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

October 14, 2003

FDA Docket No. 00N-1484
Safety Reporting Requirements for Human Drug and Biologic Products

Dear Sir/Madam:

As leaders in the discovery, development, manufacturing and marketing of prescription medicines, the pharmaceutical business and research organizations in the J&J family of companies are committed to improving health and well being through innovative products and services. I am sending these comments on their behalf.

We fully support the FDA's goal of "protecting and promoting public health" by way of amending its safety reporting regulations. We believe that increased quality of safety reports will benefit the patient and consumers, and applaud the initiative to strengthen our safety reporting system. We are pleased to have the opportunity to comment on the FDA's Draft Proposed Rule on Safety Reporting Requirements for Human Drug and Biologic Products. We have several broad comments to make about the overall safety reporting requirements proposal. This general feedback is found below. More specific comments and recommendations as they pertain to the various sections of the draft proposed rule is included in the enclosed attachment.

Although we believe that increased quality of safety reports will benefit the patient and consumers, we are concerned that an initiative whose intention is to "eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products" is, in fact, going to have the opposite effect. Due to the additional types of new reports required and increased reporting due to the lowered threshold on the clinical trial reports, it is likely that the system will be flooded with additional Adverse Event (AE) reports, many of which will create "noise" and will obscure true signals. Companies will be focusing attention on complying with all the new regulations and requirements associated with the new reporting requirements, but it may be that the actual surveillance will not be improved since the ability to distinguish real safety risks will be obscured by artifacts in the system. This seems at odds with the FDA's recently touted strategic goal of efficient, science-based risk management.

We believe that the resources required to meet the currently proposed regulations will be vastly more than those predicted by FDA. In particular, we are concerned that there will

be a greatly increased need for very specialized staff in an environment where such resources are already scarce. In addition to the intensive re-training of current staff, new staff will need to be recruited and trained at the same time that every other company is competing for the same scarce resources. We believe this huge resource increase that will be required is real and should be acknowledged.

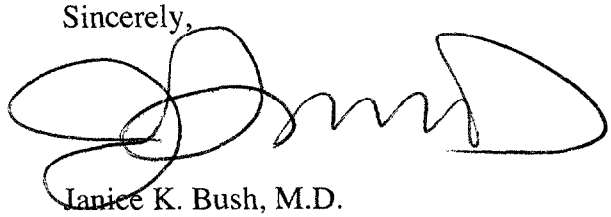
Due to the need to develop the human resources as well as additional infrastructure at our company, we suggest that an extended timeframe is appropriate for implementation once the Final Rule is published. We request that the FDA set a date for implementation 18 months after the Final Rule is published in the Federal Register, to allow time to comply with all of the new safety reporting requirements.

Another concern of ours is the "backseat" that medical judgment is taking in the proposed process. Although the FDA is requesting that licensed physicians review cases and be listed on every submitted report, the FDA is also suggesting, by the proposed new definition/interpretation of "SADR", that physicians are not capable of assessing causal relationships in investigational drugs. Instead, the proposed rule sets up a paradigm whereby virtually all the clinical trial events will be classified as "related". The FDA also appears to be dismissing medical judgment by requiring reporting of certain labeled events to always be expedited. We are concerned by this change of approach and think that the under-valuation of medical judgment will also make assessment of true signals more difficult.

Finally, we commend the FDA for attempting to clarify definitions and requirements and to bring its regulations into worldwide harmonization. Nevertheless, we see many areas where the FDA is proposing changes not in keeping with ICH guidelines, CIOMS proposals or with other regulatory bodies worldwide. Requiring new activities that are specific only to the US, and especially those that are in conflict with the rest of the world, will clearly produce additional burdens for global companies. Instead of having a positive outcome of increased clarity, there will be the potential for confusion and non-compliance.

In closing, we appreciate the opportunity to comment on this important new proposal and look forward to working with FDA to ensure the safe and effective use of all prescription drug products and over the counter drug products.

Sincerely,



Janice K. Bush, M.D.
VP, Safety Strategy and Liaison,
Drug Safety and Surveillance
Johnson & Johnson

Attachment (1)

SAFETY REQUIREMENTS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS

General Comments

While we agree and support the public health rationale for the majority of the proposed changes, we submit that the resource implications to the industry are much higher than FDA has estimated.

We assume FDA intentionally wrote this proposed rule for a broad audience to include both innovators as well as generic sponsors as responsible parties to the safety reporting requirements described in this document. We support this more general, yet inclusive approach.

