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Food and Drug Administration
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Subject: **Docket No. 00N-1484**
Safety Reporting Requirements for Human Drug and Biological Products

10 October, 2003

Dear Sir/Madam:

Thank you for the opportunity to comment on the "Safety Reporting Requirements for Human Drug and Biological Products" proposed rule published in the Federal Register on March 14, 2003. Below are Genzyme's comments for your consideration.

1. **§III.C.2**

   This section states that "FDA is proposing to amend these regulations by adding 'animal and in vitro studies,' . . . to the list of examples" of safety information sources. **§312.32 (c) (ii)** states that a 15-day report is required whenever a study "suggests a significant human risk."

   - **We request clarification as to what constitutes "a significant risk" for human subjects in animal and in vitro studies, as these studies are often done with different dosing regimes, in specialized models, and with antibodies other than those under development, e.g., murine antibodies.**
   - **We suggest that a distinction be made between a non-clinical finding that requires "changes in either product administration or in the overall conduct of a clinical investigation" program as opposed to a non-clinical finding which requires information only, e.g., action is limited to (non-urgent) updating of the investigator brochure and informed consent in clinical studies.**
   - **We also request clarification on the timing and scope of the use of animal and in vitro study data usage. At what point will these studies be considered a source of safety information?**
   - **We suggest that the reporting clock for such studies start when the final study report is completed.**

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2. §IIIA 1

Suspected Adverse Drug Reaction (SADR) is a new definition which is incorporated in §§312.32 (a) and 314.80. This term refers to adverse drug experiences for which a causal relationship is considered possible. The proposed rule is built upon SADR reporting, as opposed to adverse drug experiences. The determinant of a "causal relationship" is that such a relationship "cannot be ruled out." This considerably broadens the current definition of a "reasonable possibility of a causal relationship," whereby some positive evidence of a relationship is required. The new definition assumes that a causal relationship exists unless there is specific information to refute it. The impact of the proposed definition is substantial for solicited adverse events, particularly in clinical trials. The proposed rule states that, consistent with the new definition, clinical trial serious adverse events termed "unlikely" or "remote" are to be considered as possibly related for the purposes of decisions about expedited reporting. This new SADR definition is inconsistent with that introduced in the EU Clinical Trials Directive, and we are concerned that this discordance will undermine progress achieved under ICH towards standardization of expedited reporting of serious adverse events from clinical trials.

In addition to the impact of this proposal on global harmonization, we are concerned that it may slow development of new drugs and biological products: Based on preliminary reviews of Genzyme's clinical development experience, we estimate a 10-fold increase in IND Safety reports. This will lead to a substantial increase in the number of cases submitted to already overloaded IRBs. An influx of cases might result in holds on clinical trials, not because of safety concerns, but because IRBs are unable to evaluate the information that they receive. Since expedited cases are only from patients treated with active substance, the interpretability of these case reports is very limited.

The requirement that the blind be broken prior to expediting cases has the potential to undermine clinical trials for two reasons. First, there is the potential to introduce bias as a result of the selective unblinding of cases in the active treatment group. Second, since the power of the study is driven by the number of endpoint events, unblinding of a substantial number of cases may diminish the power of the study.

For the most difficult situation in clinical safety wherein a product related safety problem mirrors the natural history of the indication for treatment, this change in definition will not provide a solution. Indeed, one mechanism proposed to correct over-reporting, namely the creation of "a list of known consequences of the disease that would not be submitted to FDA in an expedited manner as individual case safety reports," would undermine the rationale for the introduction of the change in the definition of relatedness. (For example, hepatic events in Hepatitis C patients, might plausibly be excluded from such expedited reporting by this mechanism, yet this is precisely the setting in which the original concerns about "remotely" related cases arose.) This is a problem which cannot be solved on the basis of individual case imputation and expedited reporting.

FDA proposes that for specific trials, proposals be made to ameliorate the "over-reporting" produced by this definition.

- **We propose that reverting to the traditional definition of relatedness would be the most appropriate mechanism to solve the problem produced by changing it.**

3. §314.80

In reference to, (a) Definitions, we have comments on the clarity and utility of new definitions in the proposed rule changes:

Active query is introduced to mean "direct verbal contact . . . with the initial reporter of a(n) . . . SADR or medication error by a health professional . . . representing the applicant. For SADRs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR; including, but not limited to information such as baseline data, patient history, physical exam, diagnostic results and supportive lab results."

