October 8, 2003

Via Fax and UPS

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

Re: Docket No. 00N–1484
Proposed Rule: Safety Reporting Requirements for Human Drug and Biological Products; 68 FR 12405 (March 14, 2003)

Dear Sir/Madam:

Aventis, Aventis Behring, and Aventis Pasteur together (from here on collectively referred to as Aventis) are pleased to provide the following comments on the above-referenced proposed rule entitled, "*Safety Reporting Requirements for Human Drug and Biological Products*".

The Food and Drug Administration (FDA) is proposing to amend its pre- and postmarketing safety reporting regulations for human drug and biological products to implement definitions and reporting formats and standards recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's (WHO's) Council for International Organizations of Medical Sciences (CIOMS); codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed drugs and licensed biological products; require that certain information, such as domestic reports of medication errors, be submitted to the agency in an expedited manner; clarify certain requirements; and make other minor revisions. FDA is also proposing to amend its postmarketing periodic reporting regulations for human drug and licensed biological products by revising the submission schedule and content for these reports.

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General Comments

We appreciate the time and effort the FDA has committed to revising the pre- and post-marketing safety reporting regulations. We recognize those areas in which the FDA has recommended harmonization with ICH initiatives, but are concerned that the following proposals are divergent to and may impede globalization of pharmacovigilance procedures:

- the many new and unique situations and exceptional handling (always expedited reports, 45 and 30-day follow-up reports, protocol waivers, etc...) may lead to a shift from an overall safety emphasis to individual case handling and tracking
- the increased focus in single case administrative processing will decrease the ability to perform aggregate signal analysis and detection
- the anticipated increase in follow-up and regulatory submission activities will have an economic and technical impact on the industry, with questionable added value to the quality of the safety data
- the proposed rule could also have a counterproductive effect on communication with health care professionals both in spontaneous notification and clinical trial arena (physician's harassment) and investigators
- inconsistency with EU regulations and ICH Guidelines on the definitions of SADR/ADR and the resulting regulatory reporting differences.

Currently, companies are able to highly leverage their pharmacovigilance activities because the requirements are predominantly objective and can be automated. The new proposals in the Tome introduce many activities which are not conducive to automation and will be burdensome and result in increased headcount and costs for the industry. It is not apparent that the volume or quality of the reports will be increased enough to justify this extra burden

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

"A noxious and unintended response to any dose of a drug ("biological" for proposed Sec. 600.80(a)) product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out."

A primary objective for development of the Proposed Rule as explained by FDA was to bring U.S. Federal Regulations in better alignment with guidelines of the ICH. Aventis disagrees with the adoption of this new term and definition and believes that the FDA definition of SADR/ADR should be consistent with that agreed to in ICH E2A. The ICH E2A Guideline provides two different definitions for adverse drug reactions (ADRs): (i) for the pre-approval clinical experience and (ii) for marketed medicinal products. The FDA proposed rule does not differentiate between the approval/marketing status of a product. It defines an SADR as "an noxious and unintended response to *any dose...*" whereas the ICH Guideline applies this exclusively to pre-approval clinical experience. For marketed medicinal products the ICH Guideline defines an ADR as a noxious and unintended response "which occur at *doses normally used...*"

The FDA has also proposed an interpretation of "a reasonable possibility that the experience may have been caused by the drug" that is different from that of ICH E2A. Although both the FDA and ICH include in their definitions that a causal relationship with the drug should be a "reasonable possibility", meaning that "the relationship cannot be ruled out", they appear to have a different interpretation of "reasonable possibility" or "reasonable causal relationship". The FDA states that it would "indicate that causality could not be ruled out with certainty", while ICH notes that it "is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship".

Aventis believes that the FDA proposal will create a situation where the definition of positive causality is much more inclusive than other regulatory guidances based on the ICH definition specifically, *EU Clinical Trial Directive Final Guidance on Adverse Events (AEs)* [section 6.2.2 Assessment of Causality, April 2003]. This may produce a situation where a Sponsor who conducts global clinical trials may have conflicting adverse event reporting obligations.

"FDA seeks comment as to whether the agency should use the alternative definition of SADR instead of the proposed definition of SADR."

"FDA seeks comment as to whether use of the proposed or alternative definition of SADR would lead to significant increases in reporting to the agency beyond what FDA has identified in the following paragraphs."

Aventis believes that the alternative definition of SADR would significantly increase the number of expedited IND Safety Reports, which we believe the FDA is underestimating. Considering cases currently assessed as "probably not related" to be causally associated SADRs, would result in increased unblinding for regulatory reporting and investigator and IRB/EC notification. Increased unblinding would lead to fewer patients completing a trial and would necessitate larger patient enrollment and extend the duration of clinical trials.

