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

Re: Docket 00N-1484, Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products (68 Federal Register 12406-12497; March 14, 2003)

Comments submitted electronically to fdadockets@oc.fda.gov

Dear Sir/Madam:

The following comments on the above-captioned Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products (Proposed Rule) are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures, and markets leading prescription medicines for humans and animals and many of the world's best-known consumer brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier, and more productive lives. The company has three business segments: health care, animal health and consumer health care. Our products are available in more than 150 countries.

Pfizer supports a Risk Management approach to ensuring availability of and access to safe and effective medicines by those who need them and we commend the Agency for proposing a risk-based approach for safety reporting that would allow more focus on serious suspected Adverse Drug Reactions (ADRs). We also strongly support the Agency's stated goals of "more effective and efficient safety reporting to regulatory authorities worldwide" and eliminating unnecessary reporting burdens "so that companies can focus on the safety profiles of their products and not on the different reporting requirements of

different regions." Worldwide harmonization of safety reporting requirements is an exceedingly important component of a risk-based approach to enhancing access to medicines by those who will benefit and, as a consequence, will also benefit the public health. Thus, we endorse FDA's participation in Industry-Regulator consensus forums, such as the International Conference on Harmonization (ICH) and the Council for International Organizations of Medical Sciences (CIOMS), to maintain global consistency and harmonization on this important topic. To this end, we believe that any revision to the requirements for safety reporting should be harmonized with global efforts and should be fully integrated into the Agency's ongoing Risk Management initiatives.

We endorse the Agency's proposal to:

a) Eliminate duplicative reporting of safety-related information in annual reports for NDAs and BLAs;
b) Adopt ICH Guideline E2C on PSURs to replace NDA periodic reports for new products, particularly the International Birth Date and data lock point concepts;
c) Use MedDRA as the standard coding terminology for classifying adverse event terms;
d) Eliminate expedited reporting on cases from class action law suits; and
e) Establish a minimum data set for non-serious suspected ADRs.

However, we believe that the Proposed Rule has many inconsistencies and, if implemented, would have the undesired consequence of creating many practical difficulties for both Industry and the Agency. These inconsistencies may be counterproductive to FDA's goals of "more effective and efficient safety reporting to regulatory authorities worldwide." Indeed, rather than make it easier for the Agency (and companies) to identify potential safety problems – one of the stated purposes of the Proposed Rule – we believe that certain aspects of the Proposed Rule may have the opposite effect. Indeed, some of the new concepts proposed by FDA will complicate, confuse, and otherwise impede harmonization of the pharmacovigilance process endorsed by ICH and adopted by other regulatory agencies. We are entering a new era of global cooperation in drug safety that emphasizes detection, assessment, understanding, communication, and prevention of important risks in the safe use of medicines. Toward that end, we, along with major stakeholders, including FDA and other regulatory agencies, are working towards rational approaches to evidence-based Risk Management that span the development spectrum of innovative products from First in Human studies through late-stage product marketing.

We also believe that the Proposed Rule places undue emphasis on administrative aspects of safety reporting, which would add significant resource burden without adding to our mutual understanding of a product's safety profile; the Agency has underestimated the increased resource burden for these activities, as well as the overall increased burden for all new activities, by a wide

margin and has not included the anticipated burden on other stakeholders in the healthcare system.

As will be clear from our detailed comments (attached), we believe that considerable modifications to the Proposed Rule are necessary for FDA to meet its goals and to improve our mutual ability to carry out internationally consistent, high quality pharmacovigilance. We propose that, after carefully considering comments from all stakeholders, the Agency re-propose a Proposed Rule for safety reporting requirements. Further, due to the many modifications to established practice and systems that any new rule for safety reporting will require on the part of Industry and the Agency, FDA should consider implementation no sooner than 18 months following publication of a Final Rule in the Federal Register. This would be consistent with precedent established for implementation of new rules by other federal agencies.

In summary, Pfizer endorses the Agency's goals of risk-based safety reporting and incorporation of Risk Management concepts early in the product development cycle as part of a continuum in the assessment of benefit-risk for each product. We strongly believe that this should encompass a worldwide perspective and that any revision to the requirements for safety reporting should be fully integrated into the Agency's ongoing Risk Management initiatives.

We thank FDA for the opportunity to comment on this important topic and we would be pleased to respond to any questions that the Agency might have. We welcome the opportunity to join other stakeholders as a sounding board for Agency ideas as the Agency proceeds with this initiative.

Sincerely,

Gretchen S. Dieck, Ph.D.

Gretchen Dieck

Detailed Comments from Pfizer to FDA Docket 00N-1484, Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products (68 Federal Register 12406-12497; March 14, 2003)

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Detailed Comments from Pfizer to FDA Docket 00N-1484, Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products (68 Federal Register 12406-12497; March 14, 2003)

I. SUMMARY

Pfizer agrees with FDA's stated aims of the Proposed Rule: Elimination of unnecessary reporting burdens and simplification, harmonization, and more efficient worldwide safety reporting. We applaud the Agency for proposing a risk-based approach to safety reporting and for certain innovations, such as proposed reduction in duplicative reports, adoption of ICH E2A and E2C guidelines, and elimination of expedited reporting for cases from class action law suits. However, Pfizer believes that an unintended consequence of the Agency's attempt to develop comprehensive new requirements is the creation of significant administrative burden and many inconsistencies, which, in turn, result in many practical limitations that could defeat FDA's stated 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 safety concerns with individual products, we believe that, on balance, the Proposed Rule would not improve the pharmacovigilance process or the public health. Rather than simplify, clarify, and harmonize, many aspects of the Proposed Rule would seem to complicate, confuse, and create disharmony with already established and evolving consensus standards for safety reporting. Further, we believe that any revision to the requirements for safety reporting should be harmonized with global efforts and should be fully integrated into the Agency's ongoing Risk Management initiatives.