- **We propose that the term active query be abandoned and replaced by two distinct concepts:**
  - ***"Verbal contact"*** which would imply contact, in-person, by telephone or by other interactive means such as video conference, between the reporter or a representative of the reporter and a health care professional representing the applicant.
  - ***"Directed query,"*** a focused line of questioning generated by a health professional which is designed to capture clinically relevant information associated with the drug product and the SADR; including, but not limited to information such as baseline data, patient history, physical exam, diagnostic results and supportive lab results. A directed query may be conducted by direct verbal contact or by other means including letter, fax, or e-mail.

SADR with unknown outcome is defined as an SADR that after active query cannot be classified as either serious or non-serious.

We note that the introduction of a third classification of "seriousness," i.e., "outcome unknown," will introduce inconsistencies with other regulatory agencies, requiring substantial changes to all systems and business processes. We respectfully ask the agency to provide evidence that uncertainty over the "seriousness" status of SADR reports poses a problem to the quality of such reports. It is not apparent that introduction of this category will improve the quality of safety information. However, it will make international harmonization of safety information more difficult, and will require extensive changes to information systems and business processes.

It is recommended elsewhere in the proposed rule that a licensed physician be responsible for the applicant's safety information. However, a requirement, such as *"SADR with unknown outcome"* that removes all medical judgment is inconsistent with that level of professional expertise and responsibility.

- **We suggest that the licensed physician's judgment, supported by appropriate internal procedures, be sufficient to determine seriousness in the infrequent situations in which outcome cannot be determined. Where a serious outcome is a reasonable possibility in the course of the natural history of the event, e.g., pneumonia, as opposed to pruritis, the default could be to assume a serious**

SADR.

4. §III.C.5

   In this section, FDA proposes to amend safety reporting regulations at §§310.305(c) (1) (i) (a), 314.80 (c) (1) (i) (a),, and 600.80(c) (1) (i) (a), to require manufacturers and applicants to immediately determine the outcome for the SADR.

   - **We respectfully suggest that FDA change " . . . determine the outcome for the SADR . . . " to "determine seriousness of the SADR" to reduce any confusion by interchanging "outcome" with "seriousness."**

5. Also found in **§III.C.5** is a proposal to amend safety reporting regulations at §310.305 (c) (1) (i) (a), 314.80(c) (1) (i) (a), and 600.80 (c) (1) (i) (a) to " . . . require manufacturers and applicants who are unable to immediately determine the outcome of an SADR . . . to continue to use active query to attempt to determine the outcome within 30 calendar days . . . ."

   Under this proposed rule change, a report of poison ivy would require a telephone call to the physician if the "seriousness" was not specified in the initial report, a scenario that adds little to the information content of the case but is burdensome to the reporter. The proposal to use direct verbal contact with the health professional reporter to determine whether an outcome is serious should not be required.

   - **We suggest that the licensed physician's judgment, supported by appropriate internal procedures, be sufficient to determine seriousness in the infrequent situations in which outcome cannot be determined.**

   Where a serious outcome is a reasonable possibility in the course of the natural history of the event, e.g. pneumonia the default could be serious. These comments pertain to all sections of the proposed rule in which active query is proposed as a means of addressing "unknown" outcome.

   - **We recommend the removal throughout the proposed rule, of the classification *SADR with unknown outcome* as well as the active query requirement and the associated 30 day report explaining the progress of the evaluation of such an SADR.**

6. §III.C.5

   This section proposes amending §§310.305 (c) (1) (v) , 314.80(c) (1) (v), and 600.80 (c) (1) (v) so that "(f)or a serious SADR that was not initially reported to the manufacturer . . . by a health care professional . . . the manufacturer . . . must contact the health care professional associated with the care of the patient using active query to gather further medical perspective on the case and to acquire a full data set for the report."

   - **We request that FDA not limit contact with the health care professional to active query (i.e. direct verbal contact), as written inquiries may sometimes be more successful or appropriate.**
   - **We request that FDA confirm that it is the implication of the proposed rule that the applicant need not contact the health professional for non-serious consumer**

reports. This inference would be consistent with the stated purpose of the proposed rule which is to direct effort from non-serious to serious reports.

