholds, sensitivity and specificity; this is overstating the capabilities of these tools at the current time. Moreover, terms such as "true effect" and "false positive" imply that there is an accepted standard against which to make a comparison. There still exists a great deal of uncertainty about the predictive value, sensitivity, and specificity of data mining tools, and additional developmental work is needed.</p>
329	PhRMA suggests revising this to read "...potential signals..."
333	<p>The draft guidance states that several data mining methods are worth considering. We suggest that it is still debatable whether data mining is worth considering, due to false positive, false negative, limitations of the data, and lack of gold standard.</p>
335-336	<p>The full name and reference for the Bayesian method is "Bayesian Confidence Propagation Neural Network" (BCPNN) (Bate, 1998). We are unaware of any statistical proof that the cut-off point for "small" is 20, and recommend that the Agency include a reference show that, empirically, small means less than 20.</p>
337	PhRMA suggests that "adverse events" be modified to "adverse event reporting" or the equivalent, so that this sentence reads: "...may provide insights into the patterns of adverse events reported for a given product..."
340-342	PhRMA suggests also adding co-morbidities and numerous potential unmeasured/unrecorded confounders as potential biases. We believe that just noting the underlying disease and concomitant medication underestimates/underemphasizes the problems and limitations that are inherent to voluntary reporting systems.
344-347	<p>In describing the limitation of AERs/VAERS data, FDA should also take into consideration the other major types of databases that may be used to conduct data mining exercises: corporate databases and the WHO database. Each of these data sources has its own limitations.</p>
347-349	PhRMA is pleased to see that the FDA regards "signals" generated by data mining as hypothesis-generating only. We suggest modification of the statement on

	considering signals that exceed a specified threshold to reflect that this can apply to both traditional methods and computational algorithms.
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Section: IV.F. Safety Signals that May Warrant Further Investigation

Line(s)	Comment
361	PhRMA suggests changing the word “typically” to “may”, so that this sentence begins: “Safety signals that may warrant further investigation...”
368	PhRMA requests that FDA provide clarification on the definition of “more than a small number of serious events thought to be extremely rare”. In addition, PhRMA recommends that the words “in the untreated population” be added to end of the statement to read as follows: 3. More than a small number of serious events thought to be extremely rare in untreated population.
375	FDA seems to be inserting the idea of “potential” medication errors into this guidance document as a consideration of a “safety signal that may warrant further investigation”. This is not an accepted term, nor is a guidance document the appropriate place to attempt to effect changes in existing regulatory requirements. We request that any mention of potential medication errors be deleted from the guidance document unless and until this concept is codified into regulation.

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

Line(s)	Comment
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	PhRMA suggests adding the word “specific” so that the sentence ends “...are not available for the specific population of interest”.
408-423	Reporting rates differ dramatically during the product lifecycle. We request that FDA clarify how these crude reporting rates will be used in the assessment of the benefit to risk balance and how the variation in reporting rates over the product’s life-cycle should be taken into account.
410-412	PhRMA is confused by the requirement to include only US cases and US exposure data in the analyses. Does this preclude an FDA interest in analyses involving global data? Applicants frequently perform their analyses of safety using fully integrated global datasets. Performing region-specific analyses will add a layer of complexity to these analyses and open up the possibility for having discrepant results. Selective reporting of region-specific analyses also adds a layer of complexity to the preparation of regulatory reports and opens the possibility of different regulatory agencies receiving differing views of the safety of a product. In addition, it is often not feasible to provide an estimate of national patient exposure. We do not routinely have access to patient-level data; the best we have is prescription data. PhRMA suggests that the guidance document incorporate the same guidance for estimating exposure as outlined in the CIOMS V document, namely: <ul style="list-style-type: none"> • total quantity sold (e.g., kg, liters) • number of packages sold (e.g., boxes, bottles) • number of units sold (e.g. tablets, vials) • number of prescriptions or treatments

	<ul style="list-style-type: none"> • number of patients • person-time: treatment-months, person-months, person-years (incidence density) • Defined Daily Dose (DDD). <p>Selecting the unit for the reporting rates should be determined on a case-by-case basis. For chronic diseases, person-years are commonly used to describe exposures. For infectious diseases, the 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.</p>
417-418	Factors that may influence reporting in certain time periods also need to be taken into account (e.g., an increase in reports of a certain adverse event following publicity about that event, spikes in reports of flu-like symptoms during certain seasons, etc.). Due to these factors, analysis of temporal trends may also be useful in interpretation of the data. As the text is currently written, calculation of only total reporting rates is suggested, and there is no consideration given to the relevance of temporal trends analysis. We suggest that lines 417 and 418 be revised to read: "Comparisons of reporting rates and their temporal trends can be valuable,"
417-423	The inadvisability of using information from spontaneous reporting systems for comparisons of drugs needs to be stated more strongly. Comparisons of drugs or drug classes based solely on data mining computations carried out using data from these databases may be scientifically invalid and should be performed and interpreted with extreme caution. It is strongly recommended that signals detected with these methods be followed up with additional analyses.
436-439	The statements that higher reporting rates may indicate a high incidence rate, and therefore a strong indicator of concern, 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 number of population exposed may be underestimated.