In addition, we are very supportive of the use of MedDRA as the medical dictionary for regulatory activities. Johnson & Johnson family of companies have invested a great deal to support the use of MedDRA since we agree that a single medical terminology used internationally will facilitate global communication of safety information. Since MedDRA has been accepted by all ICH parties as the coding terminology to be used worldwide, it would be totally unacceptable for the FDA to consider use of SNOMED for ADR reporting. We hope that the FDA will resist such urges or pressures and move forward with the planned use of MedDRA.

Section II.A.3. Terms Used In This Document

The agency does not address Investigator Initiated Studies (IIS) in this section when defining a sponsor. The FDA's definition of *sponsor* is "persons subject to premarketing safety reporting" which would include investigators for IIS. We request that the agency clarify how they anticipate IIS will be affected under the new regulations.

Section II.B.1. International Standards

The agency requested comment on potential strategies to facilitate communications with third parties who may employ non-MedDRA terminology. The agency should consider providing guidance on the mapping between alternative (non-MedDRA) terminology and MedDRA terminology.

Section II. B.4. **Bioavailability and Bioequivalence Studies Not Subject to an IND**

In the proposed rule, the agency requires that a sponsor of BA/BE trials submit expedited reports for SADRs to the agency. Please clarify whether this includes studies conducted outside of the U.S.

Section III.A.1. **Suspected Adverse Drug Reaction (SADR)**

We agree that the definition of a suspected adverse drug reaction is consistent with the ICH E2A guidance. However, we believe that the examples of relatedness provided, and therefore by extension, the FDA's interpretation of the definition, do not conform to ICH E2A. The agency defines " a reasonable relationship" as the "relationship cannot be ruled out." We believe the ICH definition of "reasonable" causal relationship means to convey that there is positive evidence to support a causal relationship. This positive evidence could come from biological plausibility, data from pre-clinical studies, behavior of similar compounds, etc. In addition, to being technically inconsistent with the ICH definition, the proposed FDA definition does not agree with the EU Clinical Trials Directive on ADR reporting. Lack of consistent definitions and interpretations between FDA and other health authorities worldwide will lead to confusion and will impact a company's ability to manage safety issues globally.

The proposed definition as well as the alternative definition of SADR provided will generate significant over-reporting of events with an improbable relationship to study drug in clinical trials. It is very likely that most events will fall under the proposed reporting category because investigators will rarely have enough information to confidently rule out a relationship, particularly given the traditionally conservative approach in considering the role of any drug in contributing to an adverse event. In addition, this new definition clearly reduces the need for careful medical judgment regarding possible relationship and may reduce the involvement of the investigators in defining the safety profile of the drug. Most of the time the 7- or 15- calendar day time frame does not allow documentation of a definitive diagnosis that would eliminate the relationship with the study drug. It is our opinion that this extensive and unnecessary reporting will have a negative impact on the safety evaluation of a new compound by overwhelming a true signal.

In addition, the effect of unblinding the majority of Serious and Unexpected SADRs in the conduct of blinded clinical trials will be to jeopardize the integrity of those studies. While the FDA offers that certain disease-related events might be excluded from expedited reporting based on protocol designation, we think this is an unwieldy approach and will not be satisfactory for the majority of studies.

The fact that the FDA even gives an example of "cannot be ruled out" as disease progression, (e.g. "In some cases an adverse event may most probably have occurred as a

result of the patient's underlying disease and not as a result of the drug, but since it cannot usually be said with certainty that the product did not cause the adverse event, it should be considered an SADR.") means that almost all SAEs from clinical trials will have to be considered as related, which will exponentially increase the number of expedited reports as well as the number of IND safety reports that have to be sent to investigators. We think this is a serious issue, and strongly urge the FDA to consider the EU Clinical Trials Directive and CIOMS VI proposals regarding reports to investigators. These propose that periodic (quarterly) line listings be submitted to investigators during Phases I – III, instead of individual expedited reports; these listings would be accompanied by a summary of the evolving safety profile of the product. We believe this to be a much more useful, efficient, and certainly less confusing way to inform investigators about safety reports.

If the FDA decides to continue with their interpretation of "related", then we request that the FDA provide or allow for a transition period for ongoing trials.

It is also quite possible that this initiative, which aims to make it easier to identify potential problems during clinical trials and post-marketing, will have the opposite impact. That is, due to the large numbers of additional reports generated by the lowered threshold and loss of medical judgment, real safety signals may be obscured. Therefore if the FDA does persist in the use of their interpretation of "related", we respectfully request that there be a formal evaluation step added to assess the utility of the initiative.

