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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 00N-1484; 21 CFR Parts 310, 312, 314, 320, 600, 601, and 606 –
Safety Reporting Requirements for Human Drug and Biological Products;
Proposed Rule; 68 Federal Register 12405

Dear Sir/Madam:

The enclosed comments on the above Proposed Rule are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). 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. In 2002, our members invested over \$32 billion in the discovery and development of new medicines.

PhRMA welcomes the opportunity to present its views on these proposed new requirements for safety reporting. As FDA is keenly aware, the safety of human drug and biological products is of paramount interest to PhRMA member companies. Significant resources are spent in assessing both pre- and post-market safety issues. As FDA can see in the detailed comments, PhRMA has significant reservations about a number of sections in this proposed rule.

PhRMA hopes that these comments are useful to the Agency as it moves forward towards a final rule. Please do not hesitate to contact me if there are any questions on any of these comments.

Sincerely,

Pharmaceutical Research and Manufacturers of America

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**Comments of the Pharmaceutical Research and
Manufacturers of America (PhRMA)**

**Docket No. 00N-1484; 21 CFR Parts 310, 312, 314, 320, 600, 601, and
606 – Safety Reporting Requirements for Human Drug and Biological
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EXECUTIVE SUMMARY

FDA has clearly dedicated extensive thought and effort in preparing its proposed comprehensive Rule covering many aspects of safety surveillance and pharmacovigilance for both pre-approval and post-approval conditions. PhRMA is in full agreement with the Agency's stated aims and purposes of the Rule:

- "To eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions."
- "More effective and efficient safety reporting to regulatory authorities worldwide."
- "Simplification, clarification, and harmonization of certain drug safety practices."

PhRMA member companies welcome many of the Agency's innovations and are pleased to acknowledge its strong support of many key aspects of the proposed Rule, among them:

- the stated objective of harmonizing pharmacovigilance principles and practices, not only internationally but within the FDA as well
- elimination of duplicative reporting of safety-related information in annual reports for NDAs and BLAs
- FDA's endorsement of ICH Guideline E2C on PSURs to replace NDA periodic reports for new products, including adoption of the International Birth Date and data lock point concepts
- use of MedDRA as the standard coding terminology for classifying medical terms in ADR reports
- elimination of expedited reporting on cases from class action law suits
- establishment of the minimum data set, and requiring only the minimum data set for non-serious SADR

PhRMA also supports the FDA's proposed risk-based approach for safety reporting that would allow more focus on serious suspected ADRs. However, PhRMA believes that an unintended consequence of the Agency's attempt to introduce a comprehensive, far reaching set of new and modified US-specific requirements is the creation of many practical difficulties and inconsistencies. PhRMA believes that the problems created will defeat the stated FDA goals of "more effective and efficient safety reporting to regulatory authorities worldwide." Rather than make it easier for the Agency (and companies) to identify potential problems – one of the stated purposes of the Proposed Rule – PhRMA believes that certain aspects of the Proposed Rule may have the opposite effect.

FDA has developed many new concepts and requirements which in PhRMA's opinion will not improve the pharmacovigilance process or public health, and may work to the contrary. Rather than simplify, clarify, and harmonize, they will complicate, confuse, and create disharmony with already established and evolving standards under other major regulatory agencies and ICH. We are entering a new era globally in drug safety with emphasis on detecting, assessing, understanding, and preventing important risks to improve the safe use of medicines. Toward that end, FDA and other regulators are

striving to introduce rational approaches to "risk management," from development through marketing. Unfortunately, in its proposed Rule, FDA has placed undue emphasis on the administrative aspects of safety reporting, in effect imposing a micromanagement approach to the minutiae of safety surveillance, which will increase not decrease reporting burdens and with no foreseeable added value toward a focus on a product's safety profile.

There is also no evidence that non-industry parties who will be materially affected by the Rule have been engaged in discussions with FDA (e.g., investigators, healthcare professionals and their professional associations, and hospitals).

In this submission, PhRMA provides comments, questions and suggestions on more than 40 different items and issues covered in the proposed Rule. As will be clear from the following summary of a sample of our concerns, PhRMA believes that considerable modifications to the proposed Rule are necessary for it to meet its goals and to improve our mutual ability to carry out internationally consistent, high quality pharmacovigilance.

- (1) **Suspected Adverse Drug Reaction (SADR).** FDA's definition and interpretation seriously compromise international harmonization of this important term by introducing a minimum causality threshold for reporting (role of the drug "cannot be ruled out"). PhRMA believes that this definition will lead to very large increases in reporting volume from clinical trials, with some estimates, including from a retrospective analysis of databases, as high as 10-fold. For many clinical trials, this represents a significant problem with respect to maintaining the blind and to sample size for efficacy, since most patients experiencing serious unexpected SADRs will be discontinued from treatment. A commensurate burden will affect investigators and IRBs, who will have to receive and manage such reports.
- (2) **Other Major Divergences from Harmonization.** Many proposed definitions and activities are specific to the US, are in conflict with ICH and other current guidance or good practice, and are considered unnecessary by PhRMA: "Active Query;" customization of ICH E2C PSURs, new variations of PSURs (viz., TPSRs, IPSRs), and different or additional reporting timelines from the rest of the ICH world; two new categories of cases, "unexpected SADR with unknown outcome" and "always expedited" reports. In addition, many aspects of the proposed Rule are at odds with the recently adopted ICH E2C Addendum, and with the pending new ICH guideline, E2D, on postmarketing expedited reporting. In general, the proposed Rule introduces an unnecessarily complicated multiplicity of reporting timelines for expedited and periodic reporting involving both SADRs and medication errors which will challenge systems, resources and compliance.
- (3) **Unexpected SADR with Unknown Outcome.** This new category of report would necessitate expedited (15-day) reporting with automatic 30-days-later follow-up reporting for every "unexpected" SADR whose "outcome" is unknown. The vast majority of such cases involve, ultimately, non-serious events, and there is already a requirement and established practice for follow-up of any clinically significant adverse event report. A new case class with a new 45-day follow-up report is

unnecessary and it will only complicate compliance requirements and add unnecessary time and cost burdens.

- (4) Active Query and Follow-up.** The proposal to require direct verbal contact by a company physician with a reporting healthcare provider ("Active Query") for *all* serious AEs, "Always Expedited" AEs, and medication errors is an inappropriate and unnecessary use of resources for several reasons: written follow-up, particularly in the form of medical records, is more accurate and is the preferred route by healthcare providers, especially since they can enlist the aid of office/clinic staff; given the busy practice of physicians, interrupting their practice by calling them repeatedly could deter them from reporting suspected adverse drug reactions; implementing this requirement outside the US will be especially difficult as a result of cultural and legal impediments; direct (or indirect) contact should not be limited to physicians but should be allowable for all properly trained and responsible professionals. The proposed 30-day follow-up report for expedited reports (even if there is no new information) to document specific efforts taken to obtain additional data, along with the reason for an inability to obtain the data, is also an unnecessary administrative burden with no perceived value. To PhRMA's knowledge, there is no evidence that existing follow-up regulations, guidances and practices have proven unsatisfactory.
- (5) Medication Errors.** PhRMA disagrees with the proposal on handling medication errors for several fundamental reasons, such as: it focuses on only one stakeholder, the pharmaceutical industry, whereas it is widely accepted that this issue requires a much broader, shared healthcare system remit; the definitions (actual and potential medication errors) lack internal logic and are in conflict with established NCC MERP standards; prescription and non-prescription products deserve separate treatment; from experience, most reported cases of medication errors either result in no adverse event(s) or in events(s) that are non-serious and self-limiting; enforcement of the rule as currently proposed will discourage voluntary reporting due to potential legal liability on the reporters. The proposed definitions and requirements in the Rule are considered inappropriate and insufficient to meet the stated goals. The broad definition of "potential" error in the Proposed Rule may produce a huge volume of reports of limited or no interest for product safety. Expedited reporting of the wide variety of medication errors proposed by FDA is a highly disproportionate requirement for the anticipated return and intended purpose.
- (6) Periodic Post-marketing Reporting.** PhRMA is very concerned about the many FDA-proposed departures from ICH and standard practices that add little if any value, especially a new set of PSUR Appendices and two new types of reports (TPSRs or IPSRs) with an unprecedented 7.5 and 12.5 year reporting schedule. Keeping track of all these varying requirements, especially for products with many different formulations, indications and uses approved at various times, is a daunting prospect which will also significantly complicate the establishment of a global PSUR system. In addition, PhRMA believes that in place of the "traditional" safety update report (TPSR, which is not traditional at all), there should be a grandfathering of "old" products to allow them to

continue to fall under the more simplified current requirements under CFR 314.80.

- (7) Licensed Physician, Responsible Party, Contact Person.** PhRMA seriously questions the value of having a licensed physician review all individual SADRs; companies invariably use well trained scientific/biomedical staff who are quite capable of doing so. PhRMA also does not agree with the proposal to provide contact information on individual physicians responsible for the content and medical interpretation of the data and information in PSURs, IPSRs, TPSRs, and MedWatch and CIOMS 1 forms. Companies currently provide a contact person who can ensure that FDA has adequate access to the appropriate medical professionals in the company in a timely manner.
- (8) Assessing Increased Reporting Frequency.** Without a scientific or methodological underpinning, the proposed Rule imposes a requirement for companies to estimate and report on increased reporting rates for serious expected SADRs and for lack of efficacy. Much development work is needed to establish if and how such an exercise can be accomplished to yield useful information and PhRMA believes that this issue should be covered under the Agency's new risk management initiatives and deleted from the proposed Rule.
- (9) Burden for All Stakeholders.** The FDA's estimate of burden to the industry appears to be extremely low in terms of the volume of individual cases and aggregate reports and associated costs of the anticipated changes. Furthermore, it has not factored in the burden to the healthcare system, whether, for example, it involves increased time and effort to handle much more frequent and intensive phone calls from company physicians ("Active Query" or other new follow-up procedures), what will become a major increase in requests to hospitals that they promptly provide discharge summaries and/or death reports, and the burden on investigators and IRBs in the face of a significantly greater number of expedited reports they must deal with.

As reflected in the above examples and in its detailed comments, PhRMA believes that significant modifications of the proposed Rule are needed to meet the stated goals and in particular to achieve real harmonization within the pharmacovigilance arena. We would welcome the opportunity to work with the Agency to achieve an optimum set of rational requirements to satisfy our mutual interest in improving the safety and safe use of medicines.

1. EXPLANATION OF COMMENTS

In view of the length and breadth of the proposed Rule and its preamble descriptions and discussion, and given coverage of the same items in several places, the comments provided here are organized not by numbered section of the Federal Register Notice, but according to specific topics or issues. In this way, PhRMA hopes that its input will more efficiently address the general concepts and objectives underlying the Proposed Rule. For mutual convenience, a citation corresponding to representative (but not all) sections of the preamble and the Proposed Rule are given with each topic or subject matter when possible.

In several places throughout FDA's introductory material, requests are made for input on specific questions raised by the Agency. Responses to each of the questions are provided in a separate section of these comments. In addition, PhRMA presents three new proposals relevant to aspects of the proposed Rule, but not considered in the Rule per se.

The rest of this document contains the following sections:

2. General Comments
3. Detailed Comments
4. Responses to Specific Questions by FDA
5. PhRMA Proposals on Issues not Covered in the Proposed Rule

2. GENERAL COMMENTS

- a. **Involvement of Stakeholders.** To best serve the public health, relevant stakeholders in addition to the pharmaceutical and biotechnology industry should be involved in both the development of the Final Rule and considerations of practical aspects of its implementation. There is no evidence that non-industry parties who will be materially affected by the Rule have been engaged in discussions (e.g., investigators, other healthcare professionals and their relevant associations, hospitals, and safety system vendors). Details on their significantly increased burden are discussed below. Mechanisms should also be established to ensure interaction within the Agency (e.g., Review Divisions, systems support) to ensure that the approach is aligned with ongoing Risk Management initiatives.
- b. **Harmonization Shortcomings.** Although FDA has made some welcome attempts to bring its regulations into worldwide harmonization, many of the proposed changes diverge markedly from ICH guidelines, CIOMS proposals, and industry practice, and may compromise FDA's impending risk management initiatives. Many proposed definitions and activities, such as SADR and medication error definitions are specific to the US, and are in conflict with ICH guidance. For example, FDA has expressed support of harmonization by claiming to adopt the ICH E2C model for PSURs, a welcome initiative. However, the Agency is proposing to

customize reports for the US, introduce new variations of PSURs (viz., TPSRs, IPSRs), and require different or additional reporting timelines from the rest of the ICH world. It is noteworthy that many aspects of the proposed Rule are at odds with the recently adopted ICH E2C Addendum, and with the pending new ICH guideline, E2D, on postmarketing expedited reporting. All such instances of disharmonization will clearly create an additional workload burden for global companies and increase the potential for confusion and non-compliance. Indeed, it makes our shared goal of protecting the public health an inefficient process. Thus, FDA's stated rationale for the new requirements - "to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions" - cannot be met and is in fact contradictory. Special concerns regarding some proposed "FDA specific" expedited and periodic reporting requirements are delineated in the Detailed Comments.

