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

To: Docket No. 00N-1484 (2000N-1484)
Re: Proposed Rule: "Safety Reporting Requirements for Human Drug and Biological Products"

To whom it may Concern:
I am pleased to submit the following comments concerning the Food and Drug Administration's publication of proposed "Safety Reporting Requirements for Human Drug and Biological Products."

My name is David Goldsmith, MD, and I am a board certified Pediatric Nephrologist with more than 20 years of experience in Drug Safety Surveillance in the Pharmaceutical Industry. I have held the position of chairperson for the PhRMA Clinical Safety Surveillance Committee, served on the ICH E2B Expert Working Group (EWG), as rapporteur for the ICH E2BM EWG, and I have participated in many of the EWG discussions for the ICH E2A and E2C Guidelines. I was the PhRMA representative to the original MedDRA working party and worked on the task force that wrote the guidance on MedDRA term selection. I have also provided input to the FDA as a member of its task force for the development of the MedWatch Forms 3500 and 3500A, and as a member of the industry advisory group for the AERS development program.

I am also a founding member of the International Society of Pharmacoepidemiology, and have served the organization as a board member, Vice President, Vice President Finance, and Chairperson for the Scientific Program Committee for 3 of their 19 International Conferences. I have been elected to fellowship of the Society and received their distinguished Service Award. Prior to joining the industry, I was an Associate Professor of Pediatrics Nephrology at Albert Einstein College of Medicine (New York) where I conducted bench and clinical research as well as providing care to children afflicted with kidney disease.

I would like to applaud the FDA on their activities to bring the regulations on safety reporting closer to the international standards set in the ICH documents, and to address the important issues raised by the Institute of Medicine (IOM) report "To Err is Human: Building a Safer Health System," and the Government Accounting Office (GAO) report concerning the safety of pharmaceuticals. However there are key points in the proposed rule which I suggest could be improved and others which may be counterproductive and detrimental to the goal of improving public safety.

1. General comment on the scope of the proposed rule.

The current proposal does not address section 312.33 (21 CFR 312.33) which deals with annual reports of safety by sponsors to INDs. Considering the finalization of the European Union Clinical Trial Directive 2001/20/EC, and the publication of their Final Detailed Guidances, it would be appropriate to modify the current safety sections of regulations to be consistent with the ICH and EU annual reports. It is appropriate to emphasize that inclusion of annual reporting requirements for INDs should however be completely consistent with the ICH and European guidelines and correct the deviations from the definitions in these documents which are indicated in my comments below.

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2. Definitions.

a. SADR:

The proposed definition is in part consistent with the ICH E2A Guidance definition of an adverse reaction. In that document the following is included "The phrase 'responses to a medicinal products' [sic] means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out." However, the Expert Working Group (EWG) and US discussion group recognized that the phrase "cannot be ruled out" is an extraordinarily high burden for reporting purposes. Indeed the only means to "rule out" a possible causal association would be an inappropriate temporal relationship, i.e., the event occurred before exposure. In contrast to diagnoses, there are no laboratory tests that can be used to "rule out" the possible association, and given causality models that can include consideration of necessary, sufficient, and contingent conditions in a multi-factorial causal relationship, it is impossible to "rule out" a contributing causal association even if other causes are clearly identified. Therefore ICH E2A EWG also included the following statement in their discussion of what should be reported: "The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship." This is also the exact statement that is included in the Final Detailed Guidance of April 2003 for the above cited European Directive 2001/20/EC. This construct places the appropriate emphasis on investigators that they should provide sufficient data to establish that facts (evidence) or arguments suggest a causal relationship; it details the responsibility of investigators to clearly and completely review the adverse events in clinical trials. Thus I would suggest adopting the ICH guidance (which the FDA agreed to) for the reporting requirements for SADRs in clinical trials rather than the impractical "rule out." I should emphasize that the change in reporting requirement would have no impact on spontaneous reports, which have an implied causality assessment on the part of the initial reporter. The adoption of my proposal would also reduce the variability inherent in individual agreements, a suggested mechanism to reduce over reporting, between sponsors and reviewing divisions on what should and should not be considered as being causally related. While the approach I suggest might not be able to provide earlier detection of a situation such as that occurred with FIAU, there is no evidence to suggest that the FDA proposal, with the possible exemptions being granted by the reviewing divisions, would provide a better solution.