We believe that considerable modifications to the Proposed Rule are necessary for FDA to meet its goals and to improve our mutual ability to carry out internationally consistent, high quality pharmacovigilance. We propose that, after carefully considering comments from all stakeholders, the Agency re-propose a Proposed Rule for comment. Further, due to the many modifications to established practice and systems that a new rule for safety reporting will require on the part of Industry and the Agency, FDA should consider implementation no sooner than 18 months following publication of a Final Rule in the Federal Register. This amount of time would be required to modify existing databases and systems to meet the new requirements (and others, such as 21 CFR Part 11) and to revise processes and train employees, contractors, and Investigators, etc. The suggested 18-month delay in implementation is consistent with recent examples of implementation of new federal regulations, such as:

- FDA delayed by 18 months the Agency's "regulations to change the labeling requirements concerning aluminum in small volume

parenterals . . . and pharmacy bulk packages" . . . in order "to give industry sufficient time to comply" with the regulations. (68 Federal Register 32979; June 3, 2003);

- FDA delayed until April 1, 2004, the effective date of certain requirements of a PDMA final rule that was published on December 3, 1999, in order to "address the concerns about the requirements raised by affected parties." (68 Federal Register 4912; Jan. 31, 2003);

- FAA delayed the effective date of a final rule "in order to give repair stations sufficient time to use FAA guidance material in preparing to operate under amended regulations to repair stations." More specifically, the final rule was to become effective 20 months after publication in the Federal Register; the FAA extended that 20 month period by an additional 180 days in order to give affected parties sufficient time to comply (68 Federal Register 12541; March 14, 2003).

In addition, we note that FDA plans to finalize the Draft Guidance for Industry titled "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" (66 Federal Register 14391-14392; March 12, 2001) prior to publishing a Final Rule on safety reporting, 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. The new rule and guidance document should be considered in tandem (alternatively, the guidance document could follow the new rule) to improve consistency and to ensure that there is a regulatory basis for the expectations outlined in the guidance document.

II. KEY POINTS

Major concerns that justify modification and re-proposal of the Proposed Rule for safety reporting are as follows:

A. **FDA's proposed definition for Suspected Adverse Drug Reaction (SADR) should be brought into alignment with international consensus.** FDA's proposed definition for SADR is inconsistent with international consensus, will seriously compromise international harmonization of safety reporting, and will unnecessarily complicate safety reporting and analysis. SADR represents an important concept in pharmacovigilance that FDA proposes to change from the accepted international consensus definition by introducing a minimum causality threshold for reporting (role of the drug "cannot be ruled out"). Application of this new definition will lead to very large increases in the number of cases that are reported from clinical trials. Based on our experience over a recent 12-month period, we calculate that

the number of expedited case reports from clinical trials would increase from 10- to 12-fold, depending on the therapeutic area in which the clinical trial was being conducted. For many clinical trials, this would represent a significant problem with respect to maintaining the blind and to sample size for efficacy, since most patients who experience serious unexpected SADRs will be discontinued from treatment. Further, such increased reporting of cases may complicate early detection and evaluation of important emergent safety signals due to dilution of resources across a dataflow that is an order of magnitude larger than that to which Investigator judgment is applied. A commensurate burden will affect Investigators and IRBs, who will have to receive, interpret, and manage such reports. See additional comment, below.

B. **Other proposed changes, such as those related to Periodic Reporting, should also be adjusted to conform with international consensus agreements.** In addition to FDA's proposed new definition of SADR, other proposed changes, such as those related to periodic reporting, also represent clear divergence from international consensus agreements or otherwise create unnecessary burden without adding value. For example, the spirit of international harmonization appears to be absent from the proposed implementation of the ICH E2C Guideline for PSUR; significant US-specific customization, new variations of PSURs (e.g., TPSRs, IPSRs), and different or additional reporting timelines clearly present major conflicts with agreements made through the ICH consensus process. Two new proposed categories of cases (e.g., "unexpected SADR with unknown outcome" and "always expedited" reports) are not categories that are recognized in ICH, CIOMS or other consensus recommendations for good pharmacovigilance practice. Further, the Proposed Rule should be re-worked to consider 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 for SADRs (and also for Medication Errors), which will challenge systems and resources. In addition reaching conclusions that may appear to be somewhat contradictory because different benchmarks. See additional comment, below.

C. **The proposal for a new class of case designated "Unexpected SADR with Unknown Outcome" is not necessary and should be abandoned.** "Unexpected SADR with Unknown Outcome" represents a new class of cases with attendant activities that will add unnecessary burdens without a clear corresponding benefit. Under Pfizer's present system and processes, the outcome is determined for virtually all spontaneously-reported cases. This new category of report would necessitate expedited (15-day) reporting with an automatic follow-up report 30 days later. The vast majority of these cases involve non-serious events; there is already a requirement and established practice for follow-up of any clinically significant adverse event report. It is unnecessary to establish a new case class and corresponding

45-day follow-up report; it will unnecessarily complicate process-related activities and add unnecessary time and cost burdens.