- c. Medication Errors.** While PhRMA recognizes the importance of monitoring for, understanding, and preventing medication errors, it questions the basis for introducing what we believe to be excessively demanding new requirements, including expedited reporting of "actual and potential" cases. The new requirements would strangely hold medication errors to a higher regulatory standard than even serious suspected ADRs. The 1999 IOM report cited (p. 12413) and other initiatives (e.g., National Patient Safety Foundation) have taken pains to point out that medical and medication errors must be treated as a system-wide issue with responsibility to be shared by all stakeholders (healthcare professionals, their associations, patients, the education system, and others). In addition, there is already an existing organizational infrastructure dedicated to collecting, reporting and assessing medication errors, namely, the Institute for Safe Medication Practices. Furthermore, the US-based National Coordinating Council - Medication Error Reporting and Prevention (NCC MERP), an independent body comprised of 24 national organizations, collaborates on interdisciplinary causes of errors and promotes the safe use of medications. NCC MERP has been active in supporting bar-coding, etc., and they also have in place a system to accept and process reports of medication errors. Placing the burden of finding and reporting medication errors on the pharmaceutical industry, especially under the definitions and requirements in the Proposed Rule, is considered inappropriate and insufficient to meet the stated goals. We also believe that the proposed new requirement for expedited reporting of "actual and potential" medication errors would create an additional, unnecessary burden on FDA's resources for little if any added value.
- d. Personal Data Privacy and Access to Information.** Although FDA briefly addresses "Patient Privacy" (e.g., p. 12475; 310.305(e)), there is considerable concern and uncertainty surrounding not only any limitations placed on companies as a result of the HIPAA Rule, but also as a result of several non-US privacy laws and regulations (EU, Canada, Japan, etc.). The new Rule would require submission of various documents

(e.g., autopsy reports, hospital records) in addition to individual case information that potentially could contain “personally identifiable information.” While it is believed that on behalf of public health, the privacy rules in the US and elsewhere allow for exemptions related to adverse experience reporting, PhRMA strongly requests that FDA provide a clear explanation of the regulatory and legal status of the process with regard to pharmacovigilance. Because the FDA expects patient details for cases outside the US, some perspective on companies’ obligations with regard to ex-US SADR reports would be helpful as well.

- e. **Quality of Postmarketing Safety Reports.** The FDA states (II.B.2) that “many of the received post-marketing safety reports are complete and of very high quality. Others are incomplete, of mediocre or poor quality or both.” Rather than addressing this problem by amending safety reporting requirements that impact all companies, including those who submit good quality reports, FDA might address this issue with individual problem manufacturers through its robust inspection process and existing powers of enforcement.
- f. **Electronic Reporting.** Although a separate proposed rule is planned for electronic filing of individual case safety reports, the agency should consider adding language to allow for optional electronic submission, at least for postmarketing safety reports. Further, FDA should clarify in the Final Rule that the data elements expected for cases requiring a full data set will be the same whether the report is submitted on a paper 3500A form (or CIOMS I form) or electronically and that no additional requirement for structured data beyond the current 3500A form will be imposed for electronic reports.
- g. **Environmental Impact/Estimate of Burden.** The FDA’s estimate of burden appears to be extremely low in terms of the volume of individual case and aggregate reports that would result from implementing the proposal; the commensurate cost associated with the proposed changes has also been underestimated by a wide margin. Furthermore, FDA has not factored in the overall burden to the healthcare system, whether, for example, it involves increased time and effort to handle much more frequent and intensive phone calls from company physicians (“active query” or other new follow-up procedures, such as for reports with unknown outcome), or what will become a major increase in requests to hospitals that they promptly provide discharge summaries and/or death reports. For companies, among the many changes the Rule would impose, the following are examples that represent significant new resource requirements (including new programming, validation, training, tracking, etc.) that are significantly underestimated by FDA: active query, new requirements for PSURs (such as Appendices) and its variants (e.g., TPSR), reports with information sufficient to consider a product administration change, exchange of information with “contractors,” unknown outcome cases, medication errors, and so forth. See section 3.q. below for more details on the estimated burden.

- h. Implementation of the Final Rule.** FDA proposes that “any final rule that may be issued regarding the proposal to require that SADRs in individual case safety reports be coded using MedDRA become effective 1 year after its date of publication in the Federal Register.” On the other hand, “FDA proposes that any final rule that may be issued based on all other proposals become effective 180 days after its date of publication in the Federal Register.” (Fed. Reg. 12405, 12449). If the Final Rule is not significantly modified from the Proposed Rule, there will be an extensive impact on systems (modification of existing safety databases and systems to meet the specific requirements of the Rule as well as other requirements, such as those in 21 CFR Part 11) and processes (which will require training of employees, suppliers, investigators, etc.). The resource implications for the industry are much higher than FDA has estimated. PhRMA requests that FDA delay the effective date of the entire Final Rule to at least 12 months after publication in the Federal Register. This would provide the necessary time for industry to evaluate and implement the required changes.

In addition, PhRMA notes that FDA plans to finalize the draft guidance for industry entitled “Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines” (announced in the Federal Register of March 12, 2001; 66 Fed Reg 14391-14392) prior to publishing the Final Rule, and then update the guidance to incorporate the requirements of the Final Rule. Many of the concepts outlined in the draft guidance have been incorporated into the proposed rule, apparently without consideration of many comments on the draft guidance that were submitted to FDA in 2001. PhRMA suggests that FDA finalize both the Proposed Rule and the draft guidance at the same time, to ensure that they are consistent, and that there is a regulatory basis for the expectations outlined in the guidance document.

3. DETAILED COMMENTS (Note: These are not presented in any special priority order)

a. Suspected Adverse Drug Reaction (310.305a, p. 12472; 312.32a, p. 12476; 314.80a, p. 12477; III.A.1., p. 12417). The new acronym (SADR) and definition are not consistent with accepted ICH adverse drug event and adverse drug reaction terminology, which has been extensively integrated into everyday industry procedure and practice, as well as by regulatory bodies (e.g., the EU Clinical Trials Directive Guidelines). As intended, ICH terminology and definitions have enabled a more harmonized approach to global safety reporting. Creating a new acronym with a definition specific to the US will create confusion and fractionate the handling of global reports. Furthermore, SADR is easy to confuse with SAE (SADR), which has become a well-recognized abbreviation for *serious* adverse event (reaction) in the US and elsewhere.

More importantly, PhRMA has serious concerns about the interpretation that “reasonable possibility” means that “the relationship cannot be ruled out.” Although this definition is

technically consistent with ICH E2A, it does not encompass all of the concepts associated with the ICH definition, nor does it agree with the EU Clinical Trials Directive on ADR reporting. Both of these documents include the concept that "reasonable causal relationship" is meant to convey that there are facts, evidence, or arguments to support an association with the drug. Such facts, evidence or arguments would include temporal relationship, a pharmacologically predictable event, positive dechallenge or rechallenge, and other factors. Confounding factors such as concomitant medications, concurrent illness, or relevant medical history should also be considered.

FDA has not provided any data or evidence that important information has been overlooked or that potentially important cases and situations have been mishandled, under current definitions and schemes. PhRMA would appreciate any such information from the Agency that it might be using to base its new proposals for a much lower threshold for reporting.

Another possible insidious effect of the new definition will be, in practice, the elimination of the important distinction between solicited and spontaneous reports, since causality assessment (currently required for solicited reports) would effectively default to "cannot be ruled out." Thus, FDA will be receiving a much greater volume of solicited reports than would ordinarily be the case. See section 3.i. for additional comments on solicited reports.

A consequence of FDA's interpretation of an SADR will be a significant increase in the number of IND Safety Reports submitted to FDA and to investigators and IRBs. PhRMA believes that the result will be the reporting of almost every serious unexpected adverse event, since a relationship can rarely be completely ruled out according to the FDA proposal. The example given by FDA in the proposal (an event most probably related to the patient's underlying disease, but for which a relationship with the investigational drug cannot absolutely be eliminated) underscores this point. Unless the event occurred before the drug was administered, it is unlikely that a relationship could ever be completely ruled out.

An informal poll of PhRMA member companies indicates that this provision would increase by 10-fold expedited reports from clinical trials. Of course, it will also mean that to be consistent, companies may have to submit the same increased numbers of cases to all other appropriate regulatory bodies, or be seen as somehow withholding supposedly important information. This increase will make the detection of true safety signals more difficult because of the increased "noise". Furthermore, investigators and IRBs have increasingly complained about the current abundance of uninformative IND Safety Reports; the proposed change will increase their administrative burden without adding any true value. (See section 5. of these comments for separate proposals on this particular issue.)

Another critical problem with the revised interpretation of "reasonable possibility" relates to the need to unblind all serious unexpected SADRs, potentially compromising the integrity of clinical trials that have a large number of serious adverse events. The Agency suggests that protocols could be written to exclude certain disease-related events that are study endpoints from expedited reporting, which is done currently for certain products. However, this is a rather unwieldy approach when applied to other common serious events that may not be study endpoints. The lower threshold for AE

reporting in clinical trials will greatly expand the number of events that require unblinding. This will have a number of statistical and clinical implications and may result in a trial that does not have the power to meet its objectives. Even if one can avoid unnecessary unblinding by using data monitoring boards/committees (DMBs) for studies that are expected to have a large number of SADRs, this would still not account for the fact that most expedited serious suspected SADR cases would be terminated from the study. Yes, the DMB would perform the unblinded review and make the determination of what should be sent to the FDA for review, which would help preserve the integrity of blinded studies, but at an additional cost and burden for drug development. Without DMBs, sponsors could be forced to unblind a majority of patients experiencing SADRs, thus compromising the statistical integrity of all blinded trials. The necessary compensatory increase in sample size to maintain the ability to test the intended efficacy hypothesis will lengthen new product development time, thus delaying new products for patients with serious and life threatening conditions.

To test for such for an adverse possibility, statisticians in one PhRMA member company have performed a retrospective analysis on one of their IND databases for a completed study that involved data on 1,513 patients, in order to gauge the effect of the new SADR definition. The results are described as follows:

In addition to a rerun of the analysis originally performed, a separate analysis was carried out in which patients with a Serious Adverse Event (SAE) were assumed removed from the trial 7 days after the SAE was reported; 41 patients had clinical efficacy endpoints between 0 and 6 days from the SAE and since these events could have been directly associated with the SAEs, censoring them might incorrectly have removed relevant clinical endpoints from the analysis.

Of the 1,513 patients providing data for the original analysis, 686 provided an endpoint and 827 (54.7%) were censored. When the proposed Rule definition was applied with a 7-day window, 269 of the patients provided an endpoint and 1,244 (82.2%) were censored. Thus, application of the new definition prevented observation of 417 (60.8%) of the endpoints. The result of this loss of endpoints was a loss of sensitivity of the trial. The original analysis demonstrated an effect of treatment with $p = 0.022$. Application of the proposed Rule caused the treatment effect to lose statistical significance ($p = 0.055$). This would have had drastic consequences for acceptance of the result by the medical community and regulatory approval of an important labeling change.

In conclusion, this analysis showed that by prematurely removing patients who are willing, and whom investigators judged are able, to remain in the trial, as would be required under the proposed new reporting requirement for SADRs, the opportunity to observe critical endpoints would have been eliminated and the sensitivity that otherwise would have demonstrated meaningful clinical effects would have been lost.

PhRMA believes that it is much more appropriate and realistic to make a judgment on a possible causal relationship based on positive reasons, rather than trying to disprove a negative ("cannot be ruled out"). FDA stresses the value and importance of health care professionals in several of the new proposals, such as requiring a licensed physician to review cases, that this physician be identified on every submitted report, and that healthcare professionals conduct active queries. However, this would seem to be in

conflict with an apparent distrust of the same medical judgment in not allowing company medical staff or investigators to rule out a possible causal relationship with the drug.

It should also be noted that regulatory reporting under FDA's proposal, particularly for serious suspected ADRs, will be based on a causality assessment by either the investigator or the sponsor, providing a form of check and balance to the process. PhRMA is concerned that the additional part of the SADR proposal, namely an automatic lower threshold ("cannot be ruled out"), will result in indiscriminate selection and reporting of cases, which will not only lead to an increase in cases, but will decrease the value of "alert" reports, especially in the eyes of investigators and IRBs simply because they are being inundated with much more data.

PhRMA is also concerned about the potential effect of the SADR proposal on drug labeling. Many more adverse events than in the past will be regarded as "drug-related" when reason and best medical judgment in determining causality are no longer prime, and many events will be listed as drug-related even though the likelihood of a true causal relationship is minimal. Many of these events, for which a causal relationship is tenuous at best, will find their way into product labeling, diluting the utility of the labeling information and potentially unfairly reflecting poorly on the product itself.

PhRMA recommends the following:

- FDA, a signatory to the Step 4 ICH E2A Guideline, should keep its regulatory definitions and interpretations consistent with those agreed by ICH, for both pre- and post-approval situations.
- FDA should solicit feedback on its proposed definition for SADR and the implications as presented above with stakeholders (other than the industry), such as investigators, IRBs, the Association of American Medical Colleges (AAMC), and the NIH, who will also bear the brunt of increased reporting.

b. Unexpected SADRs with Unknown Outcome (310.305(c)(1)(ii), p. 12473; 310.305(c)(2)(iii), p. 12474; II.B.3.b, p. 12414). PhRMA understands FDA's intent in introducing this new category of report and the requisite follow-up reporting requirements (30 calendar days beyond the initial 15 day expedited report). However, it is not clear why the current definition of serious is unable to accommodate this need; medical judgment has become an important component of decisions regarding serious vs. non-serious and it is unclear what this new category with its burden of a new follow-up tracking timeline contributes. The industry already has a requirement to follow-up any clinically significant adverse event report. The requirement for the 45-day follow-up will complicate compliance requirements and, because of tracking, data entry, and review of cases that have no new information, add unnecessary time and cost burdens to manufacturers and the Agency with minimal yield.

PhRMA disagrees with the Agency that a Sponsor may have difficulty in making an initial determination of 'serious' or 'nonserious'. Many commonly reported conditions such as headache, skin irritations, and alopecia are almost never serious by regulatory criteria or clinically significant. PhRMA proposes that all AE reports be viewed in context and that judgment be used to determine which of the indeterminate reports should be subject to special follow-up treatment. Much of the decisionmaking revolving around

'serious' and 'non-serious' was addressed with the publication of the final regulations on important medical events. In the rare instance (less than 1% of cases) that an initial determination of 'serious' or 'non-serious' cannot be made, we suggest that the default in such a setting would be to process the report as 'serious.'