The current definition may also impose substantial obstacles to timely and cost-effective completion of clinical trials. Since investigators will rarely be able to "rule out" a causal relationship, those events with no evidence or argument to support a causal relationship will force the unblinding of information on those subjects in the clinical trials with a serious and unexpected adverse event (note that the absence of evidence and argument makes it an event rather than a reaction). This will substantially interfere with the ability of maintaining adequate numbers of evaluable patients in the trial. Moreover, it is likely to promote bias in future evaluations by investigators. Investigators and ethics committees will be provided information on those subjects who were found to be on the experimental product at the time of the event, but will not be notified of the same events in subjects give placebo. Thus, if there are 16 cases of cough induced hernia in a clinical trial of a drug used to treat lung cancer, 8 taking the experimental drug and 8 receiving standard therapy, the investigators and the ethics committees would only know of the 8 cases which actually received the experimental drug. This would certainly promote a biased interpretation of any future cases. The solution to the unintended consequences of the unblinding rule is not simply identified; however I would suggest an approach that would require unblinding only in those circumstances where a decision branch was clearly established prior to breaking the blind. If there is no decision branch the unblinding only satisfies curiosity and does not help in the conduct of the trial (indeed it hinders it by creating bias), nor does it provide for additional safety of the patient or other subjects in the trial.

b. Contractor

"Under proposed § 314.80(a), the term 'contractor' is defined as persons (e.g., manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant." This definition can be interpreted to include Pharmaceutical Benefit Managers, hospitals, chain and local pharmacies and even government agencies such as the VA; indeed they all may enter into contracts with pharmaceutical companies to purchase the products and then either resell or distribute them to the consumer or to an entity closer to the consumer.

Since the proposed rule requires that the contracts with these organizations make provisions for adverse reaction reporting and for implementation of procedures to ensure that contractors are fulfilling the safety reporting obligations, a strict interpretation could lead to the absurd conclusion that pharmaceutical companies would be required to audit the Veterans Administration, PBM's and pharmacies in the US. There is no discussion in the proposed rule to provide a compelling rationale for modifying the previous requirement concerning the contractors name being on the label. Discussions at public meetings with the FDA indicate that the intent may have been to include in the definition contract sales forces and others who may be intimately involved in promotional activities for the medicinal products. One possible solution to the potential problem is to include a phase concerning promotional activities such as: "a 'contractor' is defined as persons (e.g., manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that have entered into a contract with the applicant **and whose contractual arrangements include the discussion or distribution of promotional materials with prescribers, pharmacists, or consumers**." This suggestion is offered only as a starting point for further discussion, since refinement is clearly needed.

Also see the discussion below under the heading of Medication Error concerning the consequences of including PBMs, hospitals, and pharmacies in the definition on a "voluntary" reporting system.

c. Medication Error:

The currently proposed definition can be interpreted to include off label use. The definition is, "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: Prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use." Since off label use is related to professional practice and could be prevented by restricted distribution programs, withdrawal of product from the market, etc., and can be considered to be an "inappropriate medication use" (since it is off label), there is no apparent exemption for this activity from being considered a medication error. At a recent meeting FDA staff suggested that off label use was not a medication error because it was not preventable since it was intentional. I take exception to that position; the two words are not synonymous, and off label use can be prevented. I would suggest redefining medication error as "Any preventable event that may cause or lead to **an unintentional or mistaken and** inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: Prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

The IOM report suggested that the FDA should increase its activities with physicians, pharmacists, consumers and others to deal with the problem of medication errors. I support this position, but I question the requirement to have manufacturers implement procedures (audit compliance with mandatory reports from contractors) that will in effect convert the voluntary reporting system into a mandatory one with pharmaceutical companies being the effective agent. The role of pharmaceutical companies is to discover, develop, manufacture, and advise on appropriate use of medications. The proposed rule would alter that role and impose the obligation of error avoidance, after medications left its control, on the manufacturer. I suggest that the FDA explore alternatives other than the proposed rule to reduce medication errors. However, since it is unlikely that the FDA will eliminate entirely the new requirements concerning medication errors, I am suggesting below some alternatives to improve the process, reduce the burdens, and increase its focus on those errors that are most likely to have an impact on the goals of promoting and protecting public health.