D. **Case follow-up should be conducted by properly trained and responsible professionals, including non-physicians, using a method deemed most appropriate by the company.** The proposed Active Query, which would require a company physician to have direct verbal contact with a reporting healthcare provider for all serious SADRs, Always Expedited SADRs, and Medication Errors reports, is an inappropriate and unnecessary use of resources. Companies should be permitted to focus resources on cases of greatest importance and perform follow-up by the method the company deems most appropriate. Direct (or indirect) contact with reporters should not be limited to company physicians, but properly trained and responsible professionals, as determined by the company, should also be permitted to conduct case follow-up. Written follow-up, particularly that which can be provided in the form of medical records, is often more accurate than off-the-cuff verbal recollection and is preferred by healthcare providers because copies of documents can be provided by office/clinic staff; this is less disruptive to their practice. Further, interrupting the practice of busy physicians with repeated telephone calls could deter them from reporting SADRs in the future. Cultural and legal impediments regarding personal medical data privacy, particularly outside the US, will make implementation of this requirement particularly difficult. 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. Pfizer 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 3500A and CIOMS I 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. We are not aware of any evidence that the existing regulations, guidances, and practices regarding case follow-up or ability to identify a company contact person are unsatisfactory.

E. **Sections of the Proposed Rule that relate to Medication Errors should be aligned with the standards already established by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) and the Institute for Safe Medication Practices.** FDA's proposal to require the reporting of "actual" and "potential" Medication Errors will result in pharmaceutical companies becoming engaged in the practice of medicine. This is inappropriate, undesirable, and unnecessary, given that the vast majority of medication errors are attributed to physicians, patients, and pharmacists, and not drug manufacturers. We recognize the importance of monitoring for, understanding, and preventing medication errors, but we question the proposed new requirement that would hold medication errors to a higher regulatory standard than even serious SADRs. Further, we agree

with the 1999 Institute of Medicine report cited in the Proposed Rule (p. 12413), as well as other initiatives (e.g., National Patient Safety Foundation), that conclude that medical errors 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). Root causes, and, thus, possible solutions for medication errors, ordinarily rest in areas of the healthcare system other than those under the direct control of the pharmaceutical and biotechnology industry. Thus, while we agree that all stakeholders share in the responsibility to address preventable medication errors, we disagree with the proposal set forth in the Proposed Rule for several key reasons: The Proposed Rule focuses on only one stakeholder; the definitions for actual and potential medication errors in the Proposed Rule lack internal logic and conflict with established NCC MERP standards; most reported cases of medication errors either result in no adverse event(s) or in events(s) that are non-serious and self-limiting; and voluntary reporting will be discouraged due to potential legal liability on the part of reporters. Further, we believe that prescription and non-prescription products deserve separate treatment because non-prescription products usually have a much broader therapeutic index and higher safety margin than most prescription medications. Expedited reporting of the wide variety of medication errors proposed by FDA is a highly disproportionate requirement for the anticipated return and intended purpose; we believe that the definitions and requirements in the Proposed Rule are inappropriate and insufficient to meet FDA's stated goals. For example, we anticipate that 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, particularly those cases in which there is no "event." We believe that a major source of confusion will be the inconsistency of the Proposed Rule with the preexisting standards for characterizing and prioritizing medication errors created by NCC MERP, with the participation of FDA. FDA's terms and definitions in the Proposed Rule differ substantially from the established NCC MERP error categories (A through I) and the definitions for those categories. Existing FDA guidance (e.g., Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements) refers to NCC MERP standards, but 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 regarding Medication Errors. The same uncertainty exists with respect to the Institute for Safe Medication Practices. Finally, we view this as a global issue; FDA should facilitate international consensus on how to address the issue of medication errors on a global basis. ICH is best equipped to spearhead the effort, but we suggest possible roles for NCC MERP and the Institute for Safe Medication Practices.

F. **Periodic Post-marketing Reporting should be aligned with international consensus agreements.** We are very concerned about the many FDA-

proposed departures from ICH agreements and standard practices that create significant administrative burden, but add little or no value to an understanding of the safety profile of any individual product. For example, the proposal for an extensive new set of PSUR Appendices not contemplated by ICH and two new types of periodic reports (TPSRs or IPSRs) that would have 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, each of which may be approved and marketed at various times, is a daunting prospect that will also significantly complicate the establishment of a global PSUR system. At a minimum, "old" products should be grandfathered such that they continue to fall under the more simplified current requirements (CFR 314.80) rather than the proposed "traditional" safety update report (TPSR), a newly proposed format that is not traditional.

G. **The proposed assessment of Increased Reporting Frequency should be re-evaluated for scientific validity and aligned with the Agency's ongoing Risk Management initiatives.** The Proposed Rule would impose a requirement for companies to estimate and report on increased reporting rates for serious expected SADRs and for lack of efficacy. However, we would like the Agency to clarify the thinking and scientific approach behind this proposal, which was previously abandoned by FDA for lack of scientific rigor. We believe that much work would be needed to develop and validate an approach that would yield meaningful information. This issue should be addressed under the Agency's ongoing Risk Management initiatives; without a scientific underpinning, this proposed requirement should be deleted from further consideration under the Proposed Rule.