"Unexpected SADRs with unknown outcome" is defined as SADRs for which a determination of serious or non-serious cannot be made, using the regulatory definition of serious. The word "outcome" is also used to refer to patient condition following a suspected ADR (improving, recovered, etc.). If this report category is retained, something PhRMA does not support, we recommend that this be made more explicit.

It is also unfortunate that use of this new category of cases will create discrepancies between PSURs submitted to the FDA and those submitted to other regulators. Thus, only for FDA would such cases have to be treated as a separate category in any line listings or summary tabulations.

Also, FDA states that it intends to compare information on unexpected SADRs with unknown outcome with information on similar SADRs with known serious outcomes that are on file with the agency. PhRMA requests that should this approach be taken, FDA provide the results of their analysis to the manufacturer. Industry would like the opportunity to review and comment on the data and their relevance.

PhRMA recommends the following:

- FDA should not create a discrete new case category, "Unexpected SADRs with unknown outcome."
- Instead, more explicit guidance on the management of such cases can be given, such as a default to expedited reporting depending on the nature of the case.

c. Active Query (310.305(a), p. 12372; 314.80(a), p. 12477; III.A.6, p. 12420; III.C.5, p. 12429; III.D.6, p. 12433). PhRMA supports FDA's desire to improve the quality of reports on marketed products. We agree that a focused line of questioning would help facilitate the collection of detailed, relevant clinical information. However, we do not believe that this has to be performed only by direct verbal contact. In many instances, detailed, focused questionnaires will achieve the same purpose.

Although information received via direct verbal contact is valuable, written follow-up, particularly in the form of medical records, is more accurate. When physicians are called, they typically do not have the medical records in front of them and have to rely on their recollection of the case. Given the busy practice of physicians, interrupting their practice by calling them repeatedly could deter them from reporting suspected adverse drug reactions in the future. Written communication is the preferred route of communication by many healthcare providers in responding to follow-up questions on SADRs and AEs, especially since they can enlist the aid of office/clinic staff.

The proposal to require active query for all serious AEs, always expedited AEs, and medication errors will significantly increase the workload and required resources for companies. FDA estimated that the active query requirement would take companies one hour each for a health care professional and regulatory affairs professional to determine/obtain a minimum data set, SADR outcome (if unknown), obtain a full data

set, and supporting documentation (hospital discharge summary, death certificate, autopsy report). Even if we accept FDA's one-hour estimate, this represents one hour per case per company. Some companies receive thousands of serious reports per year which would require thousands of hours per company. More time is required for complicated cases. Tracking and processing the responses require even more person-hours, which some member companies estimate at 2.5 hours for each case that generates a positive response from the reporter. Together these activities add up to an enormous time burden, particularly when multiplied across the industry. Moreover, this estimate does not account for the unsuccessful attempts to contact the reporter nor for the time spent by the reporter answering the questions.

PhRMA also questions the terminology used, "Active Query," implying that all other forms of follow-up and inquiry are passive, which is certainly not the case. The concept of "Active Query" already exists in practice, both in the context of clinical trials and spontaneous cases. However, if active query beyond the follow-up that currently exists is contemplated in the Final Rule, PhRMA expects that resource requirements will be much higher than the numbers estimated in the Proposed Rule. It would also have an inhibitory effect on spontaneous reporting once physicians realize that direct dialogue with a company representative would become the norm all too often.

PhRMA agrees with the agency that in certain situations more aggressive follow-up should be utilized to obtain additional information. However, PhRMA proposes that this activity be *recommended, but not mandated*, and only for potentially "higher risk" cases, such as serious, unexpected AEs and AEs of special interest. Furthermore, e-mail contact should be considered a valid form of active query. For other than "high-risk" cases, written follow-up should be sufficient in most instances and the use of detailed, focused questionnaires would be useful to gather more complete information. PhRMA agrees with the risk-based approach offered by CIOMS V for obtaining follow-up information.

Implementing this requirement outside the US will be even more difficult, especially in small countries that operate with limited resources. In some countries, as a result of cultural and legal differences, or established reporting schemes, direct contact of physician reporters is not usual nor is it even permitted (e.g., Italy). Also, it is common for company affiliates to receive adverse event reports from their regulatory agencies, often by letter, and not from initial reporters. Additionally, there are many co-marketing arrangements in place among companies that would require sensitivity to these ex-US differences and reporting schemes. Active query as suggested does not recognize or consider ex-US requirements.

PhRMA disagrees that Active Query should only be conducted by a licensed physician. Many of the professionals in drug safety departments or in individual country offices hold advanced scientific degrees, e.g. PhD, and have been adequately trained to obtain, process, and analyze safety information. It should be the company's responsibilities to hire individuals whom they feel are qualified to perform an activity. The proposed rule should allow nurses, pharmacists, allied health field personnel, and customer advocates who have received adverse event/pharmacovigilance, package insert, and medical terminology training to handle AE-related calls. Rather than define specific qualifications of individuals, we encourage FDA to use language similar to that stated in 21 CFR 211.25:

"Each person engaged in the ... shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions."

The physician or other qualified person responsible for the content and interpretation of the data should be allowed to decide, based on his/her expert judgment, whether Active Query (verbal contact) is necessary (e.g., determination of outcome in expected events, missing data assessed as not crucial for the assessment of a serious expected case, etc...). This decision could be mentioned in the company's file for the case.

The proposed Active Query requirement could be interpreted to include communication with attorneys who submit one or more case reports to a company on behalf of a client(s). In practice, all such communication and correspondence within a company takes place through its legal department; any such reports addressed to, or identified by, any other staff (such as safety departments) are ordinarily forwarded to legal staff for handling. Therefore, it is important that all such cases be excluded from any Active Query or similar requirement for follow-up.

FDA also proposes (III.B.2.b.) that a chronological history of all active query efforts be documented in detail in a report narrative. However, records of due diligence efforts are always maintained by companies and can be made available on request. Including such efforts in the narratives adds no value and may lead to inconsistencies that could create legal risk in the event of lawsuits. For example, there may be differences between companies or within companies in how due diligence is described in the narrative (since the person performing data entry will seek to keep the description as brief as possible) and the full record of the effort may differ enough to allow a plaintiff's lawyer to challenge the record. There is also a possibility that the proposed additional documentation would increase the length of narratives so as to interfere with electronic transmissions. If FDA mandates electronic case reporting, the ICH E2BM specification currently limits the case narrative to 20,000 characters and narratives from some companies already exceed this limit.

It is also unlikely that non-US regulators and investigators would accept medical safety reports with such administrative (and to most, extraneous) information, leading to the possibility that a different version of the narrative would have to be prepared to satisfy the FDA.

Other tools than direct verbal contact could be developed that would encourage reporters to provide accurate and complete information without negatively impacting their practice, such as:

- Forms containing the already available information, highlighting the missing information (seriousness criteria, etc...) to be returned by the reporter by fax (or e-mail).
- Standardized "full data set" questionnaires/forms for each of the "always expedited reports" that would be filled out during the initial intake and returned with highlighted missing data to be completed and returned by the reporter.
- Education programs could be developed for potential reporters (physicians, pharmacists) on the regulatory requirements and importance for reporting adverse

events and medication errors. It would improve the quality of initial reports to companies and, hence, to FDA.

Under III.D.7, FDA proposes that companies use active query to obtain and translate into English supporting documentation (i.e., autopsy reports and/or death certificates, and/or hospital discharge summaries for all deaths and hospitalizations). PhRMA disagrees with the proposal to require the routine submission of such reports. It should not be a requirement in the Final Rule. Such a requirement may infringe or breach HIPAA mandates and violate non-US country privacy rules. In some countries, including in Europe, death certificates cannot be obtained; in less developed countries, it is often impossible to obtain any of the documentation requested. As industry strives for quality data, PhRMA believes it should be up to the Applicant to have appropriate processes in place to obtain source documentation and to analyze it, as necessary, to complete a case. The burden of handling the increased volume of documentation to FDA would probably be significant; in most cases industry includes relevant information in the 3500A (or CIOMS 1) form. Separate, systematic submission of such documentation to the Agency is not necessary; in cases when the information has been supplied to the company, it could be provided to FDA to fulfill a specific need upon request or at the company's discretion. One consideration would be to require such detailed documentation, including any necessary translation, when a report or reports may represent an important safety signal. Complete translations of supporting documents on a routine basis is considered unnecessary and in many cases would not be possible in a timeframe needed to meet expedited reporting responsibilities.

The FDA also proposes that companies provide in an expedited report narrative a list of all relevant documents maintained by the applicant. However, this is in conflict with the electronic reporting provision agreed by all ICH parties. ICH E2BM specifications have fields that capture the specific types of source documents available, making it unnecessary to include such a list in the narrative.

PhRMA recommends the following:

- The concept behind "Active Query" involving special attempts at follow-up should be incorporated into the larger framework governing case follow-up practices, rather than be treated as a new, all encompassing, stand-alone requisite.
- Direct verbal contact should be recommended for limited, special circumstances – the same circumstances that are currently invoked by companies – and such approaches should be made part of guidance, not rule making.
- Direct or indirect contact should be allowable for all properly trained and responsible professionals and not limited to physicians.
- The term "Active Query" should be abandoned or changed, especially the word "active."

d. Follow-up Reports (310.305(c) and 314.80(c), various sections; III.D.6., 12433). PhRMA questions the value of requiring that, in addition to 15-day expedited follow-up reports, manufacturers must now also submit a 30-day follow-up for expedited reports (even if there is no new information) to document specific efforts taken to obtain new information along with the reason for the inability to obtain complete information. It has always been standard practice that new information is submitted when it is received, and companies are held accountable for due diligence as well as for its documentation.

Requiring additional individual reports to reiterate what is already required and available upon request is not a good use of resources at both the company as well as the Agency. For example, under this proposal, a company could submit a 15-day follow-up on Day 29 and still have to submit another report on Day 30, even though no new information was available. This extra administrative work and necessary tracking will detract from more important efforts, such as seeking appropriate follow-up.

In many cases, industry will be fairly certain when the initial report is received that no additional information is obtainable (for example, when access to contact information for the reporter and/or patient is firmly denied). If this is stated in the initial report, what is the value of sending another report in 30 days to reiterate this statement?

The 30-day follow-up reports also add an extra component of tracking compliance into the 15-day reporting process. The requirement to document all the follow-up attempts into the narrative adds administrative tracking information into the 3500A form that may not be helpful to those who use the form to review the case history (see section on Active Query above for more on this point). The manufacturer could provide this administrative tracking information if questions about the quality of the data arose during an FDA review of the case.

In addition, FDA proposes multiple timelines for the submission of follow-up for individual cases – 15 days (serious unexpected, always expedited, medication errors, etc – with full dataset), 30 days (serious unexpected, always expedited, medication errors – for initial reports without a full dataset), follow-up to 30-day reports must be submitted in 15 days, and 45 days (SADR with unknown outcome). PhRMA believes the various timelines with the different permutations will make tracking and compliance difficult. A more simplified schedule is strongly urged to reduce the complexity in worldwide reporting, preferably better harmonized than this new scheme would allow.

PhRMA recommends the following:

- FDA should simplify and unify the reporting timelines and expectations for follow-up reports, including “active query.” To PhRMA’s knowledge, there is no evidence that existing regulations, guidances and practices have proven unsatisfactory, and we see no need to change the current requirements.
- Special 30-day reports to document a company’s efforts to obtain information missing from initial reports add nothing but administrative problems without contributing to product safety or pharmacovigilance quality, and should not be included in the Rule.

e. Licensed Physician (310.305(d)(4), p. 12475; 314.80(c)(3)(E), p. 12481; II.B.2, p. 12413). The FDA proposes to require that a licensed physician at the company be responsible for the content of post-marketing safety reports submitted to the FDA, and indicates that having clerical personnel with no healthcare training prepare and submit reports is an unacceptable practice. PhRMA seriously questions the value of having a licensed physician review all individual SADRs. Furthermore, although PhRMA agrees that “clerical” personnel may be inappropriate for preparing and submitting reports, companies invariably use well trained scientific/biomedical staff who are quite capable of doing so.

PhRMA requests that FDA provide more clarity around the definition of a licensed physician and the level of responsibility that the physician would have regarding content. Must the physician be licensed in the US? Does the State of licensure matter? Must the person be located in the US?

We also request clarification regarding the requirement to have the name of the licensed physician responsible for the content and medical interpretation of the data contained within each individual report. This is logistically difficult for large global companies, where different physicians in different countries may review the initial and subsequent follow-up reports. Should the contact name be changed with each report? In that situation, who is the responsible physician? What if the physician leaves the company? What are the consequences, both from a regulatory and legal standpoint, of responsibility for content? Companies currently provide a contact person who can ensure that FDA has adequate access to the appropriate medical professionals in the company in a timely manner.