We are also concerned that differences in the definitions of SADR/ADR and the interpretation of "reasonable possibility" will lead to inconsistencies in globally conducted studies where we must adhere to multiple regulations and directives (e.g., EU Clinical Trial Directive and CIOMS VI proposals regarding reporting to investigators). This complex, increased and divergent regulatory reporting will impact each company's technological, compliance and administrative resources. We question if this will result in any real added value or improvement in the quality of safety data.

It also seems likely that the workload on clinical investigators will increase significantly. As many serious adverse events will by default drop into the SADR category, there is concern that investigators may become overwhelmed with the receipt of additional IND Safety Reports, which in turn may impact the efficiency and accuracy of their review. The result of this could be that a significant event may be overlooked.

Recommendation:

Aventis recommends that FDA redefine the definition of an SADR such that it is more in line with the ICH E2A definition for ADR.

"If sponsors, manufacturers or applicants believe that, in a specific situation, there is an alternative way(s) to handle adverse events occurring during clinical studies that would minimize "over-reporting" while assuring that reporting of SADRs would not be compromised, they are invited to propose any such alternative(s) reporting method to the agency. In such situations, if FDA does not oppose the proposed alternative reporting method, the sponsor, manufacturer or applicant would be permitted to report SADRs to the agency according to the alternative method. For example, one such alternative would be to include in study protocols or other documentation a list of known consequences of the disease that would not be submitted to FDA in an expedited manner as individual case safety reports (e.g., events that are the endpoints of the study). These adverse events would, however, be monitored by the sponsor, manufacturer, or applicant and, if they indicated in the aggregate by comparison to a control group or historical experience, that the product in the clinical study may be causing these events, the information would be submitted to FDA in an expedited manner as an information sufficient to consider product administration changes report (see sections III.B.2.c and III.D.2 of this document for discussion of this type of report)."

We recognize FDA's goal to minimize situations in which an SADR/ADR that proves ultimately to be due to a drug is not reported expeditiously to the agency because the etiology of the event is attributed to the patient's underlying disease. We appreciate the provision to identify alternative ways to handle adverse event reporting during clinical trials to minimize "over-reporting". Many companies currently indicate in clinical protocols certain disease-related events which are considered study endpoints to be excluded from expedited reporting requirements.

Recommendation:

Aventis recommends that FDA provide clarification on the process for submitting a waiver request, examples of situations which would warrant the granting of such a waiver (and examples where a waiver would not be granted), how often waivers would be granted and if industry will be able to take advantage of these or other alternative reporting methods or will they be only for exceptional situations.

III.A.5. Minimum Data Set and Full Data Set for an Individual Case Safety Report

"A "full data set" for a postmarketing individual case safety report would include: Completion of all the applicable elements on FDA Form 3500A (or the Vaccine Adverse Event Reporting System (VAERS) form for proposed Sec. 600.80(a)) (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADRs) including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error)."

Aventis would appreciate more precise definition and/or clarification of "full data set". We recommend that the determination of what constitutes "all the applicable elements" on regulatory report forms be left to the judgement of the company. As an example, in many cases the name of a concomitant medication may be sufficient while in some situations the dates of administration would be considered an important component of a full data set. If an element is not considered applicable in the judgement of the company, would this need to be indicated on the report form?

Due to increasing concerns for patient privacy, complete patient demographics may be unobtainable from the reporter. Additionally, cases received through some foreign sources will require that certain patient identification be anonymized and, therefore, this information will be unavailable on reports.

Active query to acquire certain safety information (Sections III.A.6, III.C.5, III.D.6)

"Direct verbal contact (i.e., in person or by telephone or other interactive means such as a videoconference) with the initial reporter of a suspected adverse drug reaction (SADR) or medication error by a health care professional (e.g., physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training) representing the manufacturer (applicant for proposed §§ 314.80(a) and 600.80(a)). For SADRs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product (licensed biological product for proposed § 600.80(a)) and the SADR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results."

"Even though the agency is not proposing that manufacturers and applicants request follow-up information for SADR and medication error reports in writing, the CIOMS V report describes instances when it might be appropriate to do so. FDA seeks comment as to whether the agency should permit written requests for follow-up information and, if so, in which situations should these requests be permitted."

Active query, as defined in the Tome, appears to be inconsistent with the "General Good Follow-up Practices" described by CIOMS V where it is recommended that follow-up information be obtained/ confirmed in writing. CIOMS V provides flexibility and allows for a more efficient process than proposed in the Tome.

The concept of active query already exists, both in the context of clinical trials and spontaneous cases and Aventis agrees that there are times when it is essential for expeditiously obtaining follow-up information. But we believe its use should be reserved for unexpected fatal or life threatening events and certain product technical complaints (medication errors) and not used as the routine form of follow-up contact. We agree that a focused line of questioning facilitates 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; for some types of data such as lab values we should rely more on paper copies than phone conversation. We also ask the agency to define at what point to stop

follow-up for both postmarketing and clinical trials or to mention that it is at some point acceptable to stop.