7. §III.C.5

This section contains proposals to amend §§310.305 (c) (1) (iii) (B), 314.80(c) (1) (iii) (B), and 600.80 (c) (1) (iii) (B) to require manufactures and applicants to ". . . immediately determine the minimum information for actual medication errors that do not result in an SADR and potential medication errors . . . ."

- **As noted above, we respectfully recommend that direct verbal queries may be used where necessary to provide information about a case, but should not be a mandated default means of securing minimum information on medical errors.**
- **Thus, we request that the requirement that active queries be undertaken for all actual and potential medical errors be deleted. We suggest that all medical errors be the subject of directed query (as defined in our comment #3).**

8. §III D 5

The section on Medication Errors proposes to include reporting of medication errors actual or potential, within the purview of safety reporting requirements §310.305 (c) (2) (v) (A), 314.80(c) (2) (v) (A), and 600.80 (c) (2) (v) (A). We note that potential medication errors are already covered under product complaint regulations, and are concerned that including such actual and potential errors in safety sections will duplicate complaint handling procedures and confound and undermine the effectiveness of current product complaint procedures. The proposal to require " . . . reports of actual medication errors that do not result in an SADR be submitted to FDA even though the report does not contain a minimum data set . . . " found in **§III.C.5** duplicates requirements found in the product complaint regulations.

At present only those medication errors (product complaints) that lead to product recalls need to be expedited. We are concerned that attempting to manage medical errors via the adverse drug reaction reporting system introduces redundancies as well as inconsistencies with ICH practices. The existing product complaint system is designed to address such issues and can be expanded to address the concerns about medication errors without creating duplicate reporting. Furthermore, the product complaint reporting system immediately and directly involves appropriate manufacturing and quality organizations within the applicant's organization.

- **We suggest that it may be appropriate to update product complaint regulations to require expedited reporting of medication errors.**

9. §III.C.5

This section also states that §§310.305 (c) (1) (iv) , 314.80(c) (1) (iv), and 600.80 (c) (1) (iv) will require use of active query to secure a full data set for reports of serious SADRs, always expedited reports and medication error reports. In addition, when unable to contact the health care professional, the manufacturer " . . . must include in the report for

the serious SADR: (A) The reason(s) for its inability to contact the health care professional and (B) a description of its efforts to contact the health care professional."

We are concerned that this proposal to use the 3500A to document "due diligence" activity may distort the usefulness of this document. Currently, it is often difficult to provide a medically coherent narrative while separating the information into initial and follow up sections organized by time of information receipt. The addition of a list of contact efforts will make it more difficult to provide a medically relevant narrative. Furthermore, these due diligence records would be subject to FOI requests. This raises liability concerns for both the Sponsor and the health care professional.

The time needed to collect follow-up information may be more or less than the 30 days anticipated in the proposed rule; the recommendation that such a description of efforts be provided via a 30 day follow-up report does not provide a generally applicable time point. In addition, even in patients for whom the full data set has been provided, useful follow-up information may continue to be collected. The introduction of these recommendations will redirect pharmacovigilance activities away from productive efforts to solicit medically useful information and towards documentation and reporting of compliance activities. This is not consistent with the stated intent of the proposed rule.

- **We believe that documentation of due diligence efforts are best documented in company files and not in the 3500A, and respectfully request that FDA reconsider this proposed requirement.**
- **We suggest that the FDA may wish to require of applicants that they have procedures in place to ensure that for a defined set of circumstances (e.g. expeditable cases), directed queries be undertaken to secure follow up. The means of acquiring follow-up information may include but not be limited to verbal query to the health care reporter. The applicant may be asked to indicate at the end of a serious SADR, which does not contain a full data set, that there have been appropriate efforts to collect such information and that no further efforts are to be undertaken.**

10. **§III.D.1**

    This section contains a proposal to remove the phrase ". . . 'of initial receipt of the information by the person whose name appears on the label' . . . ."

    - **Please clarify whether the 15 calendar day timeframe begins when a report is received by the manufacturer/applicant versus receipt by a distributor.**

11. Also contained in **§III.D.1** is the statement, to be included in §§310.305 (c) (2) (i) , 314.80(c) (2) (i), and 600.80 (c) (2) (i) , that "(m)anufacturers and applicants should include in postmarketing expedited safety reports a chronological history of their efforts to acquire a minimum data set and to determine the seriousness and expectedness of an SADR if there is a delay in obtaining the information."

    We believe that the individual case safety report should contain safety information and not become an instrument to monitor compliance and due diligence.