PhRMA recommends the following:

- Except for certain types of cases, such as serious unexpected suspected ADRs, it is unnecessary and impractical to require that only a licensed physician review and be responsible for individual safety cases.
- The Final Rule should state that manufacturers are empowered to determine which colleagues are appropriate for each business and regulatory function performed.
- It is also impractical and potentially confusing to require the name of “the one” responsible licensed physician on each report, and there should be no such requirement.
- FDA should clarify the meaning of “licensed physician” in the context of international operations and whether the role proposed covers both pre- and post-approval environments.

f. Life-Threatening SADR (310.305(a), p. 12472; 312.32(a), p. 12476; III.A.2, p. 12419). PhRMA agrees with the proposed addition of “or sponsor” to this definition. However, in section III.A.2 of the proposal, FDA indicates that if the investigator and sponsor have differing opinions regarding whether an SADR is life threatening, the reasons for any differences in opinion should be included in the IND Safety Report. For example, if the investigator’s opinion is that the SADR is not life threatening, the sponsor may take a more conservative approach and classify it as life threatening. PhRMA sees no value in including reasons for differences of opinion and does not agree that it is appropriate or necessary in all cases (we note that the statement describing this requirement does not appear in the proposed regulation itself).

g. Contractor (310.305(a), p. 12472; III.A.4, 12419). The definition of contractor is too broad and PhRMA suggests that the agency modify the definition to be more focused. As currently written, anyone with a business or licensing arrangement with a company would be a “contractor” (including such entities as Pharmacy Benefit Managers and hospitals). The consequences of including such a wide range of institutions are quite onerous and do not add to public safety. The proposed definition of contractor also would include licensing partners. Many companies are involved in literally hundreds of such alliances at international and local levels involving multiple partners. There are no

"standard" licensing agreements; each will have its own unique set of arrangements (in-licensing, out-licensing, co-promotion, co-marketing, co-development). In addition, licensing partners can hold independent approvals/marketing authorizations in different countries; there are also local divestment arrangements for "legacy" products that have been on the market for many years.

Given the range of possible safety reporting arrangements between "contractors" and "applicants," the Rule should not mandate that the Applicant always be responsible for safety reporting. There are certain situations where the Applicant (e.g., NDA holder, licensor) is a small company and the Contractor is a large company. In these situations, the Applicant and Contractor often have detailed written agreements whereby the Contractor is responsible for safety reporting. Therefore, the Final Rule should simply suggest that Applicants and Contractors be responsible for an agreement that specifies responsibilities for safety reporting. Further, any regulatory changes should apply only to prospective contractual arrangements, since various business partners already have a wide range of safety reporting agreements in place.

PhRMA agrees with the need for appropriate safety data exchange in any licensing or other contractual agreement, but the proposed requirement to exchange all adverse event reports within 5 calendar days with all the contractors specified, including for cases which do not meet the minimum required data set, will be inordinately complex and burdensome with no perceived added value in promoting patient safety. For contractual relationships with foreign companies, such as Japanese partners, the deadline would be almost impossible to meet because of translation needs and time zone differences. Equally, it would not be practical, or in most cases possible, for a European or US based licensor to undertake local follow-up in, for example, Japan on behalf of the Japanese licensee. It is fairly certain that the short turnaround proposed for exchange will result in poor quality reports, since it will only allow sufficient time for forwarding raw source data, with no time for appropriate follow-up or translation. In addition the proposal will require the exchange of SADR's that do not meet the minimum required data set.

It is also not clear whether the 7/15-day regulatory reporting timeframe for serious unexpected SADR's does or does not include the proposed 5 calendar days allowed for exchange of safety information with contractors.

The implications of imposing a 5-day deadline specifically when two or more companies hold independent marketing authorizations in different countries (co-marketing arrangements) are significant:

1. The partners would be expected to translate and exchange incomplete information within a period significantly shorter than expected for expedited reporting in the countries where they hold the marketing authorization.
2. There would be the need to implement two processes for handling case reports - one for co-marketing agreements and one for non-alliance reports.
3. The 5-day time frame would force companies to exchange raw data vs. a completed CIOMS/3500A form; at any given time, the partners would hold potentially different information in their respective databases, including different narratives and possibly different coding. Thus, different authorities around the world would receive different versions of the same report, which is clearly unacceptable. On the other hand, when

completed forms are exchanged this facilitates more rapid and consistent processing of the case using the same AE terms and narratives.

4. Each case would inevitably require multiple iterations and follow-up reports as more information inevitably arrives. This is highly inefficient and hardly conducive to the "quality" reports that agencies wish to receive.

PhRMA recommends the following:

- Given the complex nature of licensing agreements and the need to promote quality and efficiency and at the same time ensure that sponsors and manufacturers meet their regulatory obligations, PhRMA urges the FDA to adopt a more flexible approach in its definition of contractor and the time frames stipulated for safety data exchange. If it is the intent of the Agency to require that business alliance partners exchange adverse event reports within 5 calendar days, PhRMA suggests that the definition of contractors be restricted to paid vendors (e.g., CROs paid a fee for conducting clinical trials or providing services related to clinical safety data acquisition) and not include business alliance partners. PhRMA especially recommends the exclusion of co-marketing partner companies who hold independent approvals/authorizations in different countries for a given product.
- PhRMA recommends that provisions in the Final Rule only apply to prospective agreements to avoid the re-negotiation of hundreds of agreements already in existence. In co-development agreements when, for example, company B is conducting a study in Country X and company A is the partner and sponsor of the study, the term contractor would apply. However, when companies A and B are conducting studies in different countries with separate sponsorship status, the requirement should not apply.
- Companies should also be allowed the flexibility of allowing licensees to undertake local follow-up where appropriate and particularly in countries where local medical culture and language are important considerations.
- In the interests of promoting quality and efficiency only cases meeting valid case criteria should be exchanged with the understanding that every attempt should be made to obtain the information
- In the "redefined" contractor situations given above, it seems reasonable to exchange serious adverse event information in the 5 calendar days indicated to ensure that the manufacturer/sponsor can meet all local expedited reporting requirements. PhRMA also recommends a longer time frame for non-serious spontaneous case reports, such as monthly or quarterly.
- In co-marketing and independent sponsorship situations, we recommend that the reporting clock start when the manufacturer/sponsor of each respective company receives the minimum information and wherever possible, the time frame for regulatory submission should be no longer than 15 days from first receipt by the second company. This allows the case to be processed through the first company's case management process according to internal procedures and exchanged with the partner in no later than 15 calendar days by way of a completed CIOMS/3500A form. This would allow the second company to enter the same information promptly into their own database, eliminating the potential for discrepancies, allowing more rapid and efficient handling, and permitting submission to the authorities as appropriate. Once electronic data exchange becomes established, receipt and submission by the second company will become virtually simultaneous. Under co-development arrangements, a shorter time frame could be established for fatal/life threatening

reports to accommodate the 7 calendar day submission time frame for clinical trial cases.

h. Always Expedited Reports (310.305(c)(2)(iv), p. 1474; III.D.4, p. 12432). In its proposed safety reporting rules, FDA proposes to require that companies subject to its postmarketing safety reporting rules always submit certain SADRs in an expedited report. In the proposed rule itself, FDA sets forth 18 specific SADRs to which this always expedited report requirement would apply. *Id.* at 12474 (proposed 21 C.F.R. § 310.305(c)(2)(iv)). Additionally, FDA proposes to require always expedited reporting for “[a]ny other medically significant SADR that FDA determines to be the subject of an always expedited report (*i.e.*, may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).” 68 Fed. Reg. at 12474 (proposed 21 C.F.R. § 310.305(c)(2)(iv)(19)). In proposing this catch-all, FDA provides no indication that it would engage in notice-and-comment rulemaking before imposing always expedited reporting requirements on additional SADRs. Rather, FDA indicates that “[n]ew SADRs that become the subject of always expedited reports would be included in the agency’s current guidance for industry on postmarketing safety reporting for human drugs and licensed biological products.” 68 Fed. Reg. at 12432.

This proposed mechanism for setting forth additional SADRs subject to always expedited reports is entirely improper and contrary to both the APA and FDA’s own regulations. If FDA seeks to subject additional SADRs to always expedited reporting, it may do so -- but only through notice and comment rulemaking. A rule imposing always expedited reporting requirements for SADRs not previously subject to those requirements is a legislative rule subject to the notice and comment rulemaking provisions of the APA -- not an interpretive rule exempt from those requirements. 5 U.S.C. § 553(b)(3)(A). Legislative rules “create new legal obligations;” interpretive rules, in contrast, “simply restate or clarify existing statutes or regulations.” *Chemical Waste Mngt. v. EPA*, 869 F.2d 1526, 1534 (D.C. Cir. 1989). Indisputably, a rule requiring always expedited reporting for a SADR not previously subject to always expedited reporting would “create new legal obligations” for companies subject to FDA’s reporting requirements. *See Batterton v. Marshall*, 648 F.2d 694, 701-2 (D.C. Cir. 1980). Accordingly, FDA would have to engage in notice and comment rulemaking to adopt such a rule.

FDA is essentially proposing to use a guidance document as a substitute for notice-and-comment rulemaking. In adopting its final rule on good guidance practices, the agency itself acknowledged that it should not use guidances as a replacement for adopting regulations. 65 Fed. Reg. 56468, 56473 (Sept. 19, 2000). Nevertheless, this is exactly what the agency proposes to do here. Moreover, FDA’s proposed approach is directly contrary to the agency’s regulations regarding the non-binding nature of guidance documents. As set forth in FDA’s good guidance practice rules, guidance documents “describe the agency’s interpretation of or policy on a regulatory issue.” 21 C.F.R. § 10.115(b)(1). “Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.” *Id.* § 10.115(d)(1). FDA, however, is currently proposing to impose “responsibilities” on companies subject to its reporting regulations through guidance documents. Specifically, FDA is proposing to require always expedited reporting through its guidance on postmarketing safety. This is simply impermissible under the agency’s own regulations.

PhRMA is sympathetic to the idea that for certain events, due to their nature or severity, a standard list might be useful that would characterize such events as “always serious” but not “always expedited.” We question the value of submitting expedited reports for expected SADRs, already described in labeling, information FDA will always receive in periodic submissions.

There are other problems with the concept of “always expedited:” (i) It is questionable whether always expedited reporting of certain events should be applied to all drugs, no matter how long on the market. While these actions might be appropriate to a newly marketed drug, imposing these same rules for drugs that have well characterized safety profiles based on extensive use over many years does not seem to be an efficient use of resources. (ii) All the medical conditions and terms chosen by FDA may or may not be recognized or have the same meaning in the same way in different medical cultures outside the US. This could create discrepancies in the kinds and amount of information supplied to different regulators, another barrier to harmonization. (iii) Although PhRMA understands that “always expedited” reports relate only to post-marketing cases and that they represent adverse events, not an underlying disease, not all post-marketing reports are spontaneous. The premise for “always expedited” appears to rest on presumption of causality (spontaneous reports); however, solicited reports and cases from, say, Phase 4 trials require a causality assessment, and thus some cases may not qualify for reporting at all, let alone “always expedited.”

One of the items in the proposed FDA list is: “Confirmed or suspected transmission of an infectious agent” Although it is understandable why the Agency would want to be alerted to such situations (as expressed in the examples given), it is unclear why this suspected product defect, without a specified adverse outcome, is included within an SADR context. Also, is the absence of Stevens Johnson Syndrome an intentional omission?

In handling always serious reports, PhRMA recommends relying strictly on the verbatim term (reporter’s words) coded to a MedDRA Preferred Term on the list. It should be recognized that some cases, particularly spontaneously reported cases, may be described by reporters in terms that are not exact matches to terms on the list. In addition to exact matches, a constellation of certain other MedDRA terms may be useful in identifying cases that meet the list criteria from a clinical perspective. However, the exact MedDRA terms that might be included is the subject of much discussion among experts and MedDRA terms are subject to change with each new version (twice each year). Lists prepared outside of a global consensus process, however well-intentioned, would likely include widely differing terms and would contribute significant confusion to the case identification process. Thus, we recommend limiting application of the list to reports with terms that are exact matches to the list.

PhRMA recommends the following:

- FDA should amend any final rule it issues to eliminate the catch-all provision of proposed 21 C.F.R. § 310.305(c)(2)(iv)(19) and clarify that it will only impose always expedited reporting requirement for additional (non-enumerated) SADRs after conducting notice-and-comment rulemaking

- The category “always expedited” should be changed to “always serious” reports; all the terms would qualify as medically important, which would ensure that all such reports would be submitted to FDA in an expedited manner if they were unexpected.
- As the list is quite comprehensive, FDA should not be tempted to add to the list without a public health concern; even then, prior consultation with affected companies is recommended.
- In handling “always serious” reports, PhRMA recommends relying strictly on the verbatim term, coded to a preferred term on the list. It would be useful for the Agency and the industry to agree on appropriate MedDRA codes for the terms in the list.

i. Solicited Reports (310.305(a), p. 12472; 314.80(a), p. 12477; III.A.7, p. 12421). PhRMA appreciates the agency's clarification of the important difference between spontaneous and solicited reports. As the agency states (III.A.7): “Over the years, changes in marketing practices in the United States have led to expanded contacts between consumers and manufacturers, applicants, contractors, and shared manufacturers. This has resulted in the acquisition of new types of solicited safety information.”

Since the type of report source may still be open to interpretation, PhRMA suggests the following modification (underlined) to the next sentence in the paragraph and similarly to the comparable wording in the Rule itself: “Cases identified from information solicited by companies, such as individual case safety reports or findings obtained from a study, company-sponsored patient support program, disease management program (including free telephone information services in connection with disease management type programs), patient registry, including pregnancy registries, or any organized data collection scheme would not be considered a ‘spontaneous report’.”

It must be recognized by the FDA that under many circumstances, the company reviewing physician will determine causality for serious unexpected SADRs due to the absence of a treating physician's information and assessment; it is very difficult to obtain additional information on solicited cases. Many programs purposely keep the consumer or patient anonymous, making follow-up impossible. Often the AE information represents an ‘incidental’ finding and not the focus of the program, again making follow-up very difficult and pertinence questionable.