The pharmaceutical industry recognizes the time constraints placed on health care professionals, especially in light of managed care. There is concern that overuse of active query may be perceived by some HCPs as a form of harassment and that they will cease to provide follow-up or additional reports of adverse events if they have negative experiences of repeated verbal contacts by companies requesting information.

In addition, if active query beyond the follow-up that currently exists is contemplated in the Final Rule, there may be an undesired impact on the human and financial resources that must be applied by industry to these activities. If we are obligated to contact the HCP by telephone and then write to get the information confirmed there is a duplication of effort for both the reporter and company.

III.A.8. Medication Error

A "medication error" would be defined as: 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.

Aventis disagrees with the FDA recommendation for the capture and expedited reporting of medication errors. In our assessment, FDA has not clearly defined the specific types of medication errors that should be reported and rather the Proposed Rule addresses this issue in very broad terms. Should any medication error that is associated with an adverse event be reported or must all errors of any type be reported? The definition of medication error includes "inappropriate medication use"; in a very strict interpretation this could apply to off label use. Has FDA considered this interpretation? Where does the burden of responsibility lie for the investigation of medication errors, especially those that occur in a hospital? These may be very difficult for a company to investigate and assess, partially due to the litigious implications associated with true "inappropriate medication use".

We believe that expedited reporting is not the right tool to solve and prevent medication errors. The FDA has initiated other tools that could prevent medication errors, such as the Bar Code Label Requirement, and has held several Public Meetings on "Minimizing medication-related errors", such as:

- Evaluating Drug Names for Similarities: Methods and Approaches (June and September 2003) to discuss current screening methods to assess sound alike and look alike proprietary drug names, in order to reduce the incidence of medication errors resulting from look-alike and sound-alike names.
- Current Status of Useful Written Prescription Drug Information for Consumers (July 31, 2003)

Adverse event systems are not currently designed to efficiently handle medication errors; they can only be handled by the MedWatch System if there is an actual AE. Other types of medication errors that do not result in an adverse event should best be handled by other systems such as the DQR System.

Compliance with a mandate to report all medication errors would require significant headcount additions for many in industry. What would be the ultimate gain that FDA hopes to achieve in gathering this type of information?

In the near future, FDA will in fact issue a new rule mandating the inclusion of Bar Coding on all pharmaceutical product labeling. It is a widely supported belief that this initiative will address the real concern of medication errors for pharmaceutical products.

Recommendation:

We suggest that only medication errors that result in an adverse event should be reported as part of the FDA Proposed Rule on Safety Reporting.

III.B.2. Written IND Safety Reports

"Current IND safety reporting regulations at § 312.32(c)(1)(i) require sponsors to notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected or any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity. These written IND safety reports must be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information."

Aventis recognizes that the proposed rule contains no changes in the frequency or format for providing clinical trial investigators (and ultimately IRBs/ECs) with information on serious, unexpected adverse events associated with the use of a drug. We agree that it is imperative that investigators responsible for the conduct of studies be informed by the sponsor of findings that could adversely affect the safety of study participants.

There has been concern from industry, investigators and IRBs/ECs that the format and frequency of distribution of IND safety reports (initial and follow-up) can at times be confusing and overwhelming. *Participating investigators* may currently receive safety information from not only their respective study protocol, indication, dosage form, etc., but from **all** company sponsored clinical trials for that drug. This is particularly confusing for investigators of IND studies conducted outside the US where local regulations may conflict with the obligations required by their IND participation. Many investigators do not understand the FDA concept for safety notifications and the associated volumes of paper that may result from such notifications.

Unfortunately, several of the FDA proposals in the Tome would significantly *increase* the number of IND safety reports submitted to the FDA and provided to investigators. This would only confound a situation that many investigators have already reported to be intolerable.

The European Commission has issued the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for

human use" [(ENTR/F2/BL D (April 2002)] as part of their **Clinical Trial Directive**. The following is from section 6.4 of this guidance:

> *"The sponsor shall inform all investigators concerned on findings that could adversely affect the safety of study subjects. If appropriate, the information can be aggregated in a line listing of SUSARs in periods as warranted by the nature of the clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product.*
>
> *"In the case of blinded trials the line listing should present data on all SUSARs, regardless of the medication administered (e.g. active/placebo), thereby when possible and appropriate, the blind be maintained and the risk of inadvertently informing the investigators with regard to the identity of the medication should be avoid.*
>
> *"If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, the sponsor should issue as soon as possible a communication to all investigators.*
>
> "A safety issue that impacts upon the course of the clinical study or development project, including suspension of the study programme or safety-related amendments to study protocols should also be reported to the investigators".