H. **FDA's low Burden Estimates should be re-evaluated for the burden to Industry and should be expanded to include the burden on all stakeholders.** 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 to process and systems. Furthermore, FDA has not factored in the total burden to the healthcare system, whether, for example, it involves increased time and effort on the part of reporters to handle much more frequent and intensive phone calls from company physicians ("Active Query" or other new follow-up procedures); a major increase in requests to hospitals that they promptly provide discharge summaries and/or death reports; or the increased burden on Investigators and IRBs that will be required to understand and take informed decisions on a vastly increased volume of expedited reports.

I. **FDA expectations regarding the topics of Personal Data Privacy and Access to Information should be addressed in greater detail.** 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 (European Union, Canada, Japan, etc.) The Proposed 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, it is strongly requested 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.

We have particular concern with data privacy issues posed by Active Query. FDA has proposed that companies conduct Active Query - that is, direct verbal contact with the initial reporter of a SADR - in certain situations. As part of the Active Query, FDA has also proposed that companies obtain documentation for a report of a death or hospitalization (e.g., autopsy report; hospital discharge summary). (III.A.6., p. 12420). This proposal poses a number of patient privacy concerns and practical concerns for manufacturers. In the US, the HIPAAHIPAA privacy rule permits, but does not require, covered entities such as hospitals and health care professional (e.g., physicians and pharmacists) to disclose protected health information (PHI) in connection with reporting adverse drug events to manufacturers. Also, covered entities must comply with the "minimum necessary" standard, which directs covered entities to use and disclose only the PHI necessary to satisfy a particular purpose, such as adverse event reporting. Accordingly, covered entities may be reluctant to routinely disclose autopsy and discharge reports to manufacturers and/or the FDA, particularly since the HIPAA privacy regulation will not protect PHI following disclosure to such non-covered entities. Similar, or even more stringent, regulations governing the disclosure of patient information in foreign countries may further constrain manufacturers' ability to obtain supporting documentation described in the Proposed Rule. Under the circumstances, to require manufacturers to pursue specific documentation through Active Query may create a disincentive for physicians and patients to report an SADR. In addition to the annoyance and time-factor that Active Query would impose, physicians and patients may reasonably have privacy concerns over the release of what may be very personal information contained in an autopsy report or discharge summary that may be completely unrelated to the SADR, i.e., the patient was hospitalized due to a suicide attempt and the SADR relates to a possible allergic reaction that the patient may have had while hospitalized. From a patient privacy perspective, what may be of particular importance is that when this personal information comes into the hands of FDA, the information is not regulated or protected under HIPAA.

Further, institutional policy (hospital, local government, etc.) may dampen or block release of personally-identifiable data due to HIPAA "implementation." Also, if a matter is in litigation, a company may be prohibited from making an

ex parte contact with the "initial reporter." To address these concerns, Pfizer recommends that FDA leave it to the discretion of the company on when it is necessary and/or appropriate to conduct Active Query, and when it is necessary and appropriate to obtain and submit to FDA an autopsy report or hospital discharge summary.

J. **All aspects of the Proposed Rule should be carefully reviewed for compatibility with Electronic Reporting.** Although a separate proposed rule is being contemplated by FDA for electronic filing of Individual Case Safety Reports (ICSRs) using the ICH E2BM standard, the Agency should carefully consider the implications of the Proposed Rule for safety reporting on FDA's ongoing voluntary electronic ICSR reporting program. Significant investment to support electronic reporting has been made by companies and by FDA; certain aspects of the Proposed Rule are inconsistent with the current electronic reporting standards. For example, the following points could have the effect of derailing much of the progress made to date on electronic ICSR reporting: (a) Significant system modification and validation would be required for companies to produce, and FDA to accept, reports of potential medication errors, particularly those that do not meet the ICH E2BM specification if an event is not involved; (b) The current ICH specification for narrative field size will not permit "all available information" to be submitted for the proposed 30-day follow-up report, again requiring system modification, validation, and ICH endorsement; (c) FDA's ESTRI gateway for receipt of electronic submissions will require significant technical modification to overcome current limitations that restrict acceptance of ICSR attachments (e.g., hospital summaries and autopsy reports) because of their size; (d) The difficulties in categorizing initial or follow-up reports for foreign non-serious cases in 6-month cumulative reports that subsequently are categorized as serious for the PSUR; and (e) Practical aspects of not having a single point of entry at FDA for reports that must be filed to both an IND and an NDA (i.e., ICSRs for marketed products can be submitted electronically, but reports that are sent to FDA's Review Divisions must be sent on paper.) Further, FDA should clarify in the Final Rule for safety reporting 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.

Pfizer believes that significant modifications to the Proposed Rule must be made to meet the Agency's stated goals. We would welcome the opportunity to work with the Agency and other stakeholders to achieve an optimum set of rational requirements to satisfy our mutual interest in improving the safety and safe use of medicines.