On *page 12418 of the Federal Register,* the FDA asks for alternate ways to handle AEs during clinical trials to minimize "over-reporting". One suggestion is to survey a panel of investigators in the US and test their interpretation of the proposed definition since they will be the primary users.

Section III.A.1. **Suspected Adverse Drug Reaction (SADR) – Issue Regarding Liability Misuse**

MedWatch Form Disclaimer (that the submission of the report does not constitute an admission that the drug caused or contributed to an adverse affect): In the proposed rule (*Federal Register, page 12418*), FDA recognizes a concern that the SADRs are subject to misuse if the reports, taken out of context and used in a manner for which they were never intended, create product liability vulnerability. The FDA seeks comments as to whether the disclaimers are sufficient to protect manufacturers from the use of SADR reports in product liability actions. FDA asks that, "*...Perhaps the agency should consider also prohibiting the use of SADR reports the agency receives in product liability actions.*" We believe that the use of the disclaimer is important for the following reasons:

- However, to answer the FDA's specific question, the disclaimer is *not sufficient* to protect manufacturers from the use of SADR reports in product liability actions. The disclaimer is helpful,l but it does not prevent the use of SADRs nor the inference that the drug causes a particular event to be drawn from the fact that the company has reported other SADRs to the FDA for that same event. A manufacturer can argue to the court and/or jury that the disclaimer on the face of the Form 3500 means causation should not be inferred; however, the court/jury is free to disregard the disclaimer. Moreover, the disclaimer has little weight with the jury especially when there are multiple SADRs for the same event as the plaintiff experienced. Juries are overly influenced by the number of reports and assume causation. Importantly, even if the number is small, e.g., 2 or 3 reports, juries are free to conclude causation and that the warnings are deficient for not including additional or different language from what FDA has approved. The prejudicial affect against the company is significant and difficult to overcome when evidence of SADRs is admitted in a product liability trial as proof of causation.

- Actual prohibition of the use of SADR reports in product liability actions would be an extremely beneficial development since it would prevent the misuse of these reports in court as proof that the drug caused the adverse event. Plaintiffs attempt to use SADRs as proof that the product causes a particular adverse event merely because there are spontaneous reports of these events in company files. As a practical matter, much money, time and effort are spent in the pretrial phase of lawsuits litigating whether these types of reports are "discoverable" (required to be produced to plaintiffs) and whether the reports should be admitted into evidence during the trial. Under liberal discovery rules, a company must allow attorneys suing the company to examine these SADRs subject to certain limited restrictions (e.g., only events that are substantially similar to the event at issue, only events reported to the company up to the time the plaintiff was prescribed the drug) which some courts do not impose at all.

- If the FDA decides not to prohibit such use, then the disclaimer is still needed since it allows the company to argue that the disclaimer is the FDA's position on the issue of causation.

Section III.A.2. **A Life-Threatening SADR**

The agency proposes that a sponsor include, in the IND safety report, the reasons for "differences in opinion" between the investigator and sponsor with regard to classifying an adverse event as life-threatening. If the investigator's opinion is that the SADR is not life-threatening, the sponsor may take a more conservative approach and classify the SADR as life-threatening. We see no value in including reasons for the difference in opinion.

Section III.A.4. **Contractor**

The definition of contractor provided is too broad and vague. As currently written, the scope may include such entities as PBMs and hospitals. The implications of including such a wide range of institutions are quite onerous, and might include such activities as auditing, and will not add to public safety. We suggest that the agency modify the definition to be more focused.

In addition, given the range of possible contractual arrangements between "contractors" and "applicants", we suggest that the Final Rule allow flexibility regarding specific responsibility for reporting. We also suggest that the Final Rule should apply only to new contracts, given that sponsors already have a wide range of safety reporting agreements in place.

Section III.A.5. **Minimum Data Set and Full Data Set for an Individual Case Safety Reports (Reference also to III.C.5)**

Although we support and understand 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" may be interpreted in various ways by different reviewers. It is understood that a minimum data set requires information on four data collection fields. In contrast, a full data set may mean that all available information for remaining data collection fields will be filled in "as appropriate." We appreciate "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 or is not provided. Further guidance from the FDA as to what is expected specifically for those data fields relevant to the case is requested.

FDA proposes that for a serious SADR that was not initially reported by a HCP (e.g. consumer), the manufacturer must contact the HCP associated with the care of the patient using active query. If the HCP cannot be contacted, then reasons and a description of the efforts must be documented in the report. For OTC products, HCP information may not be available as the consumer is not under the care of a physician (the product is not prescribed by a physician). The criteria for seriousness may be derived by description of the event by the consumer, which may not have involved intervention of a HCP. Therefore, this section needs to be modified to exempt OTC products under such circumstances where there is no HCP intervention.