3. Active query

The proposed rule provides a definition of, and new requirements for, active query; the requirements include active query for SADRs to determine "if they are serious or nonserious if the manufacturer is not able to immediately make this determination" for SADRs with an unknown outcome, for SADRs without a minimal data set, for serious SADRs and medication errors without full data sets and for supporting documentation for reports of death or hospitalization. Each of these requirements represents significant new challenges which,

may not have been the intent of the FDA, may not be cost effective, and may, in fact, be impossible to achieve.

a. Determination of serious nonserious, or unknown outcome

The current regulations require sponsors and manufacturers to handle serious and non serious reports differently. The proposed rule provides a new definition for non serious as being any SADR that is determined not to be serious. One possible interpretation of this, and indeed it is the implication (to avoid circular logic) is that there must be a specific line of questioning concerning each of the possible outcomes in order to rule them out. While in some cases this is desirable, it would be inappropriate to question health professionals for each of the outcome criteria for every report. For example it might be reported that a patient had dyspepsia after taking a medication each day for three days. Reasonable health professionals would consider a line of questioning concerning death, hospitalization, disability etc. for each of these cases as inappropriate and possibly harassment. It is recognized that in extraordinarily rare instances the dyspepsia could be sufficiently incapacitating to result in hospitalization (e.g., to rule out a myocardial infarction or appendicitis), but it would be irritating to physicians to question specifically for each outcome in all cases just to be certain of finding the very rare occurrence and the almost absurd circumstance that the initial reporter would not specifically address the unusual outcome in the initial report. I recommend that the FDA consider modifying the definition of nonserious to provide for the possibility that a medically qualified individual can interpret the report without resorting to a strict line of questioning for each outcome. Active query should not be routinely required for all reports to rule out that it might be a serious report. In the case of uncertainty by the company's qualified responsible health profession, I recommend that active query be required and, if additional information to clarify the classification cannot be obtained, that the report should be classified as serious on the date that information was sought but not obtained. If the SADR is unlabeled I suggest it be subject to expedited reporting rules.

b. Active query for serious SADRs not initially reported by a health care professional.

The difficulty raised by this aspect is similar to that described above. The proposed rule requires active query for serious reports provided by reporters other than health care professionals. The determination of serious can be problematic in instances of reports provided by consumers. Letters are often filled with statements like "I got a headache that was killing me" or "I could have died from the pain." While it is conceivable that the consumer was correct because the etiology of the headache included a brain tumor or cerebral edema, and that the pain could have induced neurogenic shock, these are most unlikely circumstances. It would certainly be a waste of resources to invoke active query in every non health professional report of this nature. An alternative approach would be to require active query for non health professional reports of fatalities, and hospitalizations. In other instances it would be appropriate to require the manufacturer to document in their files the medical judgment supporting the decision to not conduct active query. The requirement for active query on this cases would need to be rewritten to reflect that it is required only if there is uncertainty regarding the outcome after review by the company qualified health professional.

c. Collection of hospital records, autopsy reports and death certificates

The proposed rule requires active query to obtain hospital records, autopsy reports and death certificates. While in the US the death certificates are a matter of public record, this may not be the case in other countries, and it is certainly not the case of most domestic autopsy reports and hospital records. In addition, with Health Insurance Portability and Accountability Act (HIPAA) implementation, it may be practically impossible to obtain hospital charts and autopsy reports despite the exemption for providing materials required by the FDA. It has been the general experience that initial reporters are not sufficiently familiar with the nuances of the act and "play it safe" by refusing to provide patient data. I recommend that the FDA include language to require active query for these documents "**where applicable law and custom permit the transfer of these documents**." Alternatively, and preferably since the proposed rule does not take into account cultural differences among nations, all aspects of active query requirements could be limited to domestic cases as are the requirements for collection and reporting of medication errors. In addition see the comments in paragraph 6 below regarding reporting format for the recommendation that the requirement to submit these documents with the SADR be amended to allow companies to keep these records and to make them available to the FDA upon request, but not required to submit them with each SADR.

d. Medication Errors

The requirement to conduct active query for medication errors presents a clearly unusual problem especially for those that are actual medication errors with a serious SADR. Since by definition all medication errors are preventable, it is a strong liability issue for the initial reporter. Active query in these circumstances is likely to be interpreted as an attempt by manufacturers to collect information exculpating themselves and thus avoiding any potential consequences of litigation. As a result, a detailed line of questioning would likely induce hostility between the initial reporter and the company, and certainly would not produce the desired results of the FDA, namely a full data set. One possible solution to this problem would be to use some of the PDUFA postmarketing safety funds to finance direct active queries by the FDA especially in the circumstances of actual medication errors resulting in SADRs.