PhRMA recommends the following:

- It is misleading to refer to solicited reports as study reports. The appropriate way to refer to the regulatory context, such as for reports of serious unexpected SADRs, is that *such cases should be treated as though they were study reports*. Programs that generate solicited reports should not be classified as studies. This has implications with respect to what is expected to be included in PSURs under “Safety Studies” (III.E.2.g., p. 12440). Programs that generate solicited reports should be covered in that section.
- Under III.A.7, it specifies (third bulleted point) that “Expedited reports for an unexpected SADR with unknown outcome from a study” would be subject to reporting under study conditions. Given the nature of solicited reports, this would generate an enormous number of cases with very little value. As discussed above

(b.), this new report category (... unknown outcome) has questionable practical relevance, but is particularly inappropriate to apply to solicited reports. PhRMA recommends that this proposed requirement for solicited reports be deleted.

j. Minimum Data Set and Full Data Set for an Individual Case Safety Report (ICSR) (310.305(a), p. 12472; 314.80(a), p. 12477; III.A.5, p. 12420). Although PhRMA supports and understands the need for full data sets, PhRMA is concerned that the definition of a full data set is unclear. "Completion of applicable elements of a 3500A or CIOMS I" may be interpreted in various ways by different reviewers. It is understood that a minimum data set requires information on four data fields: identifiable patient/subject, adverse event(s) (or outcome), suspect medication, and identifiable reporter. In contrast, a full data set may mean that all available information for remaining data collection fields must be obtained and reported "as appropriate." PhRMA appreciates "full" to mean the applicable data to understand and interpret the case, not that every data field must be completed on the 3500A or CIOMS I forms. Many times all data collection fields cannot be filled in on the 3500A form, either because such information does not exist, is not provided, or cannot be obtained on follow-up. PhRMA requests further guidance from the FDA as to what is expected for those data fields relevant to a case.

When appropriate, all pertinent data such as discharge summaries, autopsy reports, death certificates and other official medical documentation are aggressively solicited; however, success is heavily dependent on the reporter's cooperation and access to information. PhRMA believes that the full impact of HIPAA on the ability to retrieve such documents is not fully understood. If this requirement is applied to foreign adverse event cases, it is very unlikely to be successful in such countries as Japan, where it is often not possible to retrieve such information.

PhRMA recommends the following:

- PhRMA is in agreement that aggressive follow-up to obtain "complete data" should be pursued for cases that warrant this action; however, mandating this requirement for ALL adverse event cases will not significantly change the quality and/or understanding of spontaneous post-marketing adverse event reports. The algorithm proposed in the CIOMS V report is a practical and reasonable approach to the types of information that should be sought, which rightly depends on the nature of the case, and FDA should endorse it.
- The Final Rule should state that a "full data set" means the applicable data for the company to understand and interpret the case, not that every data field must be completed on the 3500A or CIOMS I form.
- For non-prescription (self-medication or Over the Counter) products, information from a healthcare professional (HCP) may obviously not be available since the consumer may not be under the care of a physician. The criteria for seriousness may be derived by description of the event by the consumer, which may not have involved intervention of a HCP. Therefore, this section needs to be modified to exempt non-prescription products.

We note that special provisions are proposed for certain types of medication error reports. See below for a detailed discussion on medication errors.

k. Medication Errors (310.05(a), p. 12472; 314.80(a), p. 12477; 314.80(c)(1)(C)(iii)(A), p. 12478; III.A.8, p. 12421; III.D.5., p. 12433). PhRMA disagrees with the proposal on handling medication errors for several fundamental reasons:

- the proposal focuses on only one stakeholder, the pharmaceutical industry, whereas it is clear that this requires a much broader healthcare system remit, where the issues rightly belong
- the definitions of "actual" and "potential" errors do not have internal logic and do not comport with FDA's endorsement (outside the Proposed Rule) of NCC MERP standards
- prescription and non-prescription products deserve separate treatment
- it is unclear whether the concept as presented encompasses clinical trial/experimental product situations
- from experience, most cases of medication errors that are reported either result in no adverse event(s) or in events(s) that are non-serious and self-limiting
- enforcement of the rule as currently proposed will discourage voluntary reporting due to potential legal liability on the reporters.

PhRMA recognizes this as an important Public Health issue but believes it should be handled outside the context of an SADR expedited reporting rule and in collaboration with other healthcare sectors. For example, PhRMA requests that the agency clarify their plans to educate healthcare professionals to submit such reports and what actions they would ultimately take on review of these reports.

The proposal to require expedited reporting of medication errors is in our opinion an extreme solution to detect potential public health problems of uncertain magnitude. PhRMA agrees that FDA should be informed of reports of medication errors received by manufacturers, but questions the rationale and value of requiring this information on an expedited basis in all cases, especially for those cases where the error is not a result of packaging or dosing information confusion.

It must be pointed out that although the IOM report of 1999 cited an estimated 44,000-98,000 deaths due to medical mistakes, only a fraction of those were related to medication errors, a point that is often lost but that should be made in the preamble to the Final Rule. Medication errors are primarily related to the practice of medicine, nursing, laboratory medicine, and pharmacy, including dispensing of medications and legibility/interpretation of prescribing information, and not to errors involving the pharmaceutical industry. Expediting reporting of a dispensing error by a health care provider should be required of the health care provider and not the manufacturer of the product.

It should also be noted that in the face of a public health threat, such as could arise from a serious medication error, there already exists a mechanism under GMP regulations (21 CFR 314.81(b)(1)) for a three-day "field alert."

The definition of an "actual medication error" includes the phrase "...whether the error was prevented prior to administration of the product or, ..." PhRMA is hard pressed to understand how the absence of an error ("error prevented") leads to an "actual" error. If anything, such a circumstance would be a potential or unrealized or dormant error. The separation into categories of medication errors according to whether or not a patient was

involved, and the connection to regulatory reporting, is an artificial and confusing construct.

According to the Institute for Safe Medication Practices, there are four potential causes of medication error: (1) Failed communication (handwriting or oral communication, drugs with similar names or packaging, missing or misplaced zeros and decimal points, confusion between metric and apothecary systems of measure, use of non-standard abbreviations, or ambiguous or incomplete orders); (2) Poor distribution practices; (3) Complex or poorly designed technology; and (4) Access to drugs by non-pharmacy personnel. As many of these causes reach far beyond control of the pharmaceutical industry, individuals and settings directly associated with dispensing medications should be involved and their quality standards enforced. In addition, when patients are responsible for self-administration, as when prescription or non-prescription products are taken in an outpatient setting, we believe that efforts to engage pharmacies, healthcare professionals, and patients would be a more direct means to prevent or reduce medication errors.

The broad definition of "potential" error in the Proposed Rule may produce a huge volume of reports of limited or no interest for product safety. It is unrealistic to expedite any "potential" medication error in the absence of a SADR. Medication errors might be more appropriately classified into different subcategories to reflect relevant medical issues, such as: name confusion, dose/formulation dispensing and/or use (administration) errors, and lack of product-label and/or packaging clarity. If such categorization were to be introduced, it would be necessary to create appropriate coding conventions, presumably within MedDRA, so as to be able to process and manage the data efficiently and consistently.

PhRMA seeks clarification on the definition for potential medication errors; the document appears to contain an inconsistency:

- Proposed Rule - potential medication error: "An individual case safety report of information or complaint about product name, labeling or packaging similarities that does not involve a patient."
- Page 12422, III.A.8, 1st column states: "Potential medication errors do not involve a patient, but rather describe information or complaint about product name, labeling, or packaging similarities that could result in a medication error in the future."

PhRMA also requests clarification on the following additional points:

- What is meant by "related to professional practice" in the definition? Are physician-prescribed overdoses or off-label use meant to be regarded as medication errors? PhRMA recommends that the definition explicitly exclude them.
- For reports of "actual" or "potential" confusion between two products, it may be appropriate to recommend that a copy of the report be sent to the other company. However, PhRMA suggests that this be included not in the Final Rule but in the accompanying Guidance.
- What are the reporting expectations in situations when consumers report on prescription or non-prescription product errors without detailed data? The

manufacturer should be allowed wide latitude when exercising judgment to determine reportability of such cases

- We believe that medication error reporting described in the proposed Rule refers to the U.S. only and not to international sources, and this should be so stated in the Final Rule. The term domestic is used in some instances but not in others in the document. For trademark-trademark confusion especially, all reports should be for the US only given the complexity of global language and pronunciation differences.
- Although PhRMA believes that FDA intends its proposals on medication errors to apply only to products marketed in the US (to post-marketing, but not pre-marketing conditions), this does not appear to be explicitly and unequivocally expressed in the Proposed Rule.
- When a medication error results in a suspected adverse reaction, should there be only one report sent to the FDA that covers both the suspected ADR and the medication error?

Another, major source of confusion and inconsistency, with implications for regulatory compliance, relates to the preexisting standard for characterizing and prioritizing medication errors, namely, that created by the NCC MERP. FDA's proposed terms and definitions differ substantially from the established NCC MERP error categories A through I and their definitions. Several companies are currently reporting medication errors according to these categories, either under a special request by FDA or as part of a Phase 4 commitment. Although FDA has endorsed the NCC MERP standards (e.g., see FDA Safety Page, Drug Topics, October 1, 2001; www.drugtopics.com), and they appear in at least one FDA guidance (Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements), there is no mention of them in the Proposed Rule. It is also very unclear what roles and responsibilities, and desirable interactions, fall to NCC MERP relative to the pharmaceutical industry and the FDA. The same uncertainty exists with respect to the Institute for Safe Medication Practices.

PhRMA recommends the following:

- FDA should align its medication error definitions in the Final Rule with the NCC MERP definitions. Any previously established reporting requirements under NCC MERP standards should be allowed to continue without interruption to avoid confusion and a potential for non-compliance.
- Expedited reporting (15 calendar days) should be required if a medication error resulted in a serious unexpected SADR.
- Medication error reports received by the applicant that do not require expedited reporting under current suspected ADR rules (serious unlabeled), be reported and discussed in aggregate in the next scheduled PSUR.
- A separate line listing and text summary of all actual medication errors associated with AE's (NCC MERP Categories E-I) collected during the reporting period should be reported in PSURs.
- Listings of "actual and potential" medication errors not associated with adverse experiences (NCC MERP categories A-D) should be reportable as line listings in a separate appendix to PSURs. For new products, this will ensure at a minimum a six month reporting interval.

- Consideration should be given to limiting the summary reporting in PSURs of actual and potential medication errors not resulting in adverse experiences to a defined period post-launch (e.g., for two years), or for a year after a new issue has been identified (e.g., name confusion) and then only specifically on request by the FDA.
- It would be important, and consistent with the identifiability criteria for SADRs, to introduce a “verifiability” criterion concerning the specific circumstances surrounding a medication error report, including an identified health care professional to whom sponsors can speak. Such verification will assure that unsupported or erroneous reports would not lead to premature or unwarranted action (e.g., a trademark change).

I. *In Vitro* Studies (312.32(b), p. 12476; III.B.1, p. 12424). The discussion of *in vitro* studies should refer specifically to relevant, important safety related information. It would be helpful if the Agency could provide other examples and guidance on the types of *in vitro* studies and findings that would warrant submission.

m. Information Sufficient to Consider Product Administration Changes (312.32(c)(1)(ii), p. 12476; III.B.2.c., p. 12425). Further clarification is needed regarding the kind of *in vitro* studies that would fall into this category. *In vitro* studies may be exploratory and unvalidated; hence, the clinical relevance cannot be adequately assessed from these studies and “appropriate medical judgment” may not be applicable to the findings.

The requirement may deter sponsors from seeking/conducting innovative tests that could, in the future, reduce the need for certain animal studies or provide more information regarding drug actions. It is the nature of exploratory work that findings may be unanticipated, but these findings may not have clinical relevance. The IND safety report is not the appropriate forum for presentation of findings from exploratory tests.

Also, the proposed requirement to submit expedited IND safety reports states that the information should be “sufficient to **consider** (*our emphasis*) changes in either product administration or in the overall conduct of a clinical investigation.” PhRMA suggests that “consider” is too vague a term, since many of these considerations take place as part of routine, ongoing study/program review sessions and safety surveillance activities, and the outcome may result in no change.

PhRMA recommends that it would be more appropriate to require expedited reporting for information that results in a proposed or actual change to medicinal product administration or in the overall conduct of a clinical investigation.

Examples of reportable information in the proposed statement indicate, “...such as reports of mutagenicity, teratogenicity, or carcinogenicity...” But it also states that the information “suggests a significant human risk.” The Final Rule should state that the sponsor should report, in an expedited fashion, only those findings of mutagenicity, teratogenicity, or carcinogenicity that the sponsor considers suggestive of significant human risk. Some mutagenicity, teratogenicity, or carcinogenicity findings are clearly species-specific or for other reasons do not infer a real or potential significant human risk; these findings should not have to be reported on an expedited basis.

n. Review of Safety Information from Foreign Regulatory Sources (314.80(b)(1), p. 12478; III.C.2., p. 12426). PhRMA requests clarification of the provision in this section requiring applicants to review safety information from foreign regulatory authorities. Under III.C.2. it refers to "... any safety information acquired or received from a foreign regulatory authority..." We believe that this is meant to refer to individual case reports. As recommended in CIOMS V, PhRMA requests the inclusion of wording stating that an applicant's mere access to publicly available databases (such as the WHO UMC (Uppsala) database) does not impose any specific obligation to access them routinely for active search. PhRMA requests that this limitation on expectations be stated in the Final Rule.

o. Lack of Efficacy Reports (III.C.7, p. 12431). PhRMA requests clarification for the possible distinction between the regulatory definition of "lack of efficacy with a drug product used in treating a life-threatening or serious disease" and reports of disease progression, as in oncology patients or other special populations where disease progression is known to occur even after currently accepted treatment has been utilized. This underscores the need to exercise caution in the use of these reports; they should be considered as potential signals to be investigated further, not an absolute demonstration that a product is not efficacious when used as labeled.