Recommendation:

Aventis believes that the EC Clinical Trial Directive provides a method, format and rationale for appropriately providing investigators with information that could adversely affect the safety of their study subjects. We recommend that FDA consider this approach for Investigator Notification for the following reasons:

- Aggregate line listings accompanied by a summary of the evolving safety profile would provide useful information to investigators and IRBs/ECs. As recommended in the EC Directive, the periodicity of these reports could be based on the nature of the clinical project or volume of reports received by the sponsor. This format would be especially helpful since IRBs/ECs often ask us to provide listings to help them have an aggregate view of the safety profile.
- Presenting all serious, unexpected, associated events in the line listings (regardless of medication administered - active drug, comparator, or placebo) would maintain the blind to the investigator. IND safety reports currently sent for verum cases only may create an investigator bias (as they are not receiving reports for comparator or placebo) and may enable an investigator to deduce drug randomization assignments for other study subjects.
- There is also provision in the EC Directive that significant safety issues would be communicated as soon as possible to the investigators. Investigators would recognize that these expedited communications represents significant safety information that is to be immediately reviewed and provided to their IRBs/ECs.

III.B.5. Investigator Reporting

*"An investigator must report to the sponsor any serious **SADR** (as defined in § 312.32 (a)) immediately and any other SADR (as defined in § 312.32 (a)) promptly unless the protocol or the investigator's brochure specifies a different timetable for reporting the SADR."*

Aventis is concerned that the use of the term "SADR" (suspected adverse drug **reaction**) is not in harmony with the rest of worldwide guidances and directives that indicate that the investigator shall immediately report to the sponsor all serious adverse **events.** Specifically, please refer to the following documents:

- European Commission's "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" (April 2003), section 5 "Investigator's Responsibilities" states that "the investigator shall report all Serious Adverse **Events (SAEs)** immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting." Please also refer to section 6.2 "Recording and Evaluation of Adverse **Events (AEs)**" and subsection 6.2.2 "Assessment of causality".
- ICH Topic E6 "Note for Guidance on Good Clinical Practice" (January 1997/July 2002) in section 4.11 "Safety Reporting", subsection 4.11.1 also states "All serious adverse **events (SAEs)** should be reported immediately to the sponsor except ..."
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 Article 16 #1 also requires the following: "The investigator shall report all serious adverse **events** immediately to the sponsor except ..."
- ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (June 1995), section 1 defines an "adverse **event**" as "any untoward medical occurrence ...which does not necessarily have to have a causal relationship with (the) treatment". The before sections further state that "an adverse event (AE) can therefore be any unfavorable and unintended sign (....), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product." This definition is also provided by above ICH Topic E6, section 1.2.

We also believe that applying the SADR definition to investigator reporting is in direct conflict with section III.B.2.b. of the Tome which states that: "...the determination of the possibility of causality (attributability) of an SADR to an investigational drug be based on the opinion of either the investigator or sponsor, which is consistent with the ICH E2A guidance". The proposed investigator reporting would result in underreporting of immediately to be forwarded serious adverse events from the investigator to the sponsor and would not be in harmony with above ICH standards and European regulatory requirements. This proposal would also impede the sponsor's ability to review and assess those SADR that the investigator does not attribute to the study drug and ultimately reduce the number of IND Safety Reports submitted to the agency.

III. C. 7. Lack of Efficacy Reports

"Instead, applicants would be required to submit to FDA expedited reports of information sufficient to consider a product administration change, based upon appropriate medical judgement, for any significant unanticipated safety finding or data in the aggregate from a study that suggests a significant human risk. For example, applicants would be required to submit information concerning reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease (see section III.D.2 of this document). In addition, applicants would be required to include in postmarketing periodic safety reports (i.e., TPSRs, PSURs, IPSRs) 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."

Although it is not entirely clear in the Proposed Rule, Aventis interprets this proposed requirement as pertaining solely to therapeutic products used to treat life-threatening or serious diseases. We maintain that this proposal cannot be applied to investigational vaccines being developed for prophylaxis or therapeutic use since by definition, these products have not had their efficacy established.

Expedited postmarketing reporting within 45 days of unexpected SADRs with unknown outcome:

III.A.3 Serious SADR, Nonserious SADR, and SADR With Unknown Outcome

"SADRs would only be classified as "nonserious" if manufacturers and applicants have determined that the reaction does not meet the definition of a serious SADR. If the outcome for an SADR is not known, a determination of seriousness cannot be made; the SADR would not default to a "nonserious" designation, but would rather be classified as an "SADR with unknown outcome"..."

Historically, FDA regulations and guidelines as well as those of other regulatory authorities and ICH, have indicated that the assignment of "serious" is given only to those ADRs that that meet defined outcome criteria. If the criteria are not met, a case is usually not to be considered "serious". Follow-up activities specifically include requesting information on the outcome of the SADR/ADR, particularly those events that have a high potential to have a serious outcome.

Recommendation:

We recommend that FDA provide clarification on the definition of "unknown outcome" as presented in the Tome. Does this term refer to the regulatory definition (e.g. serious vs. non-serious) or the medical outcome of the SADR itself?