Reporting potential medication errors will not be possible using the standards currently endorsed by the FDA for electronic reporting. The ICH E2BM and M2 guidances require that all ICSRs must include information in at least one item describing the patient. Since, by definition, there cannot be patient involvement with a potential medication error it will not be possible to effect electronic communication. Indeed the potential medication error does not fit the safety surveillance paradigm in other areas as well, and this is an additional reason to exempt potential medication errors from the expedited reporting requirements (see below), and from the full data set and active query requirements.

e. Minimal data set

The proposed regulations specify that upon initial receipt of an SADR report, the manufacturer must immediately determine, the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SADR and potential medication errors, the proposed regulation requires the manufacturer to immediately determine the minimum information for the individual case safety report. Unfortunately there are instances where any attempt to obtain the minimal data set is futile. For example, companies often receive information from a health professional that someone in the audience at a meeting asked a question concerning, or reported, an SADR or a medication error. The health profession relating the information has no other information and does not even know who the other attendee at the meeting was. If this information is provided by means other than a telephone, it would most likely be a complete waste of the manufacturer's and initial reporter's time to attempt active query. It would behoove the FDA to determine what proportion of reports without the minimum data set could be completed with active query prior to implementing regulations which may have little or no value.

f. Full data set

The proposed rule requires full data sets for all serious SADRs and to conduct active query to obtain the full data set. This approach is certainly justified for all SADRs that are both serious and unexpected, but one might question the cost/benefit for these activities for well documented and established adverse reactions. What additional information does the FDA need to evaluate the benefit-risk relationship when there is a new case of Steven's Johnson Syndrome with certain antibiotics? It is recognized that in unusual circumstances both the manufacturer and the FDA would be interested in obtaining additional information to confirm or refute hypotheses concerning risk factors, but the requirement for obtaining a full data set for expected SADRs should be reserved for these situations rather than being generalized and thus unfavorably affect the cost/benefit relationship, and interfere with the reporter/manufacturer rapport.

4. Expedited Reporting Requirements:

a. Inclusion of statements regarding activities to collect data in SADR reports to the FDA

The proposed rule would require that reports made to the FDA include the reasons that a full data set was not obtained for all medication errors, serious SADRs, and always expedited SADRs. Indeed the proposed rule specifies that manufacturers must, in the case of non professional serious SADRs, specify "(A) The reason(s) for its inability to contact the health care professional and (B) a description of its efforts to contact the health care professional," and, in the case of incomplete full data sets for health professional reports of serious SADRs, they must "(A) Submit all safety information, received or otherwise obtained, for the report; (B) Indicate the reason(s) for its inability to acquire a full data set; and (C) Document its efforts to obtain a full data set (i.e., description of unsuccessful steps taken to obtain this information)." Inclusion of items A and B

for non health professional reports and items B and C for health professional reports cannot help the FDA evaluate the medical and pharmaceutical significance of the report. Unfortunately the inclusion of this information in reports made to the FDA would require extensive and costly modifications of databases and procedures as well as time consuming revalidation of the systems, and redefinition of some items in the international standard described in the ICH E2BM guidance. Because it is appropriate for the FDA to insist that the information be documented in the company records and to be available upon request of the FDA either via special requests or during compliance audits, I recommend that the requirement be changed eliminate all the requirements for transmitting the information to the FDA in these reports.

b. Always expedited reports

The proposed rule requires that all reports of certain adverse reactions be submitted as expedited reports. While the list substantially restricts the CIOMS V listing of Medically Serious terms (and in this sense is a welcome improvement) the use of the list varies markedly from the CIOMS intent. Instead of ensuring that these terms are always regarded as serious reactions, it places them in the same area of scrutiny for reactions that are both serious and unlabeled. Review of publications concerning the FDA SRS data demonstrates that there are more than 43,000 reports of seizures (one of the always expedited terms), and that they represent about 1% of the SADR terms provided to the FDA. Given the current number of reports to the FDA which approximates 300,000 per year, there would be 3000 always expedited reports with full data sets of seizures, the vast majority of which would be known events with medications used to treat seizure disorders, and given an estimate that reviewing the case, as well as possibly the hospital chart would take at least one hour for each case, at least 2 FTEs would be required at the FDA to accomplish the work required. Thus, it should be clear that the requirement is both burdensome, and likely to provide little useful information for evaluating the benefit-risk relationship of the pharmaceuticals involved. The problem is less conspicuous with most other reactions included in the list since the background occurrence rate and/or medication associated rate are low. Two suggestions are offered: modify the requirement for these reactions to be always expedited unless they are included in the label, or alternatively, eliminate the list but include with each NDA approval the requirement to report all these reactions for appropriate medications.