PhRMA also notes the newly proposed requirement (III.C.7., III.E.1.c. and elsewhere) to include in post-marketing periodic reports "an assessment of whether it is believed that the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the drug or biological product." PhRMA assumes that all discussions of lack of efficacy in this and other contexts refer only to failure of a product in the treatment of serious or life-threatening illness. We note that any attempt to satisfy this proposed requirement would necessitate having available numerator and denominator data that are notoriously difficult to estimate or obtain. Further, a comparison of "efficacy" in premarketing trials with use of a product in the "real world" makes this all the more difficult.

PhRMA would appreciate clarification on whether the lack of efficacy reporting proposal would apply only to products under an NDA or also to monographed products.

PhRMA recommends the following:

- Approaches to estimating increased frequency of lack of efficacy require considerable development and should not be part of the new Rule. Rather, it should be relegated to FDA's ongoing risk management initiatives.

p. Postmarketing Periodic Reporting. This general topic is covered in its details in many parts of 314.80 and 600.80 as well as under III.E. For convenience, our comments are numbered.

One general concern relates to the time allowed for preparation and submission after the data lock point (60 days). Given the significant amount of new information that would be required within the core PSUR and the Appendices, the time allotted should be extended to 90 days.

p. 1. ICH E2C Addendum. PhRMA is disappointed that the Proposed Rule does not incorporate the finalized Step 4 Guideline and apply its recommendations to proposed requirements. Some of the pragmatic approaches in the Addendum (simplified reports, bridging reports, executive summary, etc.) are directly relevant to some concepts introduced, but in a non-conforming way, by FDA.

p. 2. IPSRs and TPSRs. The new requirement to submit IPSRs (Interim Periodic Safety Reports) at 7.5 and 12.5 years as abbreviated versions of PSURs is in fact more demanding than the abbreviated or addendum reports recommended by CIOMS and ICH (which many companies have already implemented). This will also complicate significantly the establishment of a global PSUR schedule and may require more documents to be written for old products where in general periodicity is annually or every 5 years but never every 2.5 years. For both IPSR and TPSR, a reporting cycle of 7.5 and 12.5 years should not be required; five year intervals after the first five years post-approval should provide adequate monitoring and assessment of the safety profile. The only exception might be when there has been approval of a new indication, dosage form, or use in a new population that may impact the safety profile, in accord with the recommendations made in the ICH E2C guideline and in the CIOMS V Report. In such cases, discussion and negotiation between the company and the FDA regarding the type of reporting required should occur prior to a new approval.

p. 3. Company Core Data Sheet (CCDS), Company Core Safety Information (CCSI). PhRMA understands and agrees with the implementation of a single CCSI for an active product (irrespective of formulation). However, an option should be provided for separate documents in special situations, consistent with the CIOMS V report and the ICH E2C Addendum recommendations.

Sponsors may not prepare Company Core Data Sheets for products that are marketed in a limited number of countries or in the U.S. only. In such situations, all relevant safety information could be contained within the U.S. package insert, or other national data sheet, as practical and appropriate. We suggest that the definition of CCSI accommodate this possibility.

It is important to note that the Proposed Rule does not allow for harmonization of these reference documents. Specifically, the use of the U.S. Package Insert is requested for TPSRs, but the CCSI for PSURs and IPSRs. This would result in variability in reportable information between these reports. It is strongly suggested that one reference document, namely the CCSI, be used whenever possible across all reports.

We note that the proposed Rule would require that a PSUR contain a copy of the CCDS/CCSI in effect at both the beginning and the end of the reporting period. ICH E2C guideline requires only the document in effect at the beginning of the period, with appropriate explanations of any proposed or actual changes. An exception is the option under E2C to include only the document at the end of the

period for 5-year reports. PhRMA recommends adopting the same scheme. See additional comments on this point under section 3.p.11.

p. 4. Data Lock Point and International Birth Date. PhRMA agrees with the proposal to use data lock points and the International Birth Date (IBD) to determine reporting timelines for postmarketing periodic safety reports.

PhRMA agrees with the possibility of alternative reporting frequencies; however, it is essential that this section also state that the manufacturer be able to negotiate with FDA exactly what reporting frequency is appropriate when a product is already the subject of, for example, annual reporting in other countries or regions.

The proposed Rule indicates that the PSUR would allow applicants to submit a single core PSUR document for products that have an approved application (i.e., NDA, ANDA, and BLA). PhRMA seeks guidance on how to handle products with multiple formulations or multiple active ingredient combinations, some of which are not approved in the US.

p. 5. TPSRs vs PSURs vs. IPSRs: “Old” vs. “New” Products. FDA has chosen to use a January 1, 1998 approval as the demarcation date for determining whether the newly defined TPSR or PSUR format and content should be used for a product. If one assumes that the new Rule will be finalized and issued around the end of 2004 and will have to be implemented in the second half of 2005, products approved in January 1998 will have been on the market for some 6 to 7 years. Taking this into account and considering that there is a myriad of products that will be on the market for considerably longer than 7 years in 2005, we do not understand why the Agency believes it necessary to require several additional kinds and amounts of information in a TPSR, beyond the current NDA periodic safety report, for such “old” products. In essence, PhRMA requests that there be a grandfathering of “old” products to allow them to continue to fall under the more simplified current requirements under 314.80. Thus, there is nothing “traditional” about the new TPSR and we question its need. If anything, it should be made optional for a company to convert to a TPSR (or, as indicated, a PSUR) type of report for such products, unless FDA wished to request that a company use the TPSR for products with special circumstances. Further complicating the situation is the requirement to prepare 7.5 and 12.5 year TPSRs. Keeping track of all these varying requirements, especially for products with many different formulations, indications and uses approved at various times, is a daunting prospect and PhRMA questions their value.

Retrofitting old products to a new TPSR report would be extremely difficult. For example, it would be necessary to identify cases that should be included in subgroups (e.g., SADRs from Class Action lawsuits, medication errors, etc.), as proposed in TPSR and PSUR/IPSR format. Difficulties in retrospectively identifying cases for subgroups is primarily a practical matter, due to the challenges of retrospective application of coding conventions and necessary changes in system capabilities. A further complication arises due to the proposal that for products with approved pediatric use supplements, PSURs and IPSRs

would be required even if the original application were approved prior to January 1, 1998.

p. 6. Individual Case Safety Report (ICSR) Submission (III.E.1., III.E.4.).

FDA is proposing that ICSRs not be included in TPSRs. Instead, ICSRs would be submitted separately on a semiannual basis (ICSRs - semiannual submission). The new requirement of semi-annual submission of Individual Case Safety Reports as 3500 A forms (paper) instead of accepting standard PSUR listings is a redundant requirement and of no perceived added value. It will create considerable complexity and unnecessary significant extra-work for the industry (e.g., trying to sort out which types of cases belong where and when, as described under III.E.4.). Semi-annual submission of ICSRs would require a similar amount of effort as preparation of TPSRs, PSURs, and IPSRs themselves and would require targeted retrieval of cases meeting TPSR/PSUR/IPSR criteria. Thus, the associated review and processing activities would essentially be equivalent to preparing a TPSR/PSUR/IPSR on a semiannual basis in addition to the proposed reporting schedule.

PhRMA recommends the following:

- Companies should be allowed to include line listings of ICSRs in TPSRs and/or PSURs/IPSRs, the standard PSUR requirement under non-US regulations.
- The proposed semi-annual report or other submission of non-expedited ICSRs should be eliminated as a requirement.

p. 7. Increased Frequency Reports (III.E.1.c., III.E.2.k.vi., etc.)(See additional comments under section o. above). It is unclear what FDA's expectations are regarding increased frequency assessment now that the requirement has been revoked. Will FDA provide some guidance and examples of the orders of magnitude and quality of the information that would be needed in exercising judgment on whether there is a "meaningful" increase for both expected serious ADRs and lack of efficacy?

p. 8. History of Safety-related Actions Taken/Actions Taken for Safety Reasons (III.E.1.f., III.E.2.c., etc.). PhRMA seeks clarification on whether these sections should include information on changes to packaging and other informational materials in response to medication error concerns. Under clinical trial suspensions (or other major changes to a study or program), would investigator or IRB initiated actions be referenced? PhRMA also questions the value of attaching to the PSUR communications sent to health care professionals, since any safety actions will be described, and in most instances this communication would have been sent to the Agency previously. PhRMA also requests clarification of the term 'Any communication.'

p. 9. Contact Person (III.E.1.h., III.E.2.k.x., III.F.4.). (Also, see comments in section e. above.) FDA is proposing that PSURs, TPSRs and IPSRs include the name and telephone number of the licensed physician responsible for the content and medical interpretation of the report. This is also the case for individual 3500A and CIOMS 1 forms. PhRMA does not agree with the proposal

to provide contact information on individual physicians responsible for the content and medical interpretation of the data and information in each report. Companies currently provide a contact person who can ensure that FDA has adequate access to the appropriate medical professionals in the company in a timely manner and this arrangement should be endorsed in the Final Rule.

p. 10. Worldwide Marketing Status (III.E.2.b., etc.). For consistency with the ICH guideline, "when known" should be added to the current bullet "Dates of market launches." FDA will be provided with information on registrations and market withdrawals. Also, because the Company Core Data Sheet lists all indications, and is provided with the PSUR, we see no reason for the additional requirement to list indications in this section. If there are differentiating safety issues related to indications, they will be covered elsewhere in the PSUR.

p.11. Changes to CCSI (III.E.2.d., III.E.2.j., etc.). There should be an option to use the CCSI in effect at the end of the reporting interval as the reference information, especially for 5-year reports. When listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the current version of the CCSI as the reference document, as long as that choice is made clear in the PSUR text. This is consistent with the recommendations in the ICH E2C Addendum, which recognizes the current existing pragmatic approaches to this process. The changes to the CCSI would be described in the PSUR section "Changes to the Reference Safety Information." This approach should be endorsed as an option in the Final Rule.

p. 12. Worldwide Patient Exposure (III.E.2.e., etc.). The Rule proposes that, when possible, data should be provided by gender and age. If these data are not available, an explanation for the lack of such information should be provided. The proposal for worldwide patient exposure should reflect the ICH E2C requirements, which does not include the requirement to provide an explanation "for the lack of such information." Applicants should be able to determine and explain the most appropriate source of exposure data for a product and use a consistent approach in the analysis. Applicants should not be required to provide an explanation "for the lack of such information". PhRMA also notes that age and gender breakdowns will not be available in most situations and requests for such data may be more appropriate as a guidance than as a regulation. In addition, the E2C guideline asks for age and/or gender breakdowns only when possible *and relevant*. Finally, PhRMA requests more clarity regarding the inclusion or exclusion of data from clinical studies. ICH guideline E2C, Section IIC, is clear on this issue and includes the statement "When ADR data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made."

p.13. Appendices to Periodic Reports (III.E.2.k.). PhRMA is very concerned about the breadth and depth of the proposed extra information that would be required in a set of Appendices, for little added value in our opinion. We believe that much of the requested information belongs within the core PSUR or elsewhere, which is already provided for under current ICH guidelines. Also, it is not obvious whether all or some of the intended Appendices (other than U.S.

labeling) must contain information from U.S. sources only or worldwide. Specific issues are as follows:

- **U.S. Labeling.** PhRMA suggests that this document, and discussion of the "local" implications vis-à-vis CCSI, be attached to the cover letter in a PSUR submission to the FDA, as recommended in the E2C guideline and widely adopted under current practice.

- **Spontaneous Reports Submitted to the Applicant by an Individual Other than a Health Care Professional.** PhRMA requests clarification regarding whether foreign and domestic reports should be separated in these tabulations. It should also be noted that many companies are currently including "consumer" report listings and tabulations within the core PSUR, and that option should be provided. It might also be useful for FDA to adopt the extensive guidance in the CIOMS V report that relates medical verification and confirmation of an initial consumer report.

- **SADRs With Unknown Outcome.** As discussed in section 3.b. above, we hope that FDA will eliminate this category of report. This new requirement will be unique to the US and unless shown to be of added value should be deleted.

- **Class Action Lawsuits.** FDA's Proposed Rule would consider SADR information compiled in support of class action lawsuits to be neither spontaneous nor "study" information because "the vast majority of SADR information from class action lawsuits is duplicative." Further, "In many cases, information in addition to the minimum data set is not available for these SADR reports and follow-up is unlikely to result in acquisition of new information" (III.A.6 p. 12421). Thus, FDA proposes that summary information on class actions be provided in periodic reports, i.e., TPSRs, PSURs and IPSRs.

PhRMA agrees with this proposed change. However, PhRMA recommends that FDA permit periodic reporting of any SADR that is legal in origin because all types of civil litigation -- not just class actions -- pose the same issues raised in the preamble to the Proposed Rule. This would include any SADR that is reported to the company via a lawsuit or contact from an attorney representing a patient; SADRs of this type are usually reported to the company later than one year or more after the event has occurred.

PhRMA proposes that these types of cases be discussed in the Overall Safety Evaluation Section, unless a specific issue is being addressed, in which case they would appear in Section 6.

PhRMA also suggests that FDA state in the Preamble to the Final Rule, if not in the rule itself, that FDA recognizes that adverse event reports should not come into evidence in any type of civil litigation because such uses are inappropriate and at cross-purposes to FDA's regulatory goals. In addition, 3500A/CIOMS I forms released by FDA could contain

standard wording, such as "It is the opinion of FDA that adverse event reports are intended for regulatory purposes only and should not be entered into civil litigation proceedings."

- **Lack of Efficacy Reports.** PhRMA believes that any information or discussion on such cases belongs within Section 8 (Other Information) of the standard E2C outline, where it specifies that this type of material be placed.