Section III.A.6. **Active Query**

FDA proposes active query of initial reporters via direct verbal contact (in person, telephone or other interactive means) for a defined type of SADR. FDA has also asked

for comment as to whether written requests for follow-up information should be permitted and, if so, under what circumstances. Please clarify whether the intent is to permit written requests *instead* of verbal contact for gathering follow-up information.

We agree that obtaining higher quality reports will be a positive step to improve public health. We also agree with the agency that the time and resources spent in the initial contact might significantly reduce the burden of follow-ups. However, the active query process required in the Proposed Rule will have a significant impact on resource requirements. We expect that the number of personnel needed to meet this requirement will be much higher than the numbers estimated in the Proposed Regulations.

In fact, our major concern is that we should focus medical resources where we have the most need. We believe that the physician 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. Such examples would be serious cases, unexpected AEs, and AEs of special interest. The rationale and decision would be documented in the file. This category of data would be presented separately as subsections in the PSUR (e.g., for events with unknown outcome, distinction would be provided between no active query or unsuccessful active query).

Although information received via direct verbal contact is valuable, written follow-up, particularly in the form of medical records, is more accurate. When physicians are called, they typically do not have the medical record in front of them and have to rely on their recollection of the case. In other situations, the initial reporter contact information that would allow for direct verbal contact may not be available or obtainable. Also, the reporter may require the request for information in writing from the company before providing any further information. The reporter may refuse to provide any information, verbal or written, without first receiving written consent from the patient for the release of medical records. Overall, we have found that written communication is the preferred route of communication of many healthcare providers in responding to follow-up questions on SADRs.

It is not specified if this proposal applies to reports originating in the US only. Reports received from ex-US sources (i.e., reports from foreign regulatory agencies, business partners/licensees) may not lend themselves to direct verbal contact.

Product Liability Issues:

Active query is direct verbal contact with the *initial reporter* of a SADR by a healthcare professional. This raises a product liability issue. If the company receives a SADR via a product liability lawsuit or from a contact by an attorney representing a patient, this rule mandates that a healthcare professional from the company have a direct conversation with the attorney representing the patient who has retained that attorney to sue the company. The likelihood of the attorney answering the "focused line of questioning designed to capture clinically relevant information" associated with the adverse event for the attorney's client is remote. On the other hand, direct contact will most likely

motivate the attorney for the patient to interview or otherwise try to obtain statements from the company health care professional that will later be used against the company in product liability litigation.

This is yet another reason why SADRs received by the company from lawsuits or attorneys representing patients should be reported periodically (see other comments above). We recommend that active query not be required in situations that would force company employees to have dialogue with attorneys suing or contemplating suing the company. Indeed, attorneys suing the company are not allowed to speak directly with employees of the company outside of the legal process in most jurisdictions.

Therefore, for all these reasons, while we agree that direct verbal contact can be of value, we also support the use of written requests to obtain follow-up information.

FDA should clarify for health care providers that adverse event reporting is excluded from HIPAA regulations, so that the lack of health care professional cooperation does not become a barrier to obtaining sufficient information to report cases. We base our concern on feedback from health care providers who have been unwilling to provide additional information due to the HIPAA regulation.

One unintended consequence of making "verbal contact" a mandatory requirement for all the proposed situations is that there might be a decrease in spontaneous reports from physicians and pharmacists who could be overburdened with requests from the industry.

J&J would like to provide some suggestions to facilitate success in achieving increased quality in adverse events that are reported:

Tools: Forms/questionnaires could be developed that would encourage reporters to provide accurate and complete information without negatively impacting their practice such as:

- Pre-filled forms containing the already available information and highlighting the missing information (seriousness criteria, etc...) to be returned by fax by the reporter.
- Standardized "full data set" questionnaires/forms for each of the "always expedited reports" that would be completed during the initial intake and faxed with highlighted missing data to be filled in and returned by fax by the reporter.

Education programs: Programs could be developed for potential reporters (physicians, pharmacists) on the regulatory requirements for reporting adverse events and medication errors. It could improve the quality of initial reports to companies.