III. DETAILED COMMENTS AND RECOMMENDATIONS

A. Suspected Adverse Drug Reaction (SADR) (310.305a, p. 12472; 312.32a, p. 12476; 314.80a, p. 12477; III.A.1., p. 12417). The new initialism (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 initialism 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, we have very serious concerns that the phrase "reasonable possibility" will be interpreted to mean "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, or 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.

Another possible result 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." It is our experience that a number of solicited reports have very limited information and, thus, FDA will be receiving a much greater volume of solicited reports than is the current case.

A consequence of FDA's interpretation of an SADR will be a significant increase in the number of IND Safety Reports submitted to FDA, to investigators, and to IRBs. Nearly every serious unexpected adverse event will be reported because a relationship with study medication would rarely be completely ruled out according to the Proposed Rule. 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.

Based on our experience over a recent 12-month period, we calculate that the number of expedited case reports from clinical trials submitted to FDA would increase from 10- to 12-fold, depending on the therapeutic area in which the clinical trial was being conducted. 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 surely make the detection of true safety signals more difficult due to the increased "noise." Furthermore, investigators and IRBs have increasingly complained about the current abundance of uninformative IND Safety Reports; the proposed change will increase the administrative burden to them without adding any appreciable value to understanding the safety profile of the drug understudy. 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 from expedited reporting if these disease related events are study endpoints. However, this is a rather unwieldy approach when applied to other common serious events that may not be study endpoints. The lower threshold for SADR reporting in clinical trials will greatly expand the number of events that would require unblinding of patient randomization. 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 a "Chinese wall" or data monitoring boards/committees (DMBs) for studies that are expected to have a large number of SADRs, most subjects that experience serious SADRs would be terminated from study. Although the DMB could perform a review of unblinded cases and determine which cases should be sent to FDA for review, there would still be an additional cost and time penalty for drug development. 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.

In addition, automatic lower threshold ("cannot be ruled out") described in the Proposed Rule will result in indiscriminate selection and reporting of cases, which will not only lead to an increase in the absolute number of cases, but will also decrease the value of "alert" reports, especially in the eyes of investigators and IRBs due to data and communication fatigue.

We are also concerned about the potential effect of the SADR proposal on the safety profile that is described in the Investigator Brochure and in Prescribing Information. 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 in the Company Core Data Sheet and labeling, even though the likelihood of a true causal relationship is minimal. Inclusion of such events dilutes the utility of labeling information.

Recommendations:

- FDA, a full participant in the development of the Step 4 ICH E2A Guideline and the Step 2 ICH E2D draft guideline, should keep its regulatory definitions and interpretations consistent with those agreed by ICH, for both pre- and post-approval situations;

- FDA should actively solicit feedback on its proposed definition for SADR and the implications, as presented above, from other key stakeholders, such as Investigators, IRBs, the Association of American Medical Colleges (AAMC), and the NIH, who will also bear the brunt of increased reporting.

B. Regulatory Clarification of the Term "Serious." One way an SADR can be used against a company relates to the regulatory classification of an event as "serious." Plaintiffs can potentially use this against the company, despite the fact that "serious" is a term of art defined in the regulation.

Recommendation:

- To guard against this type of misuse, FDA should enact the following regulation: "The term 'serious' is a regulatory term of art and does not reflect the common usage of the term by doctors and patients."

C. 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). We understand FDA's intent in introducing this new category of report and associated follow-up reporting (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 virtually all unexpected cases can be categorized by Pfizer under the current definition. The Industry already has a requirement to follow-up any clinically significant adverse event report and it is unlikely that this new category, with new follow-up and case tracking schema, will improve on the results being achieved under the current definition. The requirement for the 45-day follow-up will complicate processing and, because of tracking, data entry, and review of cases that have no new information, add unnecessary time and cost burdens to manufacturers, Investigators, IRBs, and the Agency for minimal yield. In the uncommon

instance when an initial determination of "serious" or "non-serious" cannot be made, the default should be to process the report as "serious."

Use of this new category of cases will create discrepancies between PSURs submitted to the FDA and those submitted to other Regulators. Such cases would have to be treated as a separate category only in line listings or summary tabulations provided to FDA but not to other Regulators. This is another example of divergence from international harmonization.

Recommendations:

- FDA should not create a discrete new case category, "Unexpected SADRs with unknown outcome;"
- There should be no requirement for the 45-day follow-up report if no additional information has been obtained;
- 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.

D. 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). Pfizer 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. Detailed, focused questionnaires could achieve the same purpose in many instances.

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 reached by telephone, they typically do not have the relevant 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 safety-related reports, especially since office/clinic staff can provide copies of the requested information with minimal time involvement of the physician.

The proposal to require Active Query for all serious SADRs, Always Expedited SADRs, 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 FDA's one-hour estimate is accepted, this represents one hour per case per company. We receive and process thousands of serious reports per year, which would require thousands of hours per company just to generate the query. More time is required for complicated cases. Tracking and processing the responses require even more person-hours, which we estimate at 2-8 hours for each case that generate 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.

FDA's choice of the phrase "Active Query" implies that 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 by FDA, we expect that resource requirements will be much greater than the estimates provided in the Proposed Rule. Further, Active Query would chill the desire of physicians to participate in spontaneous reporting when they realize that time-consuming dialogue for detailed follow-up would often result.