- **Information on Resistance to Antimicrobial Drug Products.** This information also logically belongs in Section 8 of a PSUR, which we believe would also be acceptable to other regulators as useful information and in the interest of harmonization. In many respects, it reflects actual or potential lack of efficacy. Furthermore, PhRMA recommends that any data of this sort be provided by geographic area, given the strong influence of the "environment" on resistance patterns.

Information regarding resistance is difficult to place in perspective. For example, there are often many reports of changes in susceptibility within a small area or hospital because of the large number of organisms tested (with the possibility of many isolates from a small number of patients), the number of antibiotics included in the testing, and the multiple centers that routinely conduct and report such testing (i.e., hospital antibiograms), often using different laboratory methodology and different interpretive criteria.

On this last point, as FDA knows, resistance of microorganisms to antimicrobial agents is the subject of intense, widespread, collaborative initiatives on how best to gauge the extent of the problem and how to manage the technical issues (FDA, other US governmental agencies, WHO, NCCLS, etc.). Pending resolution of these ongoing efforts, we believe it is premature to introduce new requirements for covering this matter within a PSUR context.

- **U.S. Patient Exposure.** There is no need to place this information in a separate Appendix when geographic breakdowns of exposure data are already routinely provided within the body of the PSUR (Section 5). We recommend that this ICH-specified approach be included in the Final Rule, rather than the use of a separate Appendix.

q. Miscellaneous Items

- Under III.B.5 (312.64(b)) **Investigator Reporting**, it specifies that "An investigator must report ... any other SADR ...promptly ..." We suggest that use of the word promptly is misleading and inappropriate, even with the qualifier that follows this statement. It implies "quickly" under common usage, yet in most clinical trial situations non-serious safety experiences would not be collected or processed until study CRFs were retrieved, which may or may not take place according to a "prompt" schedule.

- Under III.D.5. Medication Errors, p. 12433, we believe that the word “domestic” should be added before “reports of potential medication errors” in the second paragraph, first sentence.
- PhRMA does not understand why FDA proposes a special, separate PSUR and PSUR reporting schedule for products with pediatric use supplements (III.E.5.a., p. 12443). The data can readily be included as a subset of the already established “adult PSUR,” in accord with the goal of having one PSUR for all uses, etc.
- Location of Safety Records (314.80(c)(3)(i)(D), p. 12481; 314.80(c)(3)(ii)(k)(10), p.12483; III.E.1.g., p. 12438; III.E.2.k.x., p. 12441). Because safety records may be maintained in multiple locations, including multiple countries and offsite archives, only a corporate address should be required for TPSRs and PSURs. Listings of locations of safety records are maintained within the sponsor’s files and can be provided on request.
- FDA proposes adding epidemiology studies and output from databases to sources of relevant safety information that must be reported. There are untold numbers of studies conducted on medicinal products that rely on epidemiologic/pharmacoepidemiologic methods and a host of databases. The Final Rule should clearly indicate that only meaningful results from such efforts, based on judgment, need be reported. Furthermore, the Final Rule should specify that there is no obligation for a company to seek out and examine any and all such studies and databases for product-specific information.
- Industry’s Resource/time estimates by FDA cite 8 hours of health care professional, regulatory affairs professional, and clerical person time to prepare a report of information sufficient to consider a product administration change, 40 hours to prepare a PSUR, and 1 hour for a contractor to submit SADRs to companies within five business days. These figures are unrealistically low. For example, the current average time to prepare a PSUR ranges from two to four times FDA’s estimate per PSUR, even without accounting for the newly proposed appendices. This includes time to gather and analyze the information, write the report, assemble all the supporting materials and have the report reviewed and approved internally. Similarly, it is unlikely that a thorough and high quality report discussing a product administration change could be prepared and submitted in one day. And finally, FDA’s one hour estimate for exchange of information between license partners is based on FDA’s possible misunderstanding of such exchanges. Under most license arrangements, parties do not merely fax source documents (raw data) to each other; rather, companies exchange properly processed reports and, under agreement, exchange information regarding the safety of the products to ensure proper safety surveillance and consistency in their respective regulatory reporting. These exchanges require more than one hour of time. Also, it is stated in Section V.A, page 12449, that changes proposed will result in a “2% reduction in hospital-related SADRs.” Was this intended to say hospitalization due to SADRs, or SADRs that occur in hospitalized patients? We would like to have clarification on this point and learn how this number was derived.

4. RESPONSES TO SPECIFIC QUESTIONS BY FDA

a. Implications of New Definition for SADR (III.A.1., p. 12417). As already pointed out (section 3.a. above), introduction of this new acronym, definition and interpretation seriously compromises international harmonization of this important concept. As also discussed, PhRMA believes that the proposed alternative definition will indeed lead to very large increases in reporting volume from clinical trials. Some estimates, including from retrospective analyses of databases, indicate as much as a 10-fold increase. For many clinical trials, this represents a significant problem with respect to maintaining the blind and to sample size for efficacy, since most patients experiencing serious unexpected SADRs will be discontinued from treatment. A commensurate burden will affect investigators and IRBs.

b. Are Disclaimers Sufficient to Protect Manufacturers? (III.A.1., p. 12418). FDA seeks comment on whether the current "disclaimers" are sufficient to protect manufacturers, applicants, and sponsors, from the use of SADR reports in product liability actions. As mentioned above, the number of IND safety reports may increase by 10-fold without the concomitant benefit of improving report quality. Aggressive follow-up ("Active Query") would also generate more specific information regarding the SADRs. Moreover, requiring the submission of an autopsy report, hospital discharge summary, or death certificate for reports of death and hospitalization means that FDA will be in possession of highly confidential information.

PhRMA recognizes and appreciates that the current safety reporting regulations provide manufacturers, applicants, and sponsors with a disclaimer allowing them to deny that SADR reports constitute an admission that the drug or biological product at issue caused or contributed to the adverse effect. PhRMA believes, however, that the current "disclaimer-only" regime is woefully insufficient to guard against the increasing improper use of SADR reports in civil litigation. Despite the existence of the current disclaimer, plaintiffs in civil product liability lawsuits frequently attempt -- and are often permitted -- to use SADR reports as evidence that the drug caused the reported adverse event or to prove the incidence in the general population of adverse events "similar" to those alleged to have been suffered by plaintiff. Evidence of SADR reports are used both at the expert/*Daubert* stage to overcome a plaintiff's burden to establish causation, and at the trial on the merits, wherein the existence of the sometimes-voluminous reports is presented in an effort to persuade the jury that the drug must somehow be the cause of the problem. Even when judges instruct the jury on the limited uses of this evidence, there is substantial doubt whether the jurors can or do follow that instruction.

PhRMA believes that the misuse of SADR reports undermines FDA's ability to achieve its regulatory goals. The only effective way to guard against the misuse of these reports is for FDA to enact a regulation precluding the admission of: a) the SADRs themselves; b) the information contained therein

to the extent that the information is identified as coming from the SADR; and c) any reference to the SADR, except to the extent that FDA's own analysis and/or response to the reports is relevant, in which case a court may choose to permit evidence about the Agency's analysis of or response to the SADR. In addition, PhRMA believes that an expanded, strongly-worded disclaimer regarding FDA's view of the improper use of SADR reports should be set forth in the regulations and prominently displayed on all forms and documents containing case data or safety findings. Finally, PhRMA believes that supporting medical information and records collected as part of the SADR reporting process should be absolutely exempt from discovery.

Background:

PhRMA shares FDA's view that the improper use of SADR reports in civil litigation affects the integrity of the safety reporting system. At its heart, the adverse event reporting system (both as it currently exists and with the proposed enhancements) relies on two central components: first, a medical professional's voluntary decision to report a suspected adverse event, and second, a sponsor's monitoring, analysis and assessment of the adverse event. FDA has repeatedly stressed the critical value of the adverse event reporting system to the health and safety of our citizens and has thus often indicated its desire to promote voluntary reporting and to obtain higher quality SADR reports.

PhRMA shares FDA's objective of strengthening this critical safety reporting system. The misuse of SADR reports in product liability litigation interferes with that objective. Plaintiffs in litigation involving side effects of drugs frequently sue doctors along with manufacturers. In a recent study by the United States Chamber of Commerce Institute for Legal Reform, a majority of physicians surveyed, 57%, were concerned or very concerned about being sued by a patient who experienced side effects from a drug, even when the drug was indicated and properly prescribed. U.S. Chamber Institute for Legal Reform, *Pharmaceutical Liability Study Report on Findings* (July 15, 2003), p. 25. Especially given these concerns, voluntary reporters may be far less likely to report suspected events if the reporters come to believe that their reports will later be used as evidence of causation. Such an outcome would fundamentally undermine the prophylactic principle underlying the reporting system -- encourage reporting of all suspected events regardless of causation as the best way to cast a broad net that will best identify any potential safety signals.

Recommendations:

In response to FDA's invitation for comments on methods to eliminate the improper use of SADR reports in civil litigation, PhRMA makes the following recommendations. PhRMA believes that these recommended proposals are essential to effectively carrying out FDA's stated goal of expanding the quality and scope of SADR reporting and thereby improving the health and safety of our citizens:

- FDA should directly and unambiguously preclude the admission of: a) the SADRs themselves; b) the information contained therein to the extent that the information is identified as coming from the SADRs; and c) any reference to the SADRs, except to the extent the FDA's own analysis and/or response to the reports is relevant, in which case a court may choose to permit evidence about the agency's analysis of or response to the SADRs. The rule should specifically address favored back door approaches to admissibility such as through "expert" testimony or hearsay exceptions.
- FDA should expand the wording of the existing disclaimer such that it unambiguously communicates FDA's view of the proper and improper use of SADR reports.
- FDA should preclude the discovery of medical records and other documentation gathered through post-marketing surveillance.

First, PhRMA recommends that FDA promulgate a rule precluding the admissibility of the SADRs themselves except to the extent the FDA's own analysis and/or response to the reports is relevant, in which case a court may choose to permit evidence about the agency's analysis of or response to the SADRs. PhRMA believes that such a rule will prevent the misuse of SADR reports, minimize the chill on voluntary reporters, and reduce the risk of judicial findings based on unreliable scientific evidence, which is inimical to FDA's regulatory goals.

It should also be emphasized that SADR reports or the information in them are frequently brought before the jury through "expert" testimony, which can take the form of direct testimony by the expert that SADR reports prove causation, or – particularly when SADR reports previously have been ruled inadmissible to prove causation – as one of the sources of information the expert has relied upon in reaching an opinion as to causation. There is a body of developing case law reflecting that an expert's use of SADR reports is an improper method to establish causation, *see e.g. Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 464, 539-40 (W.D. Pa. 2003); *Brumbaugh v. Sandoz Pharm. Corp.*, 77 F. Supp. 2d 1153, 1156 (D. Mont. 1999), but inconsistent treatment of the question by state and federal courts poses the risks addressed above with regard to FDA's regulatory objectives. Because the tactic of utilizing expert testimony and other "back door" approaches to establish admissibility of SADR reports in civil litigation remains common, FDA should address these issues directly in crafting its

rule, and provide that information contained in SADR reports should not come before the jury.

Although PhRMA contemplated a broader proposal precluding the admissibility of SADR reports in their entirety without exception, PhRMA ultimately concluded that such an absolute rule would prove unworkable and occasionally counterproductive. For example, a manufacturer in a product liability lawsuit may find it necessary to refer to SADR reports to explain the adequacy of the product's precautionary labeling even in the absence of proof of causation. Likewise, there are often instances in which a manufacturer would want to establish that it duly recorded and forwarded adverse events to the FDA, which decided that a labeling change was not warranted. And finally, a manufacturer might want to establish the absence of any related SADR reports despite diligent post-marketing monitoring. These uses do not have the same potential to chill the reporting of SADRs as the widespread offensive use of SADRs would have. For these reasons, PhRMA believes that a rule precluding the use of SADR reports except to the extent that FDA's own analysis and/or response to the reports is relevant is the better approach.

Second, PhRMA recommends that FDA revise its existing disclaimer to clarify FDA's view as to proper and improper use of SADR reports. PhRMA believes that a strongly-worded disclaimer is essential to communicate to courts and juries that it is improper and misleading to consider SADR reports as legitimate evidence of causation. At a minimum, for the disclaimer to effectively prevent the misuse of SADR reports, and thus to protect the integrity of the system, it should clearly and unambiguously communicate FDA's view that SADR reports are spontaneous, uncontrolled reports of a particular event in a particular person and can never constitute scientific evidence that the drug actually causes the particular adverse event. PhRMA believes that this enhanced disclaimer should be set forth in the regulations and prominently displayed on all forms and documents containing case data or safety findings.

PhRMA notes that modification of the rule to preclude admissibility of SADR reports and to provide a stronger disclaimer comports with FDA's expressed desire and previous efforts to curtail the misuse of its regulatory actions in product liability litigation. In its recent Diphenhydramine labeling final rule, FDA reemphasized that the existence of a precautionary warning issued by FDA for a product cannot and should not be used as evidence that the drug caused the adverse event. As FDA explained, "To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation." 67 Fed. Reg. 72555, 72556 (Dec. 2, 2002). FDA further stated that its regulatory decisions "do not meet the standard of proof required to prevail in a tort action." *Id.* FDA relies on a range of factors, including SADR reports, in making warnings decisions. A rule precluding the admissibility of SADR reports and clarifying that SADR reports are not, in FDA's view, scientifically valid proof of causation, is entirely consistent: for the same reason FDA warnings themselves cannot be used as proof of causation,

neither can SADR reports, which sometimes inform those precautionary warning decisions.