III.D.3. Unexpected SADRs With Unknown Outcome

"Expedited safety reports for unexpected SADRs with unknown outcome would be submitted to FDA within 45 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for the unexpected SADR."

Under the proposed regulation, there would be some increase in processing and reporting those domestic cases without outcome which may currently be classified as "non-serious". They are now included in the FDA Periodic Report and would, under the proposal, need to be reported as single cases on a modified expedited basis. There would be increased reporting of foreign spontaneous SADRs since cases without outcome would now require 45-day expedited submission. This could result in foreign cases being submitted in the U.S. on a modified expedited basis, but not requiring submission elsewhere, including the country of origin.

The new 45-day report would also result in additional regulatory compliance tracking of the submissions. Furthermore, if 'outcome' information is received after the 45-day window, we assume that follow-up submission would be within 15-days for the cases newly defined as "serious", but we are unclear of how to handle follow-up for those cases that are ultimately determined to be "non-serious".

Modifications to the FDA 3500A form (section G.7) as well as modifications to databases would be required to denote this report as a 45-day follow-up.

Recommendation:

Aventis recommends that FDA withdraw their proposal to require a 45-day expedited submission for unexpected SADRs with unknown outcome. We recommend that such cases be included in the Periodic Report or PSUR.

Documentation of attempts for follow-up (Sections III.C.5, III.D.1, III.D.3, III.D.6)

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

"The agency believes that contact with a health care professional is warranted for serious SADRs because of the critical nature of these reactions. However, in those situations in which a manufacturer or applicant is unable to contact the health care professional (e.g., health care professional does not return phone calls, consumer does not permit manufacturer or applicant to contact its health care provider), it would include in its report to FDA the reason(s) for its inability to contact the health care professional and a description of its efforts to contact the health care professional."

We agree with the current FDA regulation 21 CFR 314.80 (c)(1)(ii) which states: "if additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information". This information is available to the FDA upon request. We question the FDA's intended purpose for requesting this documentation be provided in the 3500A as we believe that it:

- Provides no medically relevant additional information to the Agency.
- Produces significant additional work due to case processing and review of non-medical information. This will reduce the time we believe is better spent performing actual pharmacovigilance activities.
- May be illegal in some countries e.g. Germany (privacy regulations may prohibit our indicating that a reporter has not provided the information requested).
- Will result in extra effort for FDA staff that must review all 3500A forms even if there is no additional information (other than documentation of attempts to obtain follow-up). Will information be used to increase/ decrease FDA pharmacovigilance inspections? Will FDA notify a company if they are not satisfied with the follow-up?
- May provide information that could be used in legal actions. If an HCP refuses attempts for follow-up of a serious, unexpected case, could they later be sued if their actions contributed to an SADR/ADR not being added to the labeling?

30-day follow-up reports for certain reports that do not contain a full data set

III.D.6. Follow-up reports

"...a 30-day follow-up report would be required to be submitted in certain cases (i.e., initial serious and unexpected SADR reports, always expedited reports and medication error reports that do not contain a full data set). If a 30-day follow-up report is required and no new information is available for the report, then the manufacturer or applicant would still be required to submit the 30-day follow-up report, indicate in the report that no new information was available and include a description of the reason(s) for its inability to acquire complete information and its efforts to obtain complete information. In all other cases, if there is no new information to report to FDA on a previously submitted SADR no follow-up report would be required to be submitted to the agency."
"Expedited reports ...that do not contain a full data set at the time of initial submission of the report to FDA are subject to the 30-day followup reporting requirements under paragraph (c)(2)(vi) of this section rather than the 15-day followup reporting requirements..."

We recognize the emphasis FDA has placed on obtaining in a timely manner a full data set for certain reports (serious, unexpected SADR, always expedited reports and medication errors), but we disagree with the need to have an additional regulatory report for the sole purpose of notifying the FDA of our unsuccessful attempts at obtaining this information. The 30-day follow-up reports is an additional administrative burden that will only increase workload without

having an added value. Expedited follow-up information is currently reported to the FDA (and other regulatory authorities, as required) within 15-days of receipt, and provides prompt consistent communication of new information.

Requiring a follow-up report be submitted specifically due to incomplete full data set 30 days after the initial 15-day report:

- May result in a delay in submission of potentially important follow-up information. If additional information is received, but without a full data set, it would not be submitted to the Agency until 30 days after submission of the initial 15-day report.
- Would result in inconsistencies in the timing of expedited regulatory submissions globally. Regulatory authorities requiring submission within 15 days of receipt of follow-up could receive information well before the FDA. This inconsistency would also confound the process for investigator/ IRB/ EC notification.
- Would result in additional regulatory compliance tracking of the 30-day follow-up submissions. A confounding issue would be documenting regulatory submission compliance of 15-day follow-up reports not submitted until the 30-day report if they do not contain a full data set.
- Would result in extra work for FDA staff who would need to review follow-up reports that only contain documentation of attempts to obtain follow-up.