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. We agree with the risk-based approach offered by CIOMS V for obtaining follow-up information and we believe that e-mail contact should be considered a valid form of Active Query.

Implementing this proposed requirement outside the US will be even more difficult, especially in small countries where the healthcare system operates with limited resources and other significant constraints. 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 local company offices 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 proposed does not recognize or consider ex-US requirements.

Performance of follow-up activities, such as the proposed Active Query, should not be limited to licensed physicians. 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 responsibility 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.)

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 aall Active Query efforts be documented in detail in a report narrative. However, records of due diligence efforts are maintained by companies and can be made available on request. Including such efforts in the case narrative adds no value and may lead to inconsistencies that could create liability exposure in the event of lawsuits. There is also a possibility that the proposed additional documentation would increase the length of narratives so as to be incompatible with the ICH specifications for 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 that include such administrative 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. We disagree with the proposal to require the routine submission of such reports. It should not be a requirement in the Final Rule. This 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 described in the Proposed Rule. We believe it should be up to the company 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 I) 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. 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, for expedited reports, companies provide in the report narrative a list of all relevant documents maintained by the applicant. However, this is in conflict with electronic reporting specifications agreed by all ICH parties.

Recommendations:

- 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 not be included in a new rule;
- 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.

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; we seriously question the value of having a licensed physician review all individual SADRs. Multinational companies invariably use well-trained scientific/biomedical staff who are capable of acting in this capacity.

FDA's intent is not clear regarding use of the term "licensed" physician and the level of responsibility that this person would have regarding content of any given report. 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 proposed requirement to have the name of the licensed physician responsible for the content and medical interpretation of the data contained within each individual report. As a practical matter, this is difficult for large global companies, such as Pfizer, where different physicians and scientists in different countries may review initial and follow-up reports. Should the contact name be changed with each report? In that situation, who is the responsible person? 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.

Recommendations:

- 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 proposed role covers both pre- and post-approval environments.

F. Quality of Postmarketing Safety Reports. FDA states (II.B.2) that "many of the post-marketing safety reports that FDA receives are complete and of very high quality. Others are incomplete, of mediocre or poor quality or both."

Recommendation:

- 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.

G. Life-Threatening SADR (310.305(a), p. 12472; 312.32(a), p. 12476; III.A.2, p. 12419). We agree 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. We see no value in including reasons for differences of opinion and we do not agree that it is appropriate or necessary in all cases (we note that the statement describing this as a requirement does not appear in the Proposed Rule).

Recommendation:

- Inclusion of any stated reasons for differences of opinion should not be included in the IND safety report.

H. Contractor (310.305(a), p. 12472; III.A.4, 12419). The definition of contractor is far too broad and we suggest 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 entities such 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. We are involved in many such alliances at international and local levels involving multiple partners. There is no "standard " licensing agreement; each has 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 new 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.

We agree 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 due to 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 SADRs that do not meet the minimum required data set.

It is also not clear whether the 7- and 15-day regulatory reporting timeframe for serious unexpected SADRs 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 I/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 is received. This is highly inefficient and hardly conducive to the "quality" reports that Regulators wish to receive.

Recommendations:

- A flexible approach in definition of contractor and the time frames stipulated for safety data exchange should be adopted. If it is the intent of the Agency to require that business alliance partners exchange adverse event reports within 5 calendar days, we suggest that the definition of contractors be restricted to paid vendors that have direct responsibility for clinical work (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. We would especially recommend the exclusion of co-marketing partner companies who hold independent approvals/authorizations in different countries for a given product;
- Provisions in the new rule should 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, particularly in countries where local medical culture and language are important considerations;
- Only cases meeting valid case criteria should be exchanged, with the understanding that every attempt should be made to obtain the information to qualify a case;
- A time frame longer than 5 calendar days, e.g., monthly or quarterly, should be allowed for non-serious spontaneous case reports;
- In co-marketing and independent sponsorship situations, the reporting clock should 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 I or 3500A form. This would allow the second company to enter the same information promptly into their own database, reducing the potential for discrepancies, allowing more rapid and efficient handling, and permitting submission to the authorities as appropriate. Once harmonized electronic data exchange becomes established, it is possible to envision virtually simultaneous receipt and submission by the second company. 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.

I. Always Expedited Reports (310.305(c)(2)(iv), p. 1474; III.D.4, p. 12432).
It is reasonable to establish criteria for reporting for certain events on an expedited basis, due to their medical importance, nature or severity. However, the value of submitting expedited reports for expected SADRs is not clear, as these events are already described in labeling and FDA will receive the updated information in periodic submissions.

Additional concerns with the concept of Always Expedited include: (i) It is questionable whether Always Expedited reporting of certain events should be applied to all drugs, no matter how long on the market or how large the extent of exposure. 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 we understand that "Always Expedited" reports relate only to post-marketing cases and that they represent adverse events rather than 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 Phase 4 trials, for example, require a causality assessment, and, thus, some cases may not qualify for reporting at all, let alone "Always Expedited."

The proposal to change the definition of "medically significant" event from "jeopardy and intervention," to "jeopardy and/or intervention" raises the issue, for example, of whether placement of an intravenous line - which is consistent

with intervention for the underlying condition - would alone meet the proposed criteria.