- **We suggest as an alternative that manufacturers/ applicants be required to have procedures in place to acquire a minimum data set. Should it not be possible to collect such information, the manufacturer/ applicant should state that such efforts have been made but have been unsuccessful.**
- **It is our recommendation that this approach be applied throughout the proposed rules where ever efforts need to be made to collect information.**

12. §III.D.3

This section proposes requiring in §§310.305 (c) (2) (iii), 314.80(c) (2) (iii), and 600.80 (c) (2) (iii) submission of unexpected SADRs with unknown outcome to FDA within 45 calendar days after initial receipt by the applicant or manufacturer of the minimum data set. As noted above, we are concerned that use of the term "outcome" to signify serious or non-serious is confusing and will require a new category of classification that is inconsistent with ICH.

Again, under this proposed change, a report of poison ivy would require a telephone call to the physician if the "seriousness" was not specified in the initial report, a scenario that adds little to the information content of the case but is burdensome to the reporter. Moreover, such a report would have to be expedited on a new timeline (45 days) if the event "poison ivy" is not included in the product label. Since it is recommended elsewhere that a licensed physician be responsible for the applicant's safety information, requirements that remove all medical judgment are inconsistent with that level of professional expertise and responsibility.

- **Consistent with our previous recommendation (see point 5), we respectfully request the deletion of requirements to submit unexpected SADRs with unknown outcome to FDA within 45 days.**
- **We recommend that the licensed physician's judgment be sufficient to determine whether an additional query concerning outcome be undertaken. This should be limited to medical events in which a serious outcome is a reasonable possibility in the course of the natural history of the event, e.g. pneumonia, as opposed to pruritis.**
- **We recommend that the FDA remove from the rule both the category "outcome unknown" and the 45-day calendar requirement for expediting an "unexpected" event of "unknown" outcome.**

13. §III.D.4

This section proposes in §§310.305 (c) (2) (iv) , 314.80(c) (2) (iv), and 600.80 (c) (2) (iv) to ". . . require manufacturers and applicants to submit to FDA individual case safety reports for SADRs . . . whether foreign or domestic, that are the subject of an "always expedited" report. These "always expedited" reports would be submitted to the agency . . . no later than 15 calendar days after receipt . . . ." This section includes transmission of an infectious agent by a marketed drug or biological product. We note that submission of reports of transmission of infectious agents is partially consistent with Japanese law, allowing for ease in collection of data. However, please clarify why the proposed regulation is limited only to marketed products if the reference is made to patient/subject. It would seem that the same concerns would apply.

The "always expedited" list includes "seizures." Reports of seizures are extremely common, often in the context of another condition such as progression of a malignant neoplasm.

- **We propose that "seizures" not be included amongst the "always expedited" events.**
- **We request clarification as to whether these "always expedited" terms refer to the verbatim event reports or to the preferred term coded event in MedDRA.**
- **We recommend that the coded term be the basis for determining whether an event falls into an "always expedited" category.**

14. **§III.D.6**

This section makes reference in §§310.305 (c) (2) (vi) , 314.80(c) (2) (vi), and 600.80 (c) (2) (vi) to due diligence in the pursuit of follow-up information to expedited reports. In addition to the current requirement for submission of 15-day follow-up reports, FDA is requiring submission of 30-day reports if the full data set is not available. The 30-day report must state that this information was not available and must include a description of the reason(s) for its inability to acquire a full data set. The expedited report must include a chronological history of efforts to obtain complete information. We are concerned that sponsors will focus resources and efforts toward demonstrating due diligence rather than protecting patient safety. We believe that appropriate procedures might be required to collect such information. As noted earlier, we believe that documentation of performance of due diligence is best maintained in sponsor case files and made available for audit. Thirty days is an arbitrary value which is often an inadequate period of time (e.g. non- US cases, cases in which hospital discharge summaries or autopsy reports are required).

- **We propose that this requirement be removed.**

15. **§III.D.6**

This section also states that both 15-day and 30-day follow-up reports be submitted for actual and potential medication error reports that contain a full data set. Please clarify the circumstances under which a 30-day follow-up report would be required. Also, it is confusing to submit a follow-up 15-day report when an initial 15-day report has not been submitted.