In addition, modifications to the FDA 3500A form (section G.7) would be required to denote this report as a 30-day follow-up.

Recommendation:

Aventis recommends that FDA continue the current requirement for the manufacturer or applicant to submit follow-up information to expedited reports within 15 calendar days of receipt of new information.

We also recommend that FDA continue to require the manufacturer or applicant to maintain in their files documentation of attempts to obtain follow-up information on such cases.

III.D.4. Always Expedited Reports

"The following medically significant SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, would be subject to an always expedited report:

- *Congenital anomalies,*
- *Acute respiratory failure,*
- *Ventricular fibrillation,*
- *Torsades de pointe,*
- *Malignant hypertension,*
- *Seizure, Agranulocytosis,*
- *Aplastic anemia,*
- *Toxic epidermal necrolysis,*
- *Liver necrosis,*

- *Acute liver failure,*
- *Anaphylaxis,*
- *Acute renal failure,*
- *Sclerosing syndromes,*
- *Pulmonary hypertension,*
- *Pulmonary fibrosis,*
- *Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,*
- *Confirmed or suspected endotoxin shock, and*
- *Any other medically significant SADR that FDA determines to be the subject of an always expedited report (i.e., may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).*"

Aventis disagrees with the proposal to have medically significant SADRs, which may jeopardize the patient and/or require medical or surgical intervention to treat the patient be subject to an always expedited report. We believe this requirement would be inconsistent with the definition of Seriousness provided in both ICH E2A and ICH E2D (Step 2) "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting". Both guidances indicate to consider these events "Serious" rather than "Always Expedited Reports". In addition "confirmed or suspected transmission of an infectious agent..." may not always be considered a "medically significant SADR, which may jeopardize the patient...". For instance:

- the confirmed transmission of Parvovirus B19 in an otherwise healthy adult male, shown by seroconversion, or
- an as reported ADR "suspected transmission of Hepatitis A (seroconversion)"

would not fulfill the serious criteria provided in the before mentioned ICH guidelines and would therefore result in inconsistent reporting within ICH areas, i.e. such case reports would not be subject to expedited reporting other than in the U.S.

Some of the always expedited reports would not necessarily be important medical events according to definition and to the medical understanding of the event. Perhaps this needs further explanation or different wording.

"Medically significant" events are per definition always serious therefore will always be discussed in the Periodic Report or PSUR. If they are labeled they will indeed not be distributed in an expedited manner, however these events would be closely monitored, whether labeled or not.

There are significant considerations and discussions which go into the development of a package label. The expedited reporting of events which are included in the package insert would seem to flood the system with reports which could distract from the ability to identify true signals. In addition, this is a potential example of replacing an automated process with a manual one which will decrease efficiency and potentially result in errors.

Recommendation:

We ask the FDA to provide guidance on what is "medically significant" and suggest removing the last item: *"Any other medically significant SADR that FDA determines to be the subject of an always expedited report (i.e., may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject)."*

We also suggest to include these events, using MedDRA terminology, in a guidance rather than within a regulation.

We also ask the FDA to clarify "sclerosing syndrome" as this may have multiple definitions or interpretations.

"These SADRs would be submitted to the agency in an expedited manner whether unexpected or expected and whether or not the SADR leads to a serious outcome. The medical gravity of these SADRs requires expedited reporting."

We disagree with this proposal since expedited reporting would not only include expected and non-serious SADRs, but also events that may be the indication for the drug. This could dramatically increase the number of expedited reports submitted by a company. While we could understand the FDA requesting expedited reporting on product-specific SADRs, we question the value or added patient safety of the broad application of always expedited reports.

We also vigorously object to the FDA proposal to add SADRs to the "always expedited" list via the Post-Marketing Guideline. We feel that it is a dangerous precedent to establish requirements without them being codified.

III.D.7. Supporting documentation

FDA is requiring that "*manufacturers and applicants submit to FDA, if available, a copy of the autopsy report if the patient dies. If an autopsy report is not available, the proposed rule would require that manufacturers and applicants submit a death certificate to FDA.... If any of these documents is not in English, an English translation of the document would be required.*"

We do not see the value to the FDA for adding this requirement in the final rule. It should be the company's responsibility to have processes in place to obtain source documentation and analyze it, as necessary, to include the relevant information in the Form 3500A.

Recommendation:

Aventis recommends that FDA require companies to request copies of autopsy reports and/or death certificates only for U.S. SADRs, for the following reasons:

- We do not believe the FDA is authorized to ask for such reports for patients outside the U.S. Such requests would normally require approval by the health care professional who prepared the report and possibly by the hospital and/ or the concerned patient's relatives. Applicable data protection rules of the concerned countries may also prevent our obtaining this information.

- For autopsy and death reports prepared in other than English, the translation could represent an unacceptable burden for the applicant.