c. Medication Errors

The proposed rule would require that all medication errors be submitted as expedited reports. This includes all potential and actual medication errors, the latter including those known not to have given rise to any SADR. The requirement therefore places an undue emphasis on occurrences that are unlikely to have an effect on the benefit-risk relationship of the medication whether viewed from the individual patient or the population perspective. At a recent meeting, attended by FDA staff (PERI Sept. 29), it was pointed out that the National Coordinating Council for Medication Error Reporting and Prevention uses a more extensive an perhaps more useful classification for medication errors in that it allows for greater specificity of those errors that merit expedited reporting. It is recommended that, if requirements concerning medication errors are not removed from the proposed rule, the FDA incorporate the NCC MERP classification and eliminate requirements for expedited reporting requirements for at least categories C and D and possibly for categories A, B and E as well. These revisions would focus attention on the more meaningful and actionable medication errors.

d. Literature Reports

Several problems are raised by the combination for active query, full data sets, and the expansion of the definition of qualifying literature reports to include epidemiologic data. First, most literature reports do not provide sufficiently precise and detailed information about specific patients (unless they are case reports) to adequately fulfill the requirements for a full data set. (In over 30 years of reading medical literature, I cannot clearly recall a clinical trial report or even a case report where the product lot number was provided). Thus practically every report of an SADR in the literature will require active query (if for nothing more than some type of patient identifier needed for the minimal data set). All serious SADRs reported in any format in the literature will also require active query to gather hospital records, patient or product details that cannot be included in the original article. It is unlikely that authors will be able to afford spending the time, and repeatedly so in the case of a generic medication (see below), to respond to a detailed line of query, to attempt to gather all the information requested, and to complete the paper work usually required. It is likely they will refuse to do so. Thus the overall benefit derived from revising the regulations on literature reports

will very likely be small yet it will certainly be enormously costly. It is recommended that literature reports be exempt from the full data set and active query requirements, or at a minimum to restrict the requirement to only those SADRs that are both serious and unexpected.

Secondly, neither the current regulations nor the proposed rule specifically address literature reports concerning non proprietary medicines identified by their generic name. In the draft ICH E2D guidance there is a specific reference which calls for every manufacturer of a generic medication identified in the literature with the generic name be responsible for reporting SADRs. I would caution against this recommendation because it will magnify enormously the work effort to collect and report the data. I recognize that the duplicate reporting to the Agency will not have a substantial impact since it will be simple to identify the unique literature source, but that does not deal with wasteful efforts being expended to collect the data. I also recognize that it would be inappropriate to assign the responsibility only to the innovator of the medication making a simple solution problematic. I would suggest that the FDA explore alternatives such as temporal rotation of assignments to monitor and report the findings in the scientific literature among the manufacturers of a specific generic drug.

e. Licensed physician signoff

The proposed rule specifies in section III.F.4 that "Each completed FDA Form 3500A (VAERS Form for proposed § 600.80(c)(4)(iv)) or CIOMS I Form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed physician responsible for the content and medical interpretation of the data contained within the form (i.e., contact person for the company)." This requirement generated many questions at the above cited PERI meeting. In particular it was suggested that, in accordance with the FDA staff response at the meeting, the proposed rule be modified to explicitly state that the physician does not need to be either located or licensed domestically. It was also suggested that the requirement for a health profession not be restricted to physicians but should include a broader spectrum of professions to reflect the qualifications of the FDA staff reviewing the reports. Indeed it was noted that most of the FDA staff discussing the proposed rule at the meeting, and currently reviewing both expedited and periodic reports, were not physicians, but had professional qualifications deriving from degrees of RPh., MS, and PharmD. Industry qualifications are similar and also include degrees such as DPH, PhD, and MPH.

Since the submission of SADRs and the 3500As themselves are subject to the freedom of information act, it is strongly recommended that the information concerning name, address, telephone number, and e-mail address be redacted from the original material prior to any public distribution. This would help protect the responsible health professional from potential threats of violence and harassment.