- **We respectfully propose that you maintain statements in the <u>current</u> regulations (§§310.305 (c) (2), 314.80(c) (1) (ii), and 600.80 (c) (1) (ii) requiring the applicant to maintain records if additional information is not obtained for serious and unexpected SADRS. The current regulation is preferred to the proposed changes.**

16. **§III.D.7**

In this section FDA is proposing to ". . . require that manufacturers and applicants submit . . . a copy of the autopsy report if the patient dies . . . (or) a death certificate . . . ." Please consider that this information is abstracted into the patient record at present.

While it may be appropriate to indicate whether such information is available, we believe that it should not be necessary to routinely provide a separate copy of that document.

- **We recommend that autopsy/death certificate information should be incorporated into the patient database and the original document be retained in the applicant's files.**

17. **§III.E.4**

Regarding the semiannual submission of individual case safety reports noted in §§314.80(c) (3) (v) and 600.80 (c) (3) (v), we are concerned that periodically reported ICSRs based on listedness leads to certain inconsistencies. These inconsistencies can lead to a serious SADR being reported twice or not at all. For example, double reporting would occur for serious SADRs which are unlabelled (US) but which are listed. The first time the case would be sent as a 15-day US expedited report. The second time it would be sent as a component of the periodic ICSR. We propose that serious SADRs not be submitted twice as ISCRs.

On the other hand, serious ICSRs which are labeled in the US but not listed in the CSI would not be reported at all to the FDA. Since such cases are labeled they would not be sent as 15-day reports. Neither would they be included as periodic ICSRs, since that group consists only of listed cases, and these cases, while labeled in the US, are not listed in the CSI.

- **We recommend that such serious US-labeled but CSI non-listed cases be included as ICSRs in the semiannual submission.**

An analogous problem occurs with non-serious cases. ICSRs will be sent for non-serious unlisted cases, some of which will be for events which are labeled by the US Product Information (PI). In situations in which the US label contains many more ADR terms than the CCSI, this might mean the unnecessary submission of many non-serious, US labeled SADRs as ICSRs.

- **We recommend that provision be made to <u>avoid</u> submission of such non-serious <u>labeled</u> cases as ISCRs.**

The reverse situation will also occur with ICSRs which are listed and do not routinely appear in the PSUR listing. If these SADRS are not labeled in the US but are listed, they will not be sent as ICSRs with the semiannual submission accompanying the PSUR.

- **We propose that provision be made to <u>ensure</u> submission of such non-serious <u>unlabeled</u> cases as ISCRs.**

An additional implication is that foreign serious reports with dosage forms and formulations not approved in the US can be reported as serious listed ICSRs. In addition, such cases will be reported for non-approved indications.

The impact of these inconsistencies in reporting is not clear. It seems to us premature to initiate activities leading to such errors without an understanding of their magnitude and implications.

- **As a result of these inconsistencies, we respectfully recommend that a final rule should not be issued until the implications of the current proposals for ISCR submissions are analyzed more fully by the Agency.**

18. **§III.E.2**

This section details content for the Periodic Safety Update Reports (PSURs). We believe that a single global report format is positive. However, we are concerned that the U.S. ICSR case base contained in AERs might differ from the case base supporting the global PSUR, leading to discrepancies and inconsistencies in interpretation of the safety implications of these data sets.

We wish to comment that contrary to the suggestion in Table 12 that the proposed rules lead to savings as a result of increased efficiencies, the reverse is the case. The numerous US specific requirements introduced in the proposed rules will add to the cost rather than result in savings. At the same time, the inconsistencies between international regulatory reporting requirements will make world-wide assessment of safety information more difficult.

We wish to request clarification of some elements in the Periodic Safety Update Report **§III.E.2.c** (p 12439).

- **Should PSUR section D Changes to CCSI include changes to national labels which the applicant has not incorporated into the CCSI?**
- **Also, please clarify the PSUR section (C) *Actions taken for safety reasons*- item (iv) "clinical trial suspension." Does this include studies which stopped because of a stopping rule requirement and then restarted? Does it include actions taken in clinical trials in non-approved indications? We do not believe that it would be advisable to include such changes in the concept of "clinical trial suspensions."**
- **We recommend that only clinical trials terminated for safety reasons should be included in this section.**

19. **§III.E.2.e**

- **We recommend that further clarification be added to define which clinical trials should be included in the PSUR referenced in this section, specifically whether clinical trials that are not in marketed formulations or approved indications should be included.**

20. **§III.E.2.f.i**

For companies preparing a single global PSUR, it is better to include the line listing so that a single report is generated worldwide.