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 Expedited reports, we recommend relying strictly on the verbatim term (reporter's words) coded to a MedDRA Preferred Term on the list to avoid confusion regarding what should be reported. 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.

Recommendations:

- Reporting under the "Always Expedited" category should be triggered by an exact match of the reporter's term to a MedDRA Preferred Term that is explicitly included on the list;
- FDA should not attempt to change the list of "Always Expedited" terms without a public health concern and any proposed modification to the list should be made through the Notice and Comment rulemaking process;
- The Final Rule should retain "jeopardy and intervention" for the IME criteria.

J. Solicited Reports (310.305(a), p. 12472; 314.80(a), p. 12477; III.A.7, p. 12421). Although the Agency has clarified the important difference between spontaneous and solicited reports, the type of report source may still be open to interpretation. To further clarify, we suggest adding telephone services that are a component of disease management programs to the solicited reports category.

Recommendations:

- It is misleading to refer to solicited reports as study reports. The preferred way to view 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. We recommend that this proposed requirement for solicited reports be deleted.

K. 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 Pfizer supports and understands the need for full data sets, we are concerned that the definition of a full data set is unclear. "Completion of applicable elements of a 3500A or CIOMS I" form 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." We interpret "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.

Recommendations:

- FDA, as an involved participant in CIOMS V Working Group discussions, should ensure that the new rule is consistent with the recommendations in the CIOMS V report. Thus, FDA should adopt the CIOMS V algorithm to obtain "complete data" by aggressive follow-up for cases that warrant this action. The CIOMS V algorithm is a practical and reasonable approach to the types of information that should be sought, which properly depends on the nature of the case. 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 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 should be modified to exempt non-prescription products.

L. 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). Pfizer 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;
- The definitions of "actual" and "potential" errors do not have internal logic and are not consistent 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;
-
- Enforcement of the new rule as currently proposed will discourage voluntary reporting due to potential legal liability on reporters.

We recognize this as an important Public Health issue but we believe it should be handled outside the context of an SADR expedited reporting rule and in collaboration with other sectors of the healthcare system. What is the Agency's plan 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. Pfizer 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 one 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. Expedited 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, ..." We are 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.

The intended definition for potential medication errors should be clarified; the Proposed Rule 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."

We also request 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? We recommend 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, we suggest that this be included in the accompanying Guidance rather the in the Final Rule;
- 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 Pfizer 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 relates to the preexisting standard for characterizing and prioritizing medication errors,

namely, that created by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). FDA's proposed terms and definitions differ substantially from the established NCC MERP error categories A through I and the definitions of these categories. 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.

Recommendations:

- 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;
- Expedited reporting (15 calendar days) should be required if a Medication Error resulted in a serious unexpected SADR. Consideration might also be given to expedited reporting of any case in which a serious labeled SADR is suspected to be a direct result of a Medication Error.

M. *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.

N. 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* investigations may be non-validated, exploratory studies; 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 changes in either product administration or in the overall conduct of a clinical investigation." Pfizer 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. We recommend 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.

O. Review of Safety Information from Foreign Regulatory Sources (314.80(b)(1), p. 12478; III.C.2., p. 12426). Pfizer requests clarification of the provision in this section requiring applicants to review safety information from foreign regulatory authorities. Under III.C.2. the Proposed Rule 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, Pfizer requests the inclusion of wording stating that an applicant's mere access to publicly available databases (such as the WHO UMC (Uppsala) database) do not impose any specific obligation to access them routinely for active search. We request that this limitation on expectations be stated in the Final Rule.

P. Lack of Efficacy Reports (III.C.7, p. 12431). Pfizer 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.

We also note 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." We assume 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 difficult, if not impossible 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.

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

Recommendation:

- Approaches to estimating increased frequency of lack of efficacy require considerable development and should not be part of the new rule.

Q. 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.

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 a minimum of 90 days.

i. ICH E2C Addendum. We are disappointed that the Proposed Rule does not incorporate the finalized Step 4 ICH 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.

ii. 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.

iii. Company Core Data Sheet (CCDS), Company Core Safety Information (CCSI). Pfizer 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. We strongly suggest 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. Pfizer recommends adopting the same scheme. See additional comments on this point, below.

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

Pfizer 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, BLA). Pfizer seeks guidance on how to handle products with multiple formulations or multiple active ingredient combinations, some of which are not approved in the US.

v. 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. Pfizer believes that it would be appropriate to grandfather "old" products to allow them to continue to fall under the more simplified current requirements under 314.80. 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 Pfizer 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 sub-groups (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.

vi. 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 3500A 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.