The proposed rule would require *"that each expedited report contain in the narrative a list of other relevant documents (e.g., medical records, laboratory results, data from studies) regarding the report that are maintained by manufacturers and applicants. FDA may require, when appropriate, that copies of one or more of these documents be submitted to the agency within 5 calendar days after receipt of the request."*

Aventis believes this requirement will increase the workload in the data entry and validation of this additional information without any added value to the quality of the SADR.

Recommendation:

The narrative should focus on the medical aspect of the event and there should be limits to what non-medical information has to be included. If the FDA requires copies of such documents, e.g. due to a suspected safety problem, we believe they will ask the applicant to provide all case related source documents - regardless of what has been listed in the narrative of the concerned individual case reports.

III.D.12. Blood and Blood Component Safety Reports

FDA is proposing to require that reports of serious SARs, including fatal SARs under proposed Sec. 606.170(c), be reported to FDA using the reporting format described in proposed Sec. 600.80(c)(4). Thus the reporting facility would be required to submit a report for each individual patient on FDA Form 3500A or a computer-generated facsimile of FDA Form 3500A using the appropriate "preferred term" in the latest version of MedDRA (see section III.F of this document).

The proposed FDA reporting requirement would be very burdensome for companies collecting source plasma. Use of the FDA Form 3500A and MedDRA coding will require implementation of 510 (k) compliant database, additional training, and quality programs to comply with existing regulatory guidelines. Analyses have shown that the implementation of a compliant database requires capitalization at approximately $2-4 million dollars for an average size pharmaceutical company. The timeline for implementation is about 6-12 months. Additional headcount will also be required to maintain the database and properly submit/track the serious SAR filings mandated under the proposed rule change. Synergies with biological deviation reporting are not expected, as most of the adverse reactions are not deviations from normal processes during plasmapheresis. This proposal is unlikely to add substantive donor or plasma safety measures over current processes of collecting source plasma.

Recommendation:

Aventis recommends that FDA exempt companies collecting source plasma from the proposed FDA reporting requirement. If an exemption cannot be granted, then a clarification in the definition of serious SAR is requested.

FDA is also proposing that the terms "SAR" and "serious SAR" as used in proposed Sec. 606.170, have the same meaning as defined in proposed Sec. 600.80(a) (see sections III.A.1 and III.A.3 of this document). In general, FDA believes that any SAR related to blood donation or transfusion that requires immediate medical intervention or follow-up medical attention should be reported.

The proposed meaning of "serious SAR" is too broad when used in the context of a plasmapheresis center. The phrase "require medical or surgical intervention to prevent one of the outcomes listed in this definition" in part 600.80 could be interpreted to mean hemodynamic stabilizing methods used at the collection center, where no emergency transport was required. The vast majority (>90%) of reactions at plasmapheresis centers are vasovagal and hypotension reactions that, in general, respond well to volume replacement and leg elevation (medical intervention) but could be classified as serious SAR, according to proposed definition. Under the proposed definition, source plasma centers would have to submit approximately 30 reports per 100,000 liters collected (depending on the centers size). The overwhelming volume of reaction reports filed by centers could complicate regulatory efforts to *monitor safety of biological products* at plasma centers, the intent of this proposal.

Recommendation:

Aventis recommends that FDA define serious SAR as applied to plasma centers in a way that is consistent with 21 CFR 600.80: *serious SAR is suspected adverse reaction that results in death, inpatient hospitalization, or persistent/ significant disability of a source plasma donor.*

III.E. Postmarketing Periodic Safety Reporting

III.E.1-4 Traditional Periodic Safety Reports, Periodic Safety Update, Interim Safety Reports, Semiannual Submission of Individual Case Safety Reports

We believe the section of the FDA document dealing with PSUR requires additional clarification, specifically in regard to how it relates and conflicts with ICH E2C guidelines on this topic.

Contact person for TPSR & PSUR (III.E.1.h & III.E.2.k.xi):

"...would require another new section in TPSRs that would contain the name and telephone number of the licensed physician or licensed physicians responsible for the content and medical interpretation of the data and information contained within the TPSR. The fax number and e-mail address for the licensed physician would also be included, if available. This proposal

would provide the agency with someone to contact with any questions that may arise during review of a TPSR. FDA is proposing that the contact persons be licensed physicians because of their crucial knowledge of the medical significance of the information provided in a TPSR (III.E.1.h) and PSUR (III.E.2.k.xi)"

We do not agree with the proposal to include in the TPSR the name and contact information for the licensed physician(s) responsible for the content and medical interpretation of the report. Contact information provided with the report should remain at the discretion of the company (e.g., FDA contact with Aventis would remain the responsibility of the appropriate Regulatory Affairs representative).