The ICSRs sent to the FDA in association with a PSUR will not completely correspond to the ICH PSUR line listing. The FDA will also receive additional categories of expedited cases which are not expedited via ICH.

Non-listed, non-serious ICSRs reported to the FDA are only from the US. The line listing will include foreign non-listed cases.

- **Please clarify whether FDA will require the sponsor to make available non-US cases which are included in the PSUR as non-serious, non-listed cases?**
- **If so, please add clarification as to specific circumstances and timelines.**

21. §III.E.2.f.ii

- Health Care Professional (HCP) as referenced is not clear. **We recommend that the sponsor be permitted to define HCP in a manner is consistent with the EU to avoid having to code as individual cases as HCP US or HCP EU.** Different listings and reports will result and this will not favor the process of harmonization.
- **We request that you please clarify whether U.S. compassionate use trials are included in this category.**
- It is very positive that this section clarifies further what constitutes study information. **We request that you clarify whether these definitions are acceptable to other ICH parties.**
- **We recommend that clarification be given as to whether cases from investigator INDs should be included in the tabulations, listings, or ICSRs.**
- **We recommend that clarification be added to define when it is appropriate here to comment on specific cases and what the criteria are for selecting such cases.**

If the tabulations are derived from the cases included in the ICH PSUR line listings, the results -- and potentially the interpretation -- will be different from those based on ICSRs submitted to the FDA. These tabulations will include non-US listed events, for example. They may be further complicated by the inclusion of cases considered to be "unknown outcome" in the US and non-serious elsewhere.

- **We request confirmation that on-going studies would generally not be discussed in the safety study section of the PSUR referenced in §III.E.2.h, unless interim results are available.**
- **We request clarification of which clinical studies FDA expects to be included in the PSUR.**
- **We request inclusion of a definition of the relationship between studies discussed in this section and ICSRs, focusing on patient exposure.**

22. §III.E.2.h

- **We request that you please provide further clarification of what constitutes medically relevant lack of efficacy reports, for example, in situations other than serious or life-threatening diseases.**

- **We recommend discussion of this issue be limited to circumstances when there is meaningful information that efficacy is different from that described in the CCSI.**

23. **§III.E.2.i**

In this section the sponsor is asked to identify increased reporting frequency of listed adverse events.

- **We request that you clarify what the basis is for identifying an "increased frequency."**

- **Also, we request clarification of what the aggregate of the listed adverse event term should be when evaluated for increased frequency.**

In MedDRA, the groupings may be very small, e.g., lower level group terms, or much larger aggregates such as HLGTs. Therefore, the results of a frequency analysis will change depending on the hierarchy level evaluated. The same considerations apply to evaluation of serious unlisted terms compared to prior cumulative frequency.

24. **§III.E.2.k.iv**

In reference to the SADRs with unknown outcome appendices noted in this section, we believe that that all unexpected SADRs categorized as "unknown outcome" will already have been submitted as 45-day reports according to current proposal. Unknown outcome cases will for the ICH PSUR have been categorized as non-serious reports, and as such, we are unclear as to the purpose this proposed appendix. Although we disagree with the proposal to "quasi-expedite" this class of case, an argument might be made that it facilitates rapid case review. The merit of maintaining this division in the analysis of aggregate data is not apparent.

- **We believe that these cases should be handled as non-serious cases throughout the PSUR and respectfully suggest that FDA eliminate this appendix from its consideration. If the appendix is retained, we suggest that "unknown outcome" cases should be handled as non-serious cases for the purpose of the PSUR.**

In addition, the current safety database will require additional fields to capture unknown outcome classification.

- **We recommend clarification as to whether these reports are to be submitted for non-U.S. cases.**

25. **§III.E.2.k.vi**

- **We recommend that standards be established for what constitutes a "frequency of lack of efficacy different from the pre-marketing clinical trials" referenced in this section.** We note that such comparisons are not readily made from spontaneous report data and suggest that this information come only from well-controlled clinical trials.

26. §E.2.k.vii

We believe that the information on resistance to antimicrobial drug products referenced within this section would be dealt with in the Overall Safety Evaluation section as opposed to a separate U.S. specific appendix.