Section III.A.7. **Spontaneous Report**

The FDA proposes to define this term to clarify which reports would be considered "spontaneous". While we support providing clarity around the distinctions between spontaneous and solicited reports, and we agree that only unsolicited safety information from individuals would be considered a "spontaneous report", we are concerned about the potential implications of lumping patient support programs, disease management programs, patient registries, and other similar activities into the "study" category. Reports from a study require causality to determine reportability, and it is extremely difficult to get such assessments from treating physicians in such programs. Indeed, it is often difficult to get any follow-up at all from the physician, and coupled with the fact that many of these programs, by design, keep the patient or consumer anonymous, follow-up will be impossible in many cases. The outcome of such a situation will be that we will default to a "positive" causal relationship, since we will not have the appropriate information to rule the association out. We believe that this will result in huge numbers of non-value added expedited reports, which will both burden industry and the FDA. Our suggestion is that such reports can be included in the PSUR instead.

Section III.A.9. **Company Core Data Sheet, Company Core Safety Information**

Sponsors may not always prepare Company Core Data Sheets for products that are marketed in a limited number of countries or in the U.S. only. In these cases, all relevant safety information is contained within the U.S. package insert. In other instances where products are marketed outside the U.S., in limited EU countries, a USPI is not available. For these reasons, we suggest that the FDA expand its definition of a CCSI to include the use of a U.S. package insert or other label (e.g., the Investigator's Brochure) when appropriate.

Section III.B.1. **Review of Safety Information**

The discussion of *in vitro* studies needs to be clarified to report relevant safety related information. It would be advantageous if the agency could provide other examples of when safety data from in vitro studies should be provided.

Section III.B.2.b. **Serious and unexpected SADRs**

The term *due diligence* that sponsors must document to obtain the minimum data set for a report requires clarification. FDA should define at least the minimum requirements of due diligence they expect of a sponsor to avoid variation on this requirement from sponsor to sponsor.

Section III.B.2.c. **Information Sufficient to Consider Product Administration Changes**

Further clarification is needed regarding the kind of in vitro studies that would fall in this category. In vitro studies may be exploratory and unvalidated; hence, the clinical relevance cannot be adequately assessed from these studies and "appropriate medical judgment" may not be able to be applied 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 could 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.

In this section, there is mention that the expedited reporting is required "...in no case later than 15 calendar days after determination by the sponsor that the information qualifies for reporting under this paragraph." The wording implies that the clock starts when a finding is determined by the sponsor to qualify for reporting (e.g., suggests a significant human risk). Is this the case, or does the clock start at the time the information was first received? We request that the agency clarify when the clock starts.

Additionally, 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." We request that the agency clarify that only those findings of mutagenicity, teratogenicity, or carcinogenicity that are considered by the sponsor to suggest significant human risk qualify for expedited reporting, and not all findings of these types. Some findings of these types are clearly species-specific or for other reasons do not suggest a significant human risk.

More broadly, we recommend that FDA consider the impact of the proposal to notify participating investigators of information that might be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation, when no decision has yet been made. Such investigator notification, without clear recommendations for a change in the product administration or conduct of the investigation, will be confusing as to what action the investigator should take. We propose instead that only FDA (and not the investigator) be notified of information that might be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. This would also be consistent with ICH E2A, which only requires that such information be communicated to regulatory authorities.

Section III.C.2. **Review of Safety Information**

We understand that the provision in this section requiring applicants to review safety information from foreign regulatory authorities is limited to individual case reports obtained from the regulatory authorities. We suggest that an applicant's mere access to

publicly available databases such as the WHO database should not impose any specific obligation to actively search for reports that have not been previously received. We request agency confirmation on this issue.

Section III.C.5. **Determination of Outcome, Minimum Data Set and Full Data Set**

Some proposed changes in regulations would not improve the quality, quantity or timeliness of safety information that FDA receives. Specifically, the requirement to document efforts to obtain a full data set (i.e., description of unsuccessful steps taken to obtain this information) would not help FDA interpret an event, which is the rationale for the proposed regulation changes. Such records should be maintained in the sponsor's files and not be reported to FDA.

Section III.D.1. **Serious and Unexpected SADRs**

We question the value of "a chronological history of their [sponsor's] efforts to acquire a minimum data set" in an expedited safety report in cases when a delay in obtaining information occurs. Such records should be maintained within the sponsor's files and not be reported to FDA.

Section III.D.3. **Unexpected SADRs with Unknown Outcome**

We agree that some information about non-serious adverse drug reactions can provide important additional safety information. However, given the nature of spontaneous reporting, it is often necessary to use medical judgment and make decisions based on available information. We believe that treating all "SADRs with unknown outcome" as serious adverse events until proven otherwise without exception could result in an inefficient use of resources and focus activities on the acquisition of details that are unlikely to result in any significant new safety information.