Not all companies/applicants in the U.S. will have a licensed physician at all - especially not smaller companies. Medical/regulatory issues may be handled by "non M.D." - health care professionals (pharmacists, RNs, PharmDs.). It might be an unacceptable burden for such (smaller) companies to hire a highly paid licensed physician just to handle drug safety issues/preparation of TPSR & PSURs. It should be noted that within the European pharmacovigilance system (Volume 9 of the Rules Governing Medicinal Products in the EU) the qualification of the "qualified person responsible for pharmacovigilance" is defined as a "person (which) should have experience in all aspects of pharmacovigilance and if not medically qualified should report to, or have access to a medically qualified person". This is a much more practical approach and even the "medical qualification" is not limited to licensed physicians.

We would appreciate clarification of "licensed physician" as stated in the proposed rule, e.g., does this refer only to a U.S. licensed physician? Although it goes beyond ICH standards and EU requirements, international companies which have a pharmacovigilance "headquarter" outside the U.S. may rely on physicians licensed in other regions, e.g. in the EU, for the content and medical interpretation of safety information.

III.F.2. Medical Dictionary for Regulatory Activities (MedDRA)

"Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would require that each SADR in an individual case safety report be coded on the FDA Form 3500A, CIOMS I Form, or VAERS Form using the appropriate "preferred term" in the latest version of MedDRA in use at the time the manufacturer or applicant becomes aware of the individual case safety report. FDA is proposing to require use of MedDRA to be consistent with ICH M1."

Aventis fully concurs with the FDA recommendation that ICH agreed international drug regulatory terminology (MedDRA) be used to code ICSRs for purposes of postmarketing safety reporting to FDA and other international drug regulatory authorities. FDA has explained quite succinctly in **II.B.1. International Standards** the benefits of using MedDRA standard medical terminology and we do not feel it is necessary to restate them in our comments.

Recommendation:

Aventis recommends that FDA also require (in §§ 312.32) the use of MedDRA terminology for coding clinical trial SADRs.

SNOMED

Industry was recently informed that the Department of Health and Human Services (DHHS) has entered into a licensing agreement to make a clinical terminology database, SNOMED (Systematized Nomenclature of Medicine), available without charge to the U.S. health care industry for standardization of electronic medical records *[The Pink Sheet, September 01, 2003, Vol. 65, Iss. 35]*. The College of American Pathologists, which developed SNOMED, is encouraging FDA to use SNOMED CT "as a more appropriate terminology for the collection of safety data". The FDA has requested industry provide comments on the use of these two systems before taking further action.

The FDA has provided "Qs and As" to the Tome (Updated Aug. 28, 2003) that indicate the FDA continues to recommend use of the MedDRA terminology. *"The SNOMED initiative announced by DHHS is for standardization of electronic medical records in the United States. For purposes of postmarketing safety reporting to FDA and other international drug regulatory authorities, FDA has proposed to require that the reports from industry be coded in the ICH agreed international drug regulatory terminology (MedDRA). This remains the Agency's proposal. We believe these initiatives are not necessarily incompatible and the two terminologies effectively could coexist to advance public health goals both nationally and internationally."*

Aventis agrees with and supports the FDA proposal to required the use of MedDRA and is opposed to changing the required clinical terminology database to SNOMED for the following reasons:

- FDA as one of the core ICH sponsors supported the planning and implementation of MedDRA as the clinically validated medical terminology for regulatory authorities and the regulated industry.
- The regulators and industry have been in the process of implementing MedDRA with major efforts including major costs.
- Without MedDRA there will be no electronic transmission of ICSRs in the EU and Japan.
- Without the use of MedDRA FDA will be cut off from the international exchange of ADR data on an expedited and periodic basis which will also impact labeling.
- Two different coding systems to be used by global companies would represent a totally unacceptable financial and regulatory compliance burden.
- The harmonized global analysis of safety data could be compromised with negative consequences for the public health as related to drug related safety hazards.
- With reference to ICH and global harmonization initiatives, the use of SNOMED would put FDA in a position of isolation that does not agree with harmonization initiatives.

From a technical point of view:

- SNOMED allows for very detailed coding that is very complicated and requires excellent medical knowledge that consequently may impact coding consistency which is a critical point.
- It appears that data analysis using SNOMED terminology would not be trivial due to the combination of different axis fields.

- MedDRA hierarchy supports data analysis suitable for ADR data.
- MedDRA hierarchy provides flexibility for specific as well as for broad searches.
- MedDRA coding is supported by a large number of lowest level terms, which provide synonyms, more detailed terms or lexical variants. Consistent coding is therefore supported, even if a coder has only basic medical knowledge.
- SNOMED might be used for patient safety reports (adverse events due to medical procedures) by hospitals etc, but is definitely not acceptable for adverse event reporting.
- Electronic submission as per ICH E2B(M) indicates that MedDRA coding is to be used.

On behalf of Aventis, Aventis Behring, and Aventis Pasteur we appreciate the opportunity to comment on the proposed rule entitled "*Safety Reporting Requirements for Human Drug and Biological Products*" and thank you for your consideration.

Sincerely,

Steve Caffé, M.D.
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