Recommendations:

- 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.

vii. Increased Frequency Reports (III.E.1.c., III.E.2.k.vi., etc.) (See additional related comments above and below). It is unclear what FDA's expectations are regarding increased frequency assessment described in the Proposed Rule now that the former 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)? Also, "lack of efficacy" and "increased frequency" reports can also be used against companies in litigation. However, these reports are intended to be no more than signals indicating that the company or FDA may need to look further. To guard against this type of misuse, FDA should enact a regulation that provides as follows: "FDA recognizes that 'lack of efficacy' and 'increased frequency' reports are no more than signals indicating that FDA may need to investigate the matter further."

viii. History of Safety-Related Actions Taken/Actions Taken for Safety Reasons (III.E.1.f., III.E.2.c., etc.). Pfizer 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? Pfizer 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. Pfizer also requests clarification of the phrase 'Any communication.'

ix. Contact Person (III.E.1.h., III.E.2.k.x., III.F.4.). (Also, see related comments, 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. Pfizer 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.

x. 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.

xi. 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.

xii. Worldwide Patient Exposure (III.E.2.e., etc.). The Proposed Rule indicates 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." We also note that age and gender breakdowns will not be available in most situations and requests for such data may be more appropriate as guidance than as a regulation. In addition, the E2C guideline asks for age and/or gender breakdowns only when possible *and relevant*. Finally, we request 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."

xiii. Appendices to Periodic Reports (III.E.2.k.). Pfizer 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. 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:

a. **U.S. Labeling**. We suggest 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.

b. **Spontaneous Reports Submitted to the Applicant by an Individual Other than a Health Care Professional.** Pfizer requests clarification on whether or not 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.

c. **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.

d. **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.

Pfizer agrees with this proposed change. However, Pfizer recommends that FDA permit periodic reporting of <u>any</u> 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.

Pfizer 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.

e. **Lack of Efficacy Reports.** Pfizer 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. "Lack of efficacy" and "increased frequency" reports can also be used against companies in litigation. However, these reports are intended to be no more than signals indicating that the company or FDA may need to look further. To guard against this type of misuse, FDA should enact a regulation that provides as follows: "FDA recognizes that 'lack of efficacy' and 'increased frequency' reports are no more than signals indicating that FDA may need to investigate the matter further."

f. **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 some respects, it may reflect actual or potential lack of efficacy. Furthermore, we recommend 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 and class 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.

g. **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.

xiv. Miscellaneous Items

a. 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.

b. 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.

c. It is not clear 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.

d. **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.

e. **Epidemiology Studies and Output from Databases.** 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.

f. **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.

IV. RESPONSES TO SPECIFIC QUESTIONS POSED 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 initialism, definition, and interpretation seriously compromises international harmonization of this important concept. As also discussed above, we believe that the proposed alternative definition will indeed lead to very large increases in reporting volume from clinical trials. We estimate a 10- to 12-fold increase, depending on the focus of the clinical trial. For many clinical trials, this represents a significant concern 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. FDA states that "perhaps the agency should consider also prohibiting use of SADR reports the agency receives in product liability actions." "Accordingly, FDA seeks comment on the need for any further action to promote submission of SADR reports to the agency and guard against their misuse, as well as FDA's legal authority to take any such action." (III.A.1., p. 12419).

As mentioned above, the number of IND safety reports may increase by 10- to 12-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.

Pfizer believes that the current "disclaimers" are not sufficient given the misuse of the reports in litigation. For example, plaintiffs use the reports to suggest, if not assert, that -- as a consequence of a medication being the subject of reports -- the medication is a bad medication, that the medication caused the adverse event, that one medication is worse than another, the incidence rate or frequency of occurrence of an adverse event, or that the company did not act properly in responding to the reports because of their number or the fact that some are labeled as "serious," even though that label is defined and mandated by the regulations.

These misuses of adverse event reports do nothing to encourage a more robust reporting system, like the one proposed by FDA in the Proposed Rule. Specifically, a more interactive reporting system as proposed may deter physicians from reporting SADRs if the more detailed SADRs may be misused in civil litigation.

Pfizer, therefore, requests that FDA clarify the proper role of these reports in the Final Rule for safety reporting. In particular, because the effect of any disclaimers or limitations are often overwhelmed at trial by the adverse event reports themselves or their number, 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 being referenced 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. In this way, the risk of SADRs being misused at trial would be greatly reduced.

At the same time, Pfizer suggests that the FDA also modify the agency's current disclaimer regulations, 21 C.F.R. §§ 310.305(g), 312.32(e), and 314.80(k), so as to further clarify the proper purpose of these SADRs. Pfizer proposes that the regulations state as follows:

> "Disclaimer. FDA recognizes that SADRs, separately or together, do not provide a valid scientific basis for asserting a scientific association between the use of the medication or SADR, a causal relationship between the use of the medication and the SADR(s), the frequency or incidence rate of the SADR with use of the medication, and/or how the occurrence of the SADR with one medication might compare with another. FDA also recognizes that the SADR and/or information submitted under this section do not constitute an admission that the drug caused or contributed to an adverse effect."

Moreover, FDA should enact a regulation requiring that the language contained in the disclaimer regulations, 21 C.F.R. §§ 310.305(g), 312.32(e), and 314.80(k) [as proposed above], shall be included on the mandatory reporting form, FDA Form 3500A.

C. **Breaking the Blind for Serious SADRs that are Not Study Endpoints (III.A.5., p. 12420).** We assume 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.), Pfizer 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).** We have provided extensive comment on verbal vs written inquiries above. We believe that FDA should allow for written follow-up, including email, 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 Expedited."

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. Pfizer 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 incompatibility 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.

We also wish to express concern 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.

Further, it is important to note that the ICH E2BM specification for electronic case reporting is not designed to accommodate SNOMED CT®, the CTCAE version 3.0, or any medical terminology other than MedDRA. Adoption of SNOMED CT®, the CTCAE version 3.0, or other medical terminologies for coding adverse events would cause electronic case reporting to grind to a halt in the US.