We agree that efforts should be undertaken to obtain follow-up information on many types of adverse drug reactions when the seriousness of a specific adverse event cannot be determined initially. However, some commonly reported conditions such as headache, skin irritations, and alopecia are almost never serious by the regulatory criteria. We propose that all AE reports be viewed in context and that judgment be used to determine which of the indeterminate reports should be forwarded within the 45 day reporting timelines.

Section III.D.4. **Always Expedited Reports**

We understand that "always expedited" reports are to be submitted only for post-marketing reports and only when reported as adverse events, not as the underlying disease. As the list is quite comprehensive, we request that the FDA not add to the list without a defined public health concern. A separate consideration would be to include these events in guidance rather than within a regulation. Any modification to such a listing, if codified in a regulation, would take a long time to revise.

We also support the proposal for Sponsors to create listing of events that are known consequences of the disease and that would not be reported to the FDA in an expedited manner. At regular intervals, e.g. in the ISS or annual reports, review of adverse events in this category could specifically address whether any unexpected trends suggest a drug-associated etiology.

Section III.D.5. **Medication Errors**

We believe that the term "potential medication error" is too broad to meet a valid safety reporting need. As defined in the Proposed Rule, it may produce a huge volume of reports of limited or no interest for product safety. It is impractical to expedite any "potential" medication error in the absence of SADR. It appears also that medication errors might be more appropriately classified into different subcategories that might include potentially relevant medical issues, such as: name confusion, dose-formulation dispensing errors, and lack of product-label clarity. We request that the agency clarify their plans to educate healthcare professionals to submit such reports and what actions they would ultimately undertake upon review of these reports.

While it is of value to discuss experience with all medication errors in periodic reports, expedited reporting of medication errors without SADRs diverts company resources to activities of questionable public health value.

In addition, we recommend that the Final Rule include language to specify that off-label use of a product not be considered to be "inappropriate" use.

Section III.D.6. **Follow-up Reports**

FDA proposes that if a 30-day follow-up report is required for a case and no new information is obtained, a 30-day follow-up must be submitted indicating that no new information was available which includes a description of the reasons for the manufacturer or applicant's inability to obtain additional information and efforts made in an attempt to obtain this information.

While we understand the rationale for the 30-day follow-up reports, we feel that it adds no additional value to the current process. Going through this exercise of documentation

of unsuccessful attempts in obtaining additional information in a formal 30-day letter will take resources away from seeking active query follow-up. Follow-up on the designated cases would automatically be submitted as 15-day reports.

The 30-day follow-up reports add an extra component of tracking compliance into the 15-day reporting process. Also the requirement to document all the follow-up attempts into the narrative adds administrative tracking information into the Medwatch form that may not be helpful to one who wants to use the Medwatch form to review the case history. The manufacturer could provide this administrative tracking information if questions about the quality of the data arose during an FDA review of the case.

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

Section III.D.7. **Supporting Documentation**

Although an autopsy report or death certificate may be useful, to require them seems an onerous burden and one that may not be practical. For instance, autopsy reports are generally not part of the hospital medical record and may be extremely difficult for the company to obtain, especially outside of the United States. The same applies to death certificates that are often not issued until months following the death. In addition, if supporting documentation is not in English, obtaining translations within 15 days is unlikely to be possible.

Please consider making these data optional for expedited reports. If these documents are provided to the manufacturer as part of the follow-up process then the manufacturers can submit them, but a requirement to submit them for all fatalities or hospitalizations seems to put an undue burden on manufacturers.

Due to implementation of electronic submission for safety reports, FDA needs to inform the industry how such documents should be submitted, as they are not currently accommodated in the E2B file format.

Section III.E.1.c. **Increased Frequency Reports**

The rationale for increased frequency reports is unclear, as past experience with this has been unsatisfactory. Without guidance on a methodology to calculate increased

frequency, it is not likely to yield useful information. We propose that this requirement be dropped.

Sections III.E.1.h. And III.F.4. **Contact Person**

FDA is proposing that each completed 3500A or CIOMS I form 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 TPSRs.

The requirement for a licensed physician could be difficult to meet and needs clarification regarding the country in which licensing is required and whether an active license is required.

Overall, we do 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 CIOMS I form. Companies currently provide a contact person who can ensure that FDA has access to the appropriate medical professionals in the company in a timely manner, and we believe that this approach is adequate.

Section III.E.2.b. **Worldwide Marketing Status**

For consistency with the ICH guidelines, "when known" should be added to the current bullet "Dates of market launches."