Section: V. Beyond Case Review: Investigating a Signal Through Observational Studies

Line(s)	Comment
449-451	This paragraph notes that signals that may warrant additional investigation can be further evaluated through carefully designed observational studies. In addition, use of observational studies should be generally considered when they can shed light on the emerging safety profile of novel molecular entities, new indications, etc., and the signals that are being investigated, as long as the studies are methodologically valid and logistically feasible. The application of observational studies goes beyond the evaluation of drug exposure, i.e., safety event endpoint associations, and may include natural history of disease, as well as patient characterizations and drug utilization studies. Many US-based automated health databases are claims-based. In addition, existing and new international data sources that are based on healthcare data are becoming increasingly available for use in observational studies.

Section: V.A. Pharmacoepidemiologic Safety Studies

Line(s)	Comment
465	PhRMA strongly supports 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. However, the regulatory reporting of adverse events reported in these types of studies,

	specifically, expedited and/or periodic adverse event reporting, is unclear. The draft ICH E2D and Safety Tome, and CIOMS V documents seem to imply that any organized attempt to collect data in the post-marketing environment should be categorized as “solicited data”. PhRMA interprets this to mean that data from pharmacoepidemiologic studies would be categorized as solicited, and would be reported in accord with the post-marketing regulations for expedited and periodic study reporting. PhRMA requests clarification regarding whether these data should also be included in an IND Annual Report. In addition, regardless of how these data are reported, we request clarification regarding whether they should be segregated from mainstream pre- and post-marketing periodic reports.
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.
476	The guidance document states that there may be “rare” occasions when a pharmacoepidemiology study is launched prior to approval. However, sponsors may elect to conduct studies on disease natural history during the clinical development program, and therefore, we suggest that the word “rare” be deleted from this sentence.
481-491	Although PhRMA agrees that pharmacoepidemiologic safety studies offer advantages over controlled trials when assessing uncommon or delayed adverse events, in the setting of a very rare event, pharmacoepidemiology studies also have limitations and may not have the power to detect differences in rates. It is also important to understand that such studies do not provide early signal detection or real time data. It typically takes years of observational research to confirm or refute a potential signal.
485-487	PhRMA suggests deleting the words “where the main difficulty is that they”, so that this sentence reads “On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients...”
489-493	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 in clinical trials will also result in serious bias. In addition, there are methods to adjust for confounders, effect modifiers and other bias in observational studies. As noted above, it is important to be aware of the strengths and limitations of observational studies as well as those of clinical trials.
511	While PhRMA agrees that it is desirable to conduct more than one study, this is frequently not feasible. In the setting of a rare or very rare event, and the need for medical records to validate the data, there are often very limited options for conducting even a single safety study. Therefore, PhRMA recommends the addition of a statement such as: “However, in the case of pharmacoepidemiologic studies of rare events, more than one study may not be feasible” to the end of the paragraph (line 513).
526	Not all studies are hypothesis driven, and thus, may not need power calculations.
527	The method for data collection and management should be provided only when it is an <i>ad hoc</i> study for data collection.
530-551	It would be helpful if FDA also acknowledged and provided guidance on the use of non-US automated databases, which are increasingly available. Further, since the use of automated databases will not be feasible for studying all safety risks, the Agency should provide guidance on primary data collection methods, including the use of publicly- or privately-funded cohort studies already collecting data in the US

	and Europe (e.g., NHANES, EuroSCAR).
553	PhRMA supports the statement on the high desirability of validation in automated database studies, although it should be noted that circumstances such as medical data privacy legislation may significantly inhibit these efforts.