5. Periodic Reporting Requirements:

The FDA is to be complimented on their revision of the postmarketing periodic reporting requirements. Many of the changes are closely aligned with the CIOMS working groups and the ICH E2C guidance. The inclusion of increased frequency analysis corrects a problem associated with the removal from expedited reporting requirements and the maintenance of the TPSR avoids complicating factors associated with many older products. A few areas, in particular the appendices, could be clarified or eliminated.

a. Appendix iv SADRs with unknown outcome.

See the above discussion regarding the use of medical judgment. The suggested changes should eliminate all reports in this category. Either good medical judgment on the part of the company's responsible health professional would allow the classification, or, in the absence of further information from the reporting health professional and in the face of persistent uncertainty on the part company health professional, the report should be handled as an expedited report. It is recommended that this appendix be eliminated from the proposed requirements.

b. Appendix x location of safety records.

This appendix "would contain a list of the current address(es) where all safety reports and other safety-related records for the drug product or licensed biological product are maintained. The list of addresses would provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues." This requirement needs to clarify that the safety records are those held

by the manufacturer rather than the source records of hospitals and physicians that provided the initial data. Indeed there is the distinct possibility that the source records held by the initial reporter, were not accurately reflected in the material provided to the company.

The requirement will also impose substantial logistic problems for companies that operate internationally and make provisions for the centralization of information but not all source data. Hospital records or an initial report provided in a local language are usually maintained at the affiliate in multinational companies with only the translated data being held centrally. Even at the level of affiliates, some of the records may be stored at locations other than at the main office, and these locations are subject to change. Managing a database of the sites for storage of source material in more than 100 hundred countries and possibly as many as 200-300 hundred locations is a substantial undertaking to achieve the desired benefit of providing "rapid access to safety-related records for FDA inspections and for request by FDA for additional information concerning safety issues." Note that the latter benefit does not require the list of locations, but only that the organization maintains an efficient system for the retrieval of the documents held. Large companies know how to identify the responsible safety officer in each affiliate and these officers know how to rapidly identify the location(s) of the records when they are needed. Since the number and address of the locations are dynamic, any listing provided once or twice a year is likely to be inaccurate when it is needed at some time after it is provided. Because compliance with the requirement cannot generate information that will improve the agencies ability to protect and promote public health, I suggest eliminating it.

6. Reporting Format
    a. Electronic Submissions

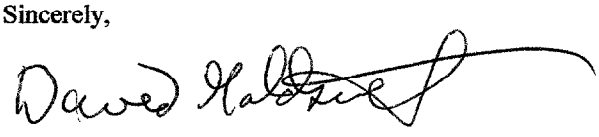
Although, the proposed amendments for electronic submissions are beyond the scope of the proposed rule, the FDA should be credited with the inclusion of anticipated benefits such as the fact that "Electronic submission of these reports will obviate the need for submission of two copies." However the FDA also needs to consider how some of the proposed regulations will affect the current ICH standard. As indicated above, this is particularly pertinent for potential medication errors, but it also needs to be considered for the new attachments that the FDA proposes to require for SADRs that are fatal or result in hospitalization. The current standard, that has been agreed to by all the ICH parties (including FDA), for electronic submissions provides for the specification of the documents such as autopsy reports and hospital records) that are held by the sender of the electronic message, but do not make provisions for their inclusion. The implication being that finalization of the proposed rule in its current format will retard the development of electronic submissions and require further elaboration of the guidance.

    b. MedDRA

The FDA's support of MedDRA and its incorporation of the terminology in the proposed regulations is laudable. Recently HHS has entered into agreements for the use of an alternative terminology (SNOMED) in particular for electronic health records. SNOMED is a terminology with over 300,000 terms many of which are not applicable to pharmacovigilance and safety reporting. The classification is one of the best for avoiding information loss at the point of encoding. However the needs of pharmacovigilance are not strictly tied to preventing information loss, but are more closely aligned with data retrieval and identification of signals. The granularity of SNOMED as compared to MedDRA would hamper the identification of new signals due to the high specificity of each term. I recommend that the FDA maintain its current position as expressed on the FDA website http://www.fda.gov/oc/initiatives/barcode-sadr/qa-sadr.html.

I want to again thank the FDA for the opportunity to comment on the proposed rule, and would look forward to working with them and others on this very important matter. Should you need any clarification please feel free to contact me at address or phone numbers included in the letter head.

Sincerely,



David Goldsmith, MD FISPE