Section III.E.2.c. **Actions Taken for Safety Reasons**

Under clinical suspensions, would investigator or IRB initiated actions be referenced? We request agency clarification on this issue.

In addition, under clinical suspensions, we recommend that the FDA include those studies that have been stopped due to action by the Data Safety Monitoring Board.

Section III.E.2.d. **Changes to CCSI**

For events where listedness is changed, we propose that the CCSI in effect at the time the SADR is reported be used for the PSUR. The PSUR would then address changes in dates, and the reasons for the labeling changes.

Section III.E.2.i. **Overall Safety Evaluation**

It has been our experience that European assessors prefer a modified format with this information included in Section 6 immediately following the discussion of cases. We propose to summarize conclusions/insert executive summary in this section.

Section III.E.2.k.iii. **Spontaneous Reports Submitted to the Applicant by an Individual Other than a Health Care Professional**

Please clarify whether the foreign and domestic reports are to be separated in these tabulations.

Section III.E.2.k.v. **Class Action Lawsuits**

We support and appreciate the FDA Proposed Rule for the changes related to class action lawsuits; that is, that the FDA will allow reporting of SADRs contained in class action lawsuits to be made as part of the PSUR. However, it should also be noted that companies often receive large numbers of SADRs from litigation that is not part of a class action lawsuit. For instance, in some jurisdictions, plaintiffs will "join" large numbers of plaintiffs in a single lawsuit that is not a class action. "Joiners" of large numbers of plaintiffs in a single lawsuit presents the same reporting problems that FDA addresses with the class action appendix to the PSUR. We believe FDA's proposal for reporting SADRs from class action lawsuits filed against the company should be extended to include not only class action lawsuits but lawsuits in which multiple plaintiffs are "joined". The same rationale for allowing class action lawsuit SADRs to be filed on a periodic basis applies to these multiple plaintiff lawsuits as well. Therefore, we ask FDA to clarify that the rule permits periodic reporting of any SADR that arises from a "legal" origin, i.e. any SADR that is reported to the company via a lawsuit or contact from an attorney representing a patient. It should be noted that SADRs of this type are usually reported to the company later than one year or more after the event has occurred.

We propose that these 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.

Section III.E.2.k.vi. **Lack of Efficacy Reports**

We propose that this not be a separate appendix but rather moved to the body of the report and discussed within the Lack of Efficacy section.

Section III.E.2.k.vii. Information on Resistance to Antimicrobial Drug Products

We propose that the domestic cases be a subset from the worldwide cases in order to gain useful information. We request that FDA comment on this suggestion.

Section III.E.2.k.ix. U.S. Patient Exposure

We propose to add this information to the body of the report in the exposure section subset by regions for worldwide submission to all regulatory authorities, e.g. in the form of an exposure by region table.

Section III.E.2.k.xi. Contact Person

Again, we do not agree with the proposal to provide contact information for the individual physicians responsible for the content and medical interpretation of the data and information. Companies currently provide a contact person who can ensure that FDA has access to the appropriate medical professionals in the company in a timely manner, and we believe that this is adequate.

Section III.E.3. Interim Periodic Safety Reports (IPSRs)

We proposed that the acronym "IPSR" should not be used because this nomenclature conflicts with European usage of "interim safety update report" denoting a safety update in response to a safety signal focusing mainly or only on the safety signal. We also suggest that if the agency wants a "renewal" PSUR, it should offer the ability to submit multiple PSURs and a bridging document that tie in with the International Birth Date (IBD).

Section III.E.4. Semiannual Submission of Individual Case Reports

We see no public health rationale for submitting case reports on a semiannual basis when analyses of these cases are provided in PSURs. We request that the agency delete this requirement.

Section III.E.5.a. Reporting Intervals

The proposed reporting intervals represent a significant workload increase due to US approval date versus the IBD; the number of submissions required over a 15-year period would increase dramatically under the Proposed Rule. We propose to submit PSURs according to the highest frequency requested by any regulatory agency, and that the

company determine the optimal data lock date within the limitations of the required frequency (i.e. regulatory agency determines the frequency and the company determines the data-lock date).

Comments to Proposed Regulations

Section(s) 310.305(a), 312.32(a), and 314.80(a) Definitions
The agency should be consistent with the current ICH definition and interpretation of an SADR, specifically regarding the use of "a reasonable possibility". See comments for *Section III.A. Definitions, Section IIIA.1. Suspected Adverse Drug Reactions (SADR)* above.