- **We propose that it would be appropriate to discuss such issues regardless of the region affected, and suggest that FDA not limit focus to the US as these are not US specific issues.**

27. §III.E.2.k.viii

- **Please consider that implementation of the proposal found in this section will require modification to the existing safety database.**

28. §III.E.2.k.x

- **We request clarification as to whether FDA is seeking lists including archival (off-site) storage, "mirror files" (in quality assurance, subsidiary offices), etc., or just records of the official file holder.**

29. §III.E.2.k.xi

- **We request that FDA please provide further clarification regarding the term, "licensed" physician.** Does the physician in question need to be licensed in the place (state, country) in which the company is headquartered or in any state? What about physicians trained and licensed outside of the US?

30. §III.E.4

This section states "(t)he current approved U.S. labeling would be used as the reference point to determine whether an SADR is unexpected or expected, and the CCSI would be used to determine whether an SADR is unlisted or listed."

- **Please consider how this will impact expedited reporting of those events which may be "expected" but not "listed".**

- **We request clarification as to FDA's intent in using two reference documents.**

31. §II.E.4

As stated earlier, it is confusing to submit a follow-up 15-day report with an initial 15-day report had never been submitted, as specified in this section.

- **We request clarification of the rationale for this proposal given the implication for current reporting systems.**

32. §III.E.5

The proposal states ICSR submissions should occur every six months in this section.

- **We request that you clarify whether this requirement would be consistent with submission of PSURs (every 6 months for the first 2 years, then annually for the next 3 years, and then every 5 years thereafter) or if submissions would continue to be every 6 months for the life of the product.**

33. **§III.F.2**

This section concerns the Use of MedDRA §§310.305 (d) (2), 314.80(c) (4) (ii), and 600.80 (c) (4) (ii).

Genzyme Corporation, like the majority of biopharmaceutical companies in the industry, has devoted a great deal of time, effort, and costs towards planning, development, and validation of computerized systems and the creation of business processes, including personnel training needed to introduce the MedDRA dictionary into drug safety reporting.

- Because of the complexity of MedDRA it was necessary to development a Centralized Coding operation to provide consistent coding practices.
- Legacy safety data have been recoded from other dictionaries to MedDRA terms.
- Standardized safety data outputs have been adapted to include MedDRA terms.
- Software systems have been developed and validated to allow for both browsing and coding applications to the drug safety and clinical databases.
- Electronic individual case safety reports are MedDRA coded for the transmissions to regulatory authorities in Europe and Japan.

Our experience shows that the resource estimates for the introduction of MedDRA, estimated on page 12459, in the proposed rule, section V.D 2 Costs of MedDRA, are underestimated. Although Genzyme is a mid-sized company, our costs in introducing MedDRA exceed those estimated for large firms.

Although it is a great improvement over WHOART and COSTART for purposes of signal detection, MedDRA's granularity already poses some problems. A system such as SNOMED, with its very large number of terms is unlikely to be suitable for the analytic needs of drug product safety.

An important feature of MedDRA is its translation into other languages, thereby facilitating international standardization of medical vocabulary. This is an exceedingly important feature of the dictionary which must be supported and extended.

- **We strongly recommend that MedDRA be retained as the international medical terminology.**

34. **Examples of Cost Savings – general comment**

We are concerned that costs and savings shown in various tables may not be an accurate reflection of what we might anticipate. Below, we present two examples:

Table 12 cites savings of 38.8 million dollars annually, including 24.3 million dollars for PSUR submissions. We are concerned that this may not include costs incurred due to differences that continue to exist between international submission regulations. We believe that we may actually find an increase of costs.

Table 16 shows hourly compensation estimates discussed in V.D.1.c. Our concern is that there is a difference between hourly wages and the overhead expenses included in determining Full Time Employee (FTE) true cost to the company. Therefore, the information in this table may not be the best representation to determine estimates of cost.

- **We request clarification as to whether a 3rd party critique has been conducted for these savings estimates. If not, we suggest that perhaps such a review could be beneficial.**

We urge the agency to re-evaluate components of the rule after reviewing all the comments and having an opportunity to consider fully the total burden of new requirements, balanced against gains for the public health, and to re-propose the rule based on this finer tuned evaluation.

Genzyme appreciates the opportunity to comment on the "Safety Reporting Requirements for Human Drug and Biological Products" proposed rule. Please contact me at (617) 374-7275 or Joanna Haas at (617) 768-8023 should you have any questions regarding this letter.

Cordially,

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