PhRMA appreciates the wording FDA incorporated in the recent Diphenhydramine labeling final rule emphasizing that the existence of a precautionary warning issued by FDA for a product cannot and should not be used as evidence that the drug caused the adverse event. A similar strongly worded disclaimer regarding FDA's view of the improper use of SADR reports would provide at least minimal protection to manufacturers against the misuse of SADR reports in litigation. PhRMA believes that such a disclaimer is absolutely necessary, whether issued in addition to, or in place of, a stronger rule precluding admissibility of SADR reports.

Third, PhRMA is growing increasingly concerned about the discoverability of medical records and other source information gathered by manufacturers as part of their post-marketing surveillance obligations. FDA's objective of obtaining more complete information about spontaneous adverse events is necessarily frustrated by the discoverability of medical records in product liability litigation. Medical providers have less incentive to submit patient records and other necessary information to the manufacturer or to FDA if those records may be disclosed in litigation. PhRMA recognizes that the redaction of patient and reporter identities from medical and other records offers some protection to medical providers and patients. Because physician malpractice claims are frequently alleged in product liability lawsuits, however, PhRMA is concerned that medical providers will be reluctant to trust third-party redaction and will instead opt not to submit records in the first instance. Accordingly, PhRMA recommends a bright-line rule that "back-up" or "source" materials gathered or created as part of a company's drug safety surveillance program should be absolutely exempt from civil discovery.

Legal Authority:

FDA has requested comment on its legal authority to craft a rule precluding the misuse of SADR reports in civil litigation. Based on the essential need to regulate the improper use of SADR reports in order to ensure a vibrant and effective post-marketing safety surveillance system, as well as FDA's own prior regulatory activity in this precise area, PhRMA believes that FDA has the legal authority to craft such protections as part of its overhaul to the rule.

First, because the integrity and functionality of the safety reporting system have been committed to FDA's care, FDA has authority to fashion regulations necessary to protect this system and, through it, the public health and safety. FDA has previously found it has authority to regulate the adverse event reporting system and ensure that it meets public health needs. FDA's regulation in this area has included establishing control over the use of adverse event information in judicial proceedings. FDA has previously prohibited the discoverability of patient and voluntary reporter identifying information from SADR reports except in narrow circumstances, (see 21 C.F.R. § 20.63(f)), because "the public health value of adverse event reporting outweighs the individual needs of plaintiffs to discover the identities

of a voluntary reporter or a patient, other than the plaintiff, who is the subject of the report.” 60 Fed. Reg. at 16966.

PhRMA believes that the same public health considerations that led FDA to protect patient and voluntary reporter identifying information from discovery strongly counsel action in this instance. Wide variations exist among state and federal court procedures regarding admissibility of SADR reports and their permitted uses in product liability litigation. The resulting inconsistencies frustrate compliance with the overall system by discouraging voluntary reporters from making reports and providing supportive information. Survey data confirm the reporters' concerns about their own exposure in product liability suits involving pharmaceutical products. Their justifiable anxiety that anything they say can and will be used against them, and that their reports may contribute to the proliferation of lawsuits, threatens to erode the foundation of the reporting system. FDA has the authority to protect the public health value of the reporting system by precluding admissibility of SADR reports in civil litigation.

Second, FDA's authority to protect the adverse event reporting system and thereby public health includes the authority to preempt state and local law. As FDA is aware, federal preemption may be found where a state law “stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress” or “interferes with the methods by which a Federal law is designed to reach its goals.” 60 Fed. Reg. 16962, 16966 (April 3, 1995) (internal quotation marks and citation omitted). A regulation that clearly and unambiguously preempts state law will stand when the “agency's choice to preempt ‘represents a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute’” unless Congress would not have sanctioned the accommodation. *Id.* (quoting *United States v. Shimer*, 367 U.S. 374, 383 (1961)).

In the context of regulating discoverability of patient and reporter identifying information, FDA found that it had “sufficient legal authority to preempt State and local laws, rules, regulations, and other requirements that would permit or require the disclosure of the identities of health care professionals who voluntarily report adverse events and the patients or other individuals named in those reports. Although Congress did not expressly preempt State law in this area, the agency finds Federal preemption to be appropriate because such State or local laws, rules, regulations, or other requirements would impede FDA's ability to monitor product safety after approval to ensure that human drug products, biologics, and medical devices are safe and effective for their intended uses. . . . Thus, under principles of preemption law, congressional intent to preempt State law can be inferred.” 60 Fed. Reg. at 16963 (citation omitted). FDA found that state and local laws permitting or requiring disclosure of patient and voluntary reporter identifying information “hinder[ed] FDA's monitoring scheme” and would possibly “deter voluntary reporting” or “chill the willingness of reporters to provide information to FDA.” *Id.* at 16966. Therefore, FDA specifically provided in 21 C.F.R. 20.63(f)(2) that “No State or local governing entity shall establish or continue in effect any law, rule, regulation, or other requirement that permits or requires

disclosure of the identities of the voluntary reporter or other person identified in an adverse event report except as provided in this section.”

PhRMA agrees with FDA’s preemption analysis and believes it applies with equal force to the issue of protecting the safety reporting system by, *inter alia*, precluding admissibility of SADR reports, modifying the current disclaimer to more clearly express FDA’s view of the purpose of SADR reports, and precluding the discovery of medical records gathered through post-marketing surveillance. State rules of evidence, insofar as they cover documents created under FDA mandate and threaten to interfere with FDA’s regulatory objectives, are subject to preemption to the same extent as other state laws.

c. Breaking the Blind for Serious SADRs that are Not Study Endpoints (III.A.5., p. 12420). PhRMA assumes that the discussion on this point (middle column, bottom of p. 12420) should refer to “other serious *unexpected* SADRs;” unexpected is not mentioned. As inferred above (5.a.), PhRMA believes that this problem would not arise if the definition of SADR were made compatible with the guidance given under ICH. Under the conditions posed by FDA, however, it is difficult to address the issue because one will generally not know in advance if such events will “occur at a rate high enough” to compromise the overall blinding.

d. Use of Written Requests for Active Query (III.A.6., p. 12421). PhRMA has elucidated its position on verbal vs. written inquiries under section 3.c. above. We believe that FDA should allow for written follow-up in all cases except those that represent a clear and significant potential risk to patients, such as deaths suspected to be drug related or even for those events that might be regarded as “always serious.”

e. Effect of HHS Announcement on Possible Use of SNOMED CT®. Implications for Use of MedDRA (III.F.2, p. 12444). Although FDA does not raise this issue within the proposed Rule, it has asked for comment on the perpetual-use licensing agreement for SNOMED CT® announced by the Department of Health and Human Services (<http://www.fda.gov/oc/initiatives/barcode-sadr/qa-sadr.html>). See the “Qs and As” on the Safety Reporting Requirement for Human Drug And Biological Products Proposed Rule as posted on the FDA’s web site, updated August 28, 2003. The possible use of SNOMED CT® for Regulatory communication has come as a surprise to the industry and it has not been able to review the new version of that terminology, or to consider whether it can be adequately mapped to MedDRA. MedDRA was developed by industry and regulators via the ICH consensus process to facilitate regulatory communication of medical terms in Europe, Japan, and the US. PhRMA urges the Agency to resist any efforts to shift from MedDRA to SNOMED CT®, at least for ADR reporting and use in coding data from clinical trials. Companies have for some time expended and are continuing to expend many millions of dollars and extensive time and resources in order to understand, implement and maintain MedDRA, including creation of conventions for use, SOPs, training programs, systems modification, and technical support. Having to cope with yet another new coding terminology for the foreseeable future would be

nothing short of disastrous. Among the many major problems will be the disconnect between the US and other country regulatory requirements involving MedDRA, which will undermine any semblance of harmonization of suspected ADR reporting and analysis. It will take much study to determine whether the two terminologies are compatible with regard to medical concepts or if mapping would be readily achievable.

PhRMA is concerned about a further complication, namely, the June 10, 2003, introduction of the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) by the National Cancer Institute (NCI) for adverse event reporting (<http://ctep.cancer.gov/reporting/ctc.html>). The NCI, certain US-based oncology study groups, and oncology-oriented groups within government agencies, including FDA, have stated intentions to fully implement the CTCAE in October 2003 for adverse events, regardless of chronicity or modality, in oncology clinical trials. Tentative, incomplete mapping of approximately 319 CTCAE terms to MedDRA version 6.0 was published by the NCI in September 2003; however, fundamental concerns regarding expression of event severity remain. We are not aware of any plan to review and update the CTCAE as new versions of MedDRA are released. Application of one medical terminology to clinical trials and another terminology to safety reporting creates unnecessary data reconciliation tasks and is counterproductive.

5. PhRMA PROPOSALS ON ISSUES NOT COVERED IN THE PROPOSED RULE

This section is meant to introduce three new ideas that relate to aspects of the proposed Rule but that are not mentioned or considered within the document. PhRMA believes that if these proposals are accepted, they would improve the ability of industry, investigators, and the Agency to focus on important, priority safety issues and make the pharmacovigilance process more efficient.

a. A New Process for Informing Investigators and IRBs About Serious Suspected ADRs. PhRMA urges the Agency to consider the recent proposals under the EU Clinical Trial Directive and Guidelines, and by the CIOMS VI Working Group (on which the Director of FDA's Office of Safety participates) regarding expedited reports to investigators. Instead of forwarding them as they occur (under current IND regulations), it is far more meaningful and practical to send them periodically (e.g., quarterly) during Phase I-3 studies as line listings to investigators. These periodic notices would be accompanied by a summary of the evolving safety profile of the investigational product. Currently, the regulations require industry to send each qualifying report individually in a 3500A format, which for investigators and IRBs can be difficult to track, aggregate, analyze, and interpret. Discussion with investigators and IRBs confirms that this process is often very difficult to manage, especially for a compound involved in many trials with large numbers of patients. Although the Agency would continue to receive individual reports in an expedited fashion, periodic summaries of safety information, that would include more than just expedited reports, would be more informative and useful for investigators and IRBs, and would be much easier for them to manage administratively.

It would also enable IRBs to fulfill their oversight responsibilities in a more meaningful way. Companies would continue to update their Investigator Brochures as usual.

b. Incidental Findings from ICSRs. This topic is relevant to section II.B.2. (Quality of Post-marketing Safety Reports) in the preamble of the proposed Rule.

During the course of follow-up data collection for a spontaneously reported adverse experiences, medical concepts beyond the reporter's original, verbatim adverse experience term(s) are often introduced as part of the patient's clinical course or medical history. These concepts, which are not the focus of the reporter's reason for contacting the Company and for which no causal association with the use of the drug or vaccine is stated or implied, have been described in the CIOMS V report as "incidental findings".

CIOMS V defines incidental findings as follows:

An incidental event, adverse or otherwise, is one that satisfies the following criteria: although it occurs in reasonable clinical temporal association with the use of a drug product, it is not the intended subject of a spontaneous report (i.e., it did not prompt the contact with the pharmaceutical company or the regulator) and there is no implicit or explicit expression of possible drug causality by the reporter, other parties cited in the medical record, or the company's safety review staff.

Companies are increasingly being asked by FDA to code all clinical events, including incidental findings, that are abstracted from medical records, discharge summaries, etc., which occur at any point after introduction of the suspect drug/vaccine. This practice decreases the ability to identify the reporter's focus of the report to the Company and increases the "noise" in the spontaneous reporting system. The Proposed Rule itself (section III.A.1; page 12417) specifies that "...for spontaneous reports, manufacturers and applicants would always be required to assume, for safety reporting purposes only, that there was at least a reasonable possibility in the opinion of the initial reporter that the drug or biological product caused the event". Miscellaneous events learned through follow-up are not necessarily "reported" by the initial reporter in the usual sense; therefore, there is no reason to presume that the reporter considered them related to the drug/biologic product. Not everything that happens to patients after they take a drug should be considered a suspected adverse drug reaction.

Recommendation: PhRMA recommends that the CIOMS V definition of incidental findings be incorporated into the Final Rule. We propose to exclude coding unrelated "incidental" adverse experiences obtained in response to a request for follow-up information from Section G(8) of Form 3500A and item 7 of VAERS and CIOMS forms. PhRMA proposes a description of the incidental findings in the narrative portion of the government forms, thus enabling an evaluator (Company or Agency) to discern the reporter's focus of the report versus incidental events. Recognizing that FDA believes that all events occurring after introduction of the suspect drug should be coded, even if the reporter mentions them incidentally, we alternatively recommend that with the adoption of ICH E2B standards for electronic reporting of individual case safety reports, FDA strongly consider use of the ICH E2B field B.2.i.3 "Term highlighted by the reporter" to differentiate the adverse reactions/events explicitly provided by the reporter versus incidental findings abstracted from follow-up information obtained by sponsors as part of efforts to obtain quality data and thus enhance surveillance of its marketed products.

c. Sharing Direct-ICSRs with Companies. The industry requests that the agency reconsider its current policy regarding sponsor access to serious adverse reaction/event reports that are sent directly to FDA, bypassing companies.

The MedWatch to Manufacturer Program, in most situations, provides sponsors with very few of the AE reports received by the FDA directly from non-company sources. Those that are forwarded are the ones received by FDA during the first three years after approval. Retrieval through the FOI process is costly and provides very limited information, which often does not allow for reconciliation of duplicate reports. In addition, even with regular requests, FOI data are only available with significant delay. Furthermore there are no regulations or guidelines on how often FOI retrievals should be conducted, or what to do with the data when obtained. This creates an asymmetry between the FDA and manufacturers with respect to knowledge of reported cases, and therefore the ability to perform good pharmacovigilance.

Other regulators routinely send manufacturers all relevant direct-reports promptly for serious cases and periodically for others. The manufacturers are then able to submit relevant reports to other regulators and share the information with company affiliates as appropriate.

PhRMA requests that FDA initiate a revised 'Report to Applicant' program to send all suspected serious adverse drug reaction reports to the relevant sponsors in an expedited manner.