Section 314.80(a) Definitions – Active query
The agency should consider that direct verbal contact not be limited to the initial reporter but broadened to include direct verbal contact with a healthcare professional familiar with the case. See comments above in *Section III.A.6.*

Section 314.80(a) Definitions – Company Core Safety Information
See comments above in *Section III.A.9. Company Core Data Sheet, Company Core Safety Information.*

Section 314.80(c) Reporting requirements
The agency should consider adding language to allow for electronic submission of post marketing safety reports. As you know, the FDA has issued draft guidance on electronic submissions for both postmarketing periodic adverse drug experience reports and postmarketing expedited safety reports.

Section 314.80(c)(3)(i)(D) TPSRs – Location of safety records
As safety records could be maintained in multiple locations, including multiple countries and offsite archives, a corporate address only should be provided. Listings of locations of safety records should be maintained within the sponsor's files.

Section 314.80(c)(3)(ii)(B)(1) PSURs – Worldwide marketing status, Dates of drug approval and renewal
FDA will be provided with information on registrations and market withdrawals. Compiling dates of renewals worldwide is a difficult, cumbersome process and we see no value to providing this information.

Section 314.80(c)(3)(ii)(B)(3) PSURs – Worldwide marketing status, Indications for use....
As the Company Core Data Sheet, which lists indications, is provided with the PSUR, we see no reason for the additional requirement to list indications in this section.

Section 314.80(c)(3)(ii)(B)(6) PSURs – Worldwide marketing status, Dates of market launches
For consistency with the ICH guidelines, consider adding, "When known" to the current bullet "Dates of market launches".

Section 314.80(c)(3)(ii)(E)(1) – PSURs – Worldwide patient exposure
The proposed wording is not clear on the inclusion or exclusion of data from clinical studies and should be revised for clarity. 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.

Section 314.80(c)(3)(ii)(E)(2) PSURs - Worldwide patient exposure
While we realize that separation of data by age and gender is part of the current ICH guideline, we believe these data will not be available in the majority of cases. Therefore, the request for this breakdown is more appropriate as part of a guidance than as a regulation.

Section 314.80(c)(3)(ii)(K)(10) PSURs - Appendices – Location of safety records
Same comment as above for *Section 314.80(c)(3)(i)(D) TPSRs – Location of safety records.*

Section 314.80(c)(4)(iv) – Reporting format – Name and Number of Licensed Physician
The current FDA Form 3500A does not include a space for the company contact person.

ADDENDUM

Background

On August 28, 2003, FDA updated the Q and A section regarding the Safety Reporting Requirement Proposed Rule with information about the impact of the potential use of the clinical terminology database, SNOMED on the proposed requirement for MedDRA use for postmarketing safety reports from industry. FDA also invited public comment on this topic. Here are J&J's comments on this issue:

MedDRA has been developed as a part of an international harmonization effort among the global pharmaceutical industry, the FDA, and health authorities in the European Union and Japan. All involved stakeholders have invested substantial time, effort and resources in this effort. We find that MedDRA provides sufficient granularity for coding adverse events and that it is relatively easy to use. It is also designed to facilitate the remapping of terms coded by other commonly used coding dictionaries (such as COSTART) to it. Thus we fully support FDA's proposal to require MedDRA as the coding dictionary for adverse event reporting. Suggestions made by others in public comments submitted to FDA to re-consider MedDRA at this time would likely delay anticipated public health benefits from implementing FDA's proposed drug safety reporting improvements.

Clarification on whether SNOMED is an acceptable alternative to FDA for collecting and/or reporting of adverse events is needed to understand FDA's view that the two terminologies could coexist effectively. We are not in favor of having SNOMED as an alternative to MedDRA for adverse event reports as this will revert back to pre-ICH days of using more than one dictionary for worldwide drug safety reporting. This will make global drug safety operations very complicated. In addition, it is unclear as to whether SNOMED would be license free outside of the U.S. So, this advantage may be a moot point to global companies.

If the FDA permits SNOMED CT as an alternate coding dictionary, strategies and approaches for facilitating seamless, cross-standard drug regulatory communications are definitely needed, especially if SNOMED were to serve as a component of a national health record. Under this scenario, a robust mapping between the two dictionaries is definitely needed. The desired outcome is that the adverse event reports in FDA's AERS database be all mapped with MedDRA regardless of what other medical dictionary that is used for the reports submitted to the agency. Conceivably, a 1 to 1 mapping between terminologies in these two dictionaries will facilitate an automated conversion of SNOMED terms to MedDRA terms.