Section: V.B. Registries

Line(s)	Comment
Footnotes 14 and 15	Reference 14 should probably be "ibid", rather than "Id". Reference 15 appears to be the same as reference 12.
564-569	The definition given for a registry is not quite clear enough to always be able to distinguish an observational study from a registry. It appears that an observational study always has a control group and a well-defined hypothesis, whereas a registry has only treated patients and an objective, but no <i>a priori</i> hypothesis. There are studies that fall in the middle ground between these two. For example, several companies have launched successful studies of growth hormone use that had no single well-defined hypothesis at the time of launch. Some of these include untreated patients. These studies/registries have been used to help answer questions as they arise. This document does not appear to include a description of this kind of study. Does this mean that they should not be performed, or should the definition of registry or observational study be modified? The CIOMS V Working Group recommended that the term "registry" be reserved for inventories of case information collected without an <i>a priori</i> research hypothesis, but held in reserve for future possible study and analysis. If this recommendation were included in the definition of registry, it would help to clarify the difference between a registry and an observational study.
571-572	The term "follow-up" in this sentence could be misunderstood to mean that follow-up information could be sought through the creation of registries. PhRMA suggests that the term "follow-up" be replaced with either "specifically address" or "evaluate".

Section: V.C. Surveys

Line(s)	Comment
625-626	This sentence recommends "...validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers". It does not make sense to do validation for many surveys. For example, how could one validate a survey for patient knowledge of label, sound-alike or look-alike trade names, etc?

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

Line(s)	Comment
637	As noted in our comments regarding case level causality assessment above (lines 252-271), we do not believe that this should be a requirement. Given the inadequacy of spontaneous report data, application of causality algorithms to a single case is fraught with misinterpretation. The ability to rule out the likelihood that the suspect drug may have contributed to an adverse experience, in most instances, becomes impossible. Therefore, most adverse experiences at the individual case report level end up with a possible association. With the exception of cases involving a positive rechallenge, there is little or no advantage in performing causality assessment on individual case reports. In addition, lack of consistency among experts in the evaluation of causality assessment for individual cases strains the already limited resources. Although a series of cases may be used to generate hypotheses concerning the association between an adverse

	experience and drug exposure, there is no methodology determined to date that is reliable and reproducible for individual causality assessment. Thus, causality assessment at the individual case level is open to a high likelihood of misinterpretation.
645	PhRMA suggests that the word "relevant" be inserted into this sentence, so that it reads: "...submit a synthesis of all relevant available safety information..."
648-697	It should be acknowledged that for extremely rare events, (e.g., osteosarcoma), assessing causality could be very difficult. Rigorous study designs, like a case-control study, and long term follow up may be needed to adequately assess causality. Guidance on the decision tree should also be provided, describing what to do if 1, 2, or 3 cases of these very rare events are reported.
654-663	PhRMA suggests that the following be added to the list of information that could be evaluated to assess the degree of causality between use of a product and an adverse event: "Background rates in general and specific patient population, if available;"
667	This section appears to indicate that further investigation of the signal through additional studies is always required. This may not be the case in every situation (e.g., it might be sufficient to change the product's label). PhRMA suggests that the document be revised to clarify this point.
669-672	PhRMA proposes that the guidance state that once FDA has completed its own assessment of the potential safety risk, it will share its conclusions with the sponsor/applicant.
673-690	Most of the factors listed here are also known as the Bradford Hill criteria for causality. However, as Bradford Hill himself pointed out "None of these viewpoints can bring indisputable evidence for or against a cause and effect hypothesis... What they can do, with greater or less strength, is to help answer the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" So in other words, these factors should not be used too rigidly.

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

Line(s)	Comment
699-741	The draft guidance states that pharmacovigilance plans may be appropriate for products that have "safety signals" identified pre- or post-approval. Again, the use of the term "signal" is confusing here and perhaps it would be clearer to use the term "safety risk" instead of "safety signal".
718	The statement regarding the frequency with which the event occurs is vague and requires clarification. "Frequency" means the number of cases. PhRMA suggests that the word "frequency" be changed to "incidence," which takes into account the number of population at risk (denominator)."
739-742	PhRMA has several concerns regarding the three criteria for pharmacovigilance plans. With regard to the first criteria, it would be a rare product for which NO safety signals were identified pre- or post-approval. Since the three factors are linked by "or", the implication is that unless a product has no identified safety signals, a pharmacovigilance plan may be appropriate. In addition, it is not clear how the third category (other significant safety concerns exist) differs from the first category (safety signals have been identified pre- or post-approval). Again this may be due to the confusion around the definition of safety signal. We recommend adding the word "serious" or "significant" to the first criteria, and deleting the third criteria, so that the sentence reads: "On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious [or significant] safety signals

	have been identified pre-or post-approval, or (2) at-risk populations have not been adequately studied.”
748	PhRMA suggests that this be revised to state: “Submission of specific serious expected adverse event reports in an expedited manner beyond routine required reporting”, as serious unexpected adverse events are routinely submitted as expedited reports.
756-761	PhRMA recommends that the document include a definition of “active surveillance”. It is unclear how the databases mentioned in this section may provide